Myalgic Encephalomyelitis / Chronic Fatigue Syndrome Advisory Committee

Report to the NHMRC Chief Executive Officer

30 April 2019

Australian Government
National Health and Medical Research Council

NHMRC

Professor Anne Kelso AO
Chief Executive Officer
National Health and Medical Research Council
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Dear Professor Kelso

I am pleased to present to you the *Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Advisory Committee Report to the NHMRC Chief Executive Officer* on behalf of the Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) Advisory Committee (the Committee).

This report identifies the research and clinical guidance needs for ME/CFS in Australia and makes corresponding recommendations for your consideration. The report also highlights the complexity of the condition and many of the key challenges facing the ME/CFS sector including from the perspective of consumers and their carers, clinicians and researchers.

The Committee released a draft of the report for public consultation earlier this year and the comments received reinforced the issues and the often divergent views on ME/CFS articulated by the Committee. The consultation process also confirmed the ME/CFS sector's support for the Committee's recommendations and the keen anticipation of their possible implementation.

As Chair, I would like to acknowledge and thank the Committee members for their contribution and commitment in preparing this report. It has been a privilege to serve as Chair and I am grateful for the diverse expertise and experience of my fellow members, which has been integral to the breadth of the report.

On behalf of the Committee, I would also like to thank the NHMRC project team for their extra-ordinary support throughout this challenging project.

Yours sincerely

Professor Kwun Fong
Chair, ME/CFS Advisory Committee
30 April 2019

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Executive Summary

Myalgic encephalomyelitis (ME), often referred to as chronic fatigue syndrome (CFS), is a complex condition and can be highly debilitating and disabling. In the absence of a diagnostic test and lack of a universally accepted case definition, defining ME/CFS remains challenging. This is further compounded by heterogeneity in symptoms, and the lack of effective management or treatment.

The only Australian prevalence estimate for ME/CFS is almost three decades old. This indicated that ME/CFS was estimated to affect 0.2-1% (48,000 - 240 000 people) of the Australian population,[1,2] which is consistent with current international estimates.[3] Australian research has made significant contributions to the field. However, the lack of significant public sector research funding over the last decade or more has triggered patients with ME/CFS and advocacy groups to call for greater awareness and recognition of the condition, an increase in research funding and a review of current Australian clinical recommendations. Similar initiatives have been established in the USA, Canada, and the UK.

Current ME/CFS research primarily focuses on understanding the pathophysiology of the condition, with a view to identifying biomarkers to assist in diagnosis and disease processes amenable to intervention. However, past research has mostly focussed on the management and treatment of ME/CFS, with an underlying assumption that the condition was primarily driven by psychosocial and behavioural factors. In combination, the uncertainties in diagnosis, disease mechanisms and management approaches have contributed to patients experiencing stigma, isolation, delays in diagnosis, misdiagnosis, lack of supportive care and unintended harm.

The Office of the National Health and Medical Research Council (ONHMRC) established the ME/CFS Advisory Committee (the Committee) to advise NHMRC's Chief Executive Officer (CEO) on the research and clinical guidance needs for ME/CFS in Australia. This Report aims to identify gaps in ME/CFS research and the status of diagnostic and treatment protocols used in Australia and internationally. It prioritises the Committee's advice and recommendations for research funding and opportunities for improved clinical guidance for ME/CFS in Australia. The recommendations put forward by the Committee are for consideration by both NHMRC and relevant Australian health care departments and agencies. The Committee acknowledges that some of the recommendations fall outside the remit and capacity of NHMRC.

The Committee's recommendations are based on the principles of consumer engagement, consistency, collaboration and capacity building. These recommendations are in alignment with NHMRC's strategy for health and medical research, which includes: the need to build research capability through investment in high quality research, facilitate and drive research translation to clinical practice and maintain a strong integrity framework promoting community trust.

The Committee recommends building Australia's ME/CFS research capacity.[i] The Committee advises that this could be achieved by funding research into the pathophysiology and aetiology of ME/CFS through a targeted call for research, and by promoting national and international collaboration. The Committee recommends boosting health services research and research translation to improve models of clinical care. This could include conducting health economic analysis to describe the impact ME/CFS has on the Australian economy so as to inform policy and service delivery. Increasing clinical awareness and education is considered by the Committee as a critical element in improving access to quality health service delivery for people with ME/CFS. Finally, the Committee recommends updating or developing new ME/CFS clinical practice guidelines to provide clinicians with an updated evidence-base for diagnostic and management/treatment strategies.

i *Research capacity* is referred to in this Report as anything that would facilitate research quantity and quality: the number of researchers, any data or physical research infrastructure and the actual body of research.

Summary of Committee's Recommendations

Summary of Committee's Recommendations for Consideration by NHMRC and Australian Health Agencies

Strategic focus 1: Research quantity and capacity building	**Objectives:** • Encourage hypothesis-generating research. • Support new and emerging researchers in the field of ME/CFS. • Encourage research translation and community collaboration. • Encourage collaborative funding initiatives both nationally and internationally. **Committee Recommendations:** • Conduct a targeted call for research (TCR) on ME/CFS pathophysiology. • Establish an Australian collaborative research consortium for ME/CFS. • For consistency in Australian research, adopt the 2003 Canadian Consensus Criteria (CCC) or the 2011 International Consensus Criteria (ICC), and the Paediatric Primer (2017) for child and adolescent patient selection and collect common data elements (CDEs).
Strategic focus 2: Improve health services research	**Objectives:** • Report the Australian burden of disease including: • DALYs to inform policy recommendations • child and adolescent impact • impact of caring roles for carers of people with ME/CFS • clarify health disparities. • Describe the economic impact of ME/CFS on the Australian economy. • Increase awareness of ME/CFS, to help inform policy on economic and social support service accessibility. • Highlight and invest funding and research opportunities in health services research fields. **Committee Recommendations:** • Undertake health economics analyses. • Highlight research opportunities in models of care and service delivery.
Strategic focus 3: Developing health advice	**Objectives:** • Provide clinicians with ME/CFS health care resources including clinical guidelines based on the latest research evidence. • Develop a clinical pathway within clinical guidelines for ME/CFS management and effective patient support. • Collaborate nationally in the dissemination and implementation of clinical resources, including the education of clinicians. **Committee Recommendations:** • Update or develop new Australian ME/CFS clinical practice guidelines and maximise their uptake by health care providers.
Additional Committee Recommendations	**Committee Recommendations:** • Develop Australian research capacity through international collaboration. • Establish an Australian collaborative biobank for ME/CFS. • Raise with AIHW collection of prevalence data and burden of disease reporting.

1. Purpose of the Report

The purpose of this Report is to advise the NHMRC CEO on the research and clinical guidance needs for ME/CFS in Australia. The Report identifies the current gaps in ME/CFS research and the status of diagnostic and treatment protocols used in Australia and internationally. It will help to inform the CEO's decision about what role NHMRC can play in this area, given its dual role in supporting health and medical research and developing evidence-based health advice for the Australian community.

2. Background

ONHMRC received a targeted call for research (TCR) submission from ME/CFS Australia (SA) in late 2016. The submission was considered against specific prioritisation criteria by NHMRC's TCR Prioritisation Committee and the NHMRC Research Committee. These Committees recognised the importance of research into ME/CFS and acknowledged that further expertise was required to articulate a research question that addressed the needs expressed in the submission.

ONHMRC received further correspondence from consumer advocacy groups (ME/CFS Australia Ltd, ME/CFS Australia (SA), Emerge Australia, ME/CFS & Lyme Association of WA and ME/CFS & Fibromyalgia Association of NSW) in the first half of 2017, offering to support NHMRC in targeting research, sourcing experts, engaging with the community and assisting with the adoption of an appropriate clinical case definition for ME/CFS.

Since then, ONHMRC has received considerable correspondence from ME/CFS advocacy groups, expressing concern over the lack of funding allocated to health services, medical infrastructure and translational research, including outdated guidelines and lack of treatment options for patients with ME/CFS. Patients have also expressed the difficulties they face including being misunderstood by health professionals, being under-represented and often ignored in their quest for understanding of what can be a very debilitating condition. Advocacy groups have endeavoured to raise awareness and educate the wider community about the above issues and have triggered significant discussions within the health portfolio.

In recognising the need to address these challenges, ONHMRC established the Committee to provide advice on the status of research and clinical guidance in Australia, and on any gaps that could be recognised to improve research funding and clinical care.

3. Context

3.1 Research context

Key Points

- Australian ME/CFS research to date has predominantly focussed on how to manage the condition, with some research on finding a cause (see Fig 1). The research has covered a wide spectrum of disciplines including epidemiology, pathophysiology (immunology, metabolic function, neurology and neurophysiology, genetics), clinical characteristics and treatment. The latter studies include drug trials and behavioural interventions.
- The dominant treatment paradigm has assumed that ME/CFS is a condition that may be initiated by a biological process but may be perpetuated or exacerbated by psychological factors.
- Understanding the pathophysiology of ME/CFS is central to developing diagnostic investigations, effective treatments and guiding improved clinician understanding and clinical management. These goals are challenging as several decades of research across many disciplines have not confirmed the mechanisms of disease, found reliable biomarkers, or established effective management or treatment.
- Developing clinical practice guidelines has been impeded by a:
  - lack of biomarkers to aid diagnosis
  - lack of evidence-based treatment approaches.
- Internationally, there is a range of educational resources available aimed at helping clinicians with diagnosis and management. These include primers, reports and guidelines. Most of them are developed by committees of relevant clinicians and patients who made recommendations based on a review of the literature and their own clinical expertise and experience.

3.1.1 Australian Government research funding

Under the *National Health and Medical Research Council Act 1992*, NHMRC administers the Medical Research Endowment Account (MREA) in order to provide assistance to institutions and people engaged in medical research and for medical research training. NHMRC awards new grants worth around $800 million each year from the MREA. Expenditure of the MREA is spread across a variety of grant types, both investigator- and priority-driven. NHMRC's grant schemes are highly competitive and only a small proportion of applications are successful (see: *Attachment A*).

As this Report was being finalised, the Australian Government made two research funding announcements that were informed by the Committee's recommendations.[ii]

NHMRC has allocated funding to successful grants relating to ME/CFS since 2000 (estimated at $1.63 million). Between 1999 and 2018, eighteen applications for ME/CFS research were received, with one project grant, one scholarship and two fellowships being funded.

ii On the 27 February 2019, the Australian Government announced a grant opportunity for a ME/CFS health economics study funded through the Medical Research Future Fund. In addition, the Australian Government announced on 27 March 2019, the allocation of $3 million to a ME/CFS targeted call for research through the NHMRC MREA. These funding opportunities were informed by a draft version of this Report.

3.1.2 Australian non-government research funding

Since 2003, the Mason Foundation has been a significant contributor to ME/CFS research funding.[4] Mason Foundation grants have been allocated to ME/CFS research conducted at various institutions, not limited to but including: the University of Melbourne's Bio21 Molecular Science and Biotechnology Institute, the University of New South Wales' Fatigue Clinic, Griffith University's National Centre for Neuroimmunology and Emerging Diseases (NCNED) and The Royal Children's Hospital - Murdoch Children's Research Foundation for paediatric studies. Further details are found at *Attachment B*.

The Stafford Fox Medical Research Foundation is another significant contributor to ME/CFS research in Australia. This foundation is currently funding a grant to Griffith University's NCNED. This research focuses on the functional changes found in calcium ion channel receptors.[5]

The Alison Hunter Memorial Foundation (AHMF) was formerly a non-profit institution dedicated to supporting advancement in scientific knowledge and medical care for ME/CFS. Recently AHMF established a formal partnership with NCNED and will now donate the entirety of its funding to supporting ME/CFS research at NCNED.

Other significant non-government funding has been contributed by hospital research funds (e.g. The Queen Elizabeth Hospital Research Foundation), John T Reid Charitable Trust and their brain study funding and university postgraduate scholarships (e.g. University of Adelaide cognitive function studies). Academic and clinical researchers have donated their time and expertise *pro bono* (e.g. South Australia brain study group and the Bio21 genome study) and patients themselves have contributed funding (e.g. donation of self-funded personal genomic data).

Further details on Australian research initiatives are at *Attachment B*.

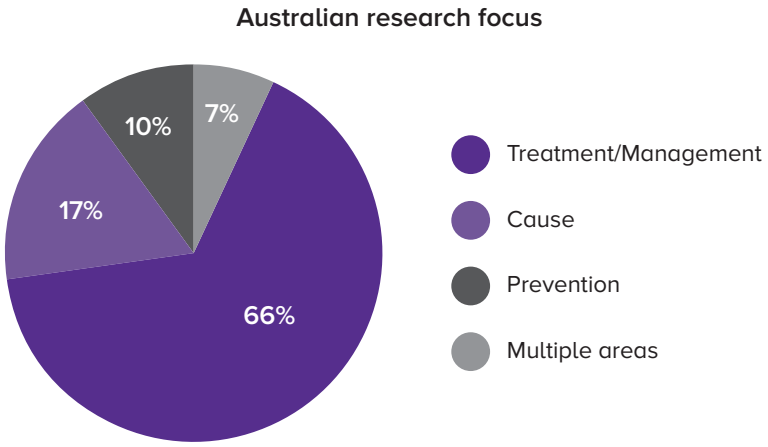

Figure 1: Australian Research Focus - Data sourced from the Mason Foundation Report – ME/CFS Research Mapping – Final Report (NOUS Group, 2016).[5]

3.1.3 International research funding

The United States National Institutes of Health (including Collaborative Research Centres)

The National Institutes of Health (NIH) is a United States (US) based medical research agency, comprised of 27 institutes and centres. As the primary federal research agency in the US, NIH is involved in conducting and supporting research and research translation and is currently leading research internationally on ME/CFS.

In late 2014 NIH began a comprehensive program to identify the research needs for ME/CFS. The *Pathways to Prevention* Workshop was convened in December 2014 to identify research gaps and future research priorities for ME/CFS. Further, in 2015 NIH co-sponsored the Institutes of Medicine (IOM) report

(IOM Report) which aimed to redefine the ME/CFS diagnostic criteria and contributed to a shift in the NIH's approach to ME/CFS research.

In May 2016, NIH published a Request for Information (RFI) to identify opportunities and strategies for ME/CFS research and training. The RFI received submissions from 30 researchers and clinicians, 21 ME/CFS organisations, including research organisations and more than 250 individual health consumers. This work led to the funding of the research consortium announced in September 2017 that awarded three grants to collaborative research centres (CRCs) and one to a data management and coordinating centre (DMCC) (*Attachment C*). The Common Data Elements (CDE) for ME/CFS is an additional project established by the National Institute of Neurological Diseases and Stroke (NINDS) at NIH and is integral to facilitating data standards for research, based on commonly understood criteria, symptoms and possible biomarkers.[6]

NIH has also initiated ME/CFS research at the NIH Clinical Centre in Bethesda, Maryland. The researchers at the NIH Clinical Centre will carry out detailed and comprehensive evaluation of several dozen people with ME/CFS, focusing on those whose symptoms can be clearly traced to an infectious-like illness and who have been sick for less than five years. These volunteers will undergo a comprehensive series of tests, including blood sampling for a range of laboratory investigations and brain scans, to help researchers learn more about the clinical and biological basis of the condition.

The Canadian Institutes of Health Research (CIHR)

The Canadian Institutes of Health Research (CIHR) is Canada's federal funding agency for health based research. It is composed of 13 institutes, four of which have an interest in ME/CFS research. The Institute of Musculoskeletal Health and Arthritis (IMHA) has taken the lead on funding of ME/CFS research focussing on diagnosis and treatment.

CIHR-IMHA started collaborating with NIH in 2016 by issuing a funding call for ME/CFS research. The funding call identified that Canada needed a nationally-focused research infrastructure. Since NIH has internal and external research programs and more resources to invest in ME/CFS research than Canada, research collaboration with NIH was identified as the best way to develop their research capacity. This would in turn contribute to the evidence base in Canada, using cohorts of current Canadian ME/CFS patients. In January 2017, CIHR-IMHA announced two Catalyst Grants dedicated to ME/CFS. These short term grants are intended to serve as seed funding to support research activities that represent a first step towards the pursuit of more comprehensive funding opportunities. In 2018 only one application was received for a project grant, which was unsuccessful.

The Medical Research Council

The Medical Research Council (MRC) is the leading medical research funding agency in the United Kingdom (UK), supporting medical research and innovation through multi-disciplinary initiatives. In 2008 MRC established an ME/CFS expert group (led by Professor Stephen Holgate) to explore ways to encourage high quality researchers into the field of ME/CFS and enhance collaborative partnerships of pre-established ME/CFS researchers. In 2011, a call for proposals was issued by the MRC for new research on the mechanisms of ME/CFS. The call focussed on the following areas: autonomic dysfunction, cognitive symptoms, fatigue, immune dysregulation, pain and sleep disorders. To date, MRC has funded 13 research grants which were awarded to interdisciplinary teams across a number of institutions. A list of research activities can be found on the MRC website.[7]

European Network on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

The European Network on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (EUROMENE) is an initiative comprised of approximately 20 countries creating an integrated network of ME/CFS researchers. The network aims to identify current gaps in ME/CFS research knowledge and assessment of ME/CFS published research. Future research will aim to focus on biomarkers and harmonisation of clinical diagnosis and patient management. The initiative aims to collect data on disease prevalence including estimates of the burden of disease in Europe. A Memorandum of Understanding was issued in 2015 outlining the following objectives for the initiative: research coordination (including shared data collection), capacity building, collaboration with relevant stakeholders and research collaboration across countries and disciplines.[8]

Myalgic Encephalomyelitis Research UK

ME Research UK is a funding organisation for biomedical research on ME/CFS. To date ME Research UK has contributed to over 40 studies on the physiological aspects of ME/CFS. Ten studies were published in 2017-18, which focussed on metabolic abnormalities, muscle fatigue, cardiovascular effects, biobank initiatives, sleep and research on patients with severe ME/CFS. The organisation aims to fund research initiatives that investigate the aetiology, pathophysiology and treatment of ME/CFS.

The Open Medicine Foundation

The Open Medicine Foundation (OMF) uses crowd funding and also receives philanthropic donations, notably a large sum from the pineapple fund. The OMF funds research at Stanford and Harvard universities and supports international collaborations that include Australia's Bio21 Institute of Molecular Science and Biotechnology. OMF has a unique place in ME/CFS research in that they are providing funds for open access research with shared data and an observational approach, not limited by hypothesis driven research.

In recent years, international research has shifted its focus to the pathophysiology of ME/CFS. This has been achieved through collaborative projects involving researchers from various fields and locations. For a more detailed summary of international research initiatives see *Attachment D.*

3.2 Clinical Guidance Context

3.2.1 Australian clinical guidelines

Royal Australasian College of Physicians: Chronic Fatigue Syndrome - Clinical Practice Guidelines 2002

The Royal Australasian College of Physicians (RACP) published the Chronic Fatigue Syndrome – Clinical Practice Guidelines in 2002.[2] The RACP guidelines were developed by an expert working group that included expertise in immunology, rheumatology, infectious diseases, neurology, sleep medicine, paediatrics, occupational health, psychiatry and general practice, as well as consumer representation. This group systematically reviewed the scientific literature on prolonged fatigue, chronic fatigue and CFS utilising a rating system for evidence that was modified from the NHMRC schema pre-dating the introduction of GRADE[9] (Grading of Recommendations, Assessment, Development and Evaluation). GRADE is an internationally recognised approach to developing guideline recommendations, and one that NHMRC now uses. The guidelines were published by the Medical Journal of Australia (MJA) in 2002 after public consultation but did not seek or attain NHMRC endorsement. These guidelines are currently available for use by Australian medical practitioners to guide the clinical care of ME/CFS patients.

There has been considerable debate and concern about the 2002 RACP guidelines, including that they recommend diagnostic criteria that could be seen to be too inclusive, not considering post exertional malaise (PEM) as a mandatory symptom, as well as recommending treatments such as graded exercise therapy and cognitive behavioural therapy. However, the historical context of these guidelines must be noted, as they were developed at a time when not much was known about ME/CFS. They provided some guidance for clinicians on a poorly recognised condition that did not have much evidence on causation, including guidance on ways to manage ME/CFS. Although the guidelines were well received by some clinicians in 2002, they were not well received by all clinicians or by ME/CFS Australia (a national organisation representing patients). ME/CFS Australia was concerned that the guidelines would result in *"further cases of misdiagnosis, inappropriate and inadequate medical care, and the promotion of widespread misconceptions about the illness."*[10]

The 2002 RACP guidelines endorsed the Centers for Disease Control and Prevention's (CDC) Fukuda (1994) diagnostic criteria[11] (*Attachment E*), which were the most widely utilised criteria at that time.[12]

2004 South Australian ME/CFS Management Guidelines for General Practitioners

The South Australian ME/CFS Management Guidelines for General Practitioners were developed in 2004 in collaboration with the South Australian Department of Human Services.[13] These guidelines were developed by a group of practising clinicians, researchers and consumers who reached consensus on the best approach to treat ME/CFS, using the most up to date information on the condition. These guidelines are a working document that contains questionnaires and checklists for health care providers.

The guidelines were produced for the South Australian health sector and were made available online nationally and internationally. The guidelines utilise the 2003 Canadian Consensus Criteria (CCC) 2003) as a tool for clinical diagnosis and recommend an abridged version of the CCC as a checklist to confirm a diagnosis of ME/CFS. More information is found at *Attachment E*.[14]

3.2.2 International clinical resources and guidelines

Currently there are a number of international clinical resources available to assist clinicians in diagnosis and management of ME/CFS. These resources are not formal guidelines and have not been developed using rigorous processes such as GRADE. This is in part due to the lack of robust evidence on aetiology, pathophysiology, and interventions for ME/CFS.

The International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis: A Primer for Clinical Practitioners

The *International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis: A Primer for Clinical Practitioners* 2014 (IACFS/ME)[15] was developed to inform health care providers on the diagnosis and treatment of ME/CFS. The Primer was developed by a committee who reviewed the published evidence and contributed their clinical experience and expertise. The Primer encourages clinicians to make a diagnosis based on the CCC. The Primer includes a number of worksheets for clinical use. The Primer has been used internationally and is referred to by a number of Australian advocacy organisations.

Frontiers in Paediatrics - Primer for Clinicians

In 2017, the journal Frontiers in Paediatrics published *ME/CFS diagnosis and management in Young People: A Primer*.[16] The Primer is the first clinical document to specifically focus on children and adolescents. This Primer includes a set of diagnostic criteria designed to provide diagnostic sensitivity within a paediatric patient population. The Primer acknowledges the use of CCC in adult diagnosis; however the Primer's working group recognised that a specific Primer was necessary for paediatric cases. The Primer is used internationally and endorsed by some Australian advocacy organisations.

Institute of Medicine – Beyond ME/CFS: Redefining an Illness (IOM Report)

The US Institute of Medicine (IOM – now known as National Academy of Medicine) tasked an expert committee to develop new diagnostic criteria for ME/CFS and to advise on whether a new name was needed for the illness. In 2015, the committee published its report, which detailed a comprehensive evaluation of the evidence and summarised the current status of ME/CFS diagnostic criteria including newly defined evidence-based criteria and new terminology for the condition. Four recommendations were made in the report based on the advice of the Committee (details of recommendations are at *Attachment F*).[17] The Committee also produced a 'Clinician's guide' to help clinicians utilise its new diagnostic criteria in their practice.

The United Kingdom's National Institute of Health and Care Excellence Clinical Guidelines

The National Institute of Health and Care Excellence (NICE) developed the *Chronic fatigue syndrome/ Myalgic encephalomyelitis (or encephalopathy): Diagnosis and Management Clinical Guidelines* in 2007 for health care providers, providing evidence-based recommendations.[18] Some patient groups have expressed concerns over the broad diagnostic criteria and some treatment options suggested in the 2007 guidelines, including graded exercise therapy. The NICE process involved an evaluation of the ME/CFS evidence base and grading of evidence. These guidelines are currently being updated and are expected to be published in October 2020. A number of stakeholder workshops have been held to promote transparency and to ensure the concerns of the ME/CFS community are addressed.

Canadian Medical Association – Clinical Practice Guidelines

In 2016, the Canadian Medical Association (CMA) published *Toward Optimised Practice: Identification and Management of ME/CFS*.[19] A committee reviewed the evidence and gaps in knowledge. The recommendations developed were based on expert opinions. The committee comprised representatives from family medicine, psychiatry and psychology as well as patients. The guidelines suggest the use of the Fukuda (1994) criteria and the CCC (2003) in combination to ensure consistency and specific diagnosis of ME/CFS. The guidelines also include a number of working documents such as symptom checklists and resources for treatment.

International Consensus Committee – International Consensus Primer for Medical Practitioners

In 2012, an international consensus panel consisting of clinicians, researchers and educators contributed to the *Myalgic encephalomyelitis International Consensus Criteria* as well as *The International Consensus Primer for Medical Practitioners*.[20] The panel aimed to provide consistent and narrower criteria to identify ME patients, as opposed to what they termed "*a multi-rubric pot that is chronic fatigue syndrome*." The primer includes a summary of pathophysiological findings and comprehensive clinical assessment and diagnostic worksheets. The Primer is targeted to primary care clinicians, specialists in internal medicine and medical school faculties for education.

4. Current Issues and Challenges

Key points

- Inconsistent use of diagnostic criteria has led to inadequately defined research cohorts and inconsistent findings in both pathophysiology and treatment.
- Estimates of the Australian prevalence and burden of disease are dated and would benefit from updated prevalence estimation and morbidity assessment.
- ME/CFS diagnosis is hampered by the lack of knowledge of its pathophysiology and aetiology.
- Defining and diagnosing ME/CFS is challenging given the heterogeneity of symptoms and the lack of diagnostic investigations.
- ME/CFS patients have described experiencing stigma, scepticism, unintended harm, isolation and lack of effective or supportive care and this has been attributed to ME/CFS being a misunderstood and poorly recognised condition.
- Controversial treatments such as graded exercise therapy have contributed to a disparity in approaches and some disengagement between patients and clinicians.
- Understanding and acknowledging patient concerns are critical in moving forward with the diagnosis, treatment and management of what can be a highly debilitating and disabling condition.

4.1 Lack of specific pathophysiology and aetiology

Although the pathophysiology and aetiology of ME/CFS are not known, a number of hypotheses exist; it has been postulated that ME/CFS may be a complex of multiple conditions rather than one single disease.[21] Determining the pathophysiology, aetiology and therefore a biological basis for ME/CFS is considered a priority, particularly for patients, as historically the condition has been misperceived as primarily psychosocial[22] and patients describe feeling stigmatised and isolated upon receiving such an explanation of their condition.[23,24]

Current hypotheses for aetiology and pathophysiology include a genetic predisposition[25], mitochondrial dysfunction[26], immune system dysfunction[27], autonomic disturbance[28], neurocognitive dysfunction and a metabolic disturbance reflected by changes in blood serum, urine and faeces.[29] This range of possible pathologies is testimony to the complexity of the illness.

4.2 Lack of consistent ME/CFS definition

Currently, there is a lack of a universally accepted definition for ME/CFS. Broad and/or varied inclusion criteria may skew research outcomes in relation to the aetiology and pathophysiology of ME/CFS, as well as the efficacy of interventions.[30] In a recent systematic review (2014), 20 different ME/CFS definitions were identified and with such differing criteria, consistency of study design becomes an issue that is reflected in research and treatment outcomes. The systematic review identified the Fukuda (1994) case definition as the most frequently used in ME/CFS research.[13]

The Fukuda (1994) criteria have been criticised as being overly broad, and not specifying the inclusion of PEM, which is described as an exacerbation of symptoms following physical or cognitive activity.[31] New case definitions have been developed to potentially better capture symptoms experienced by ME/CFS patients, and to exclude patients who do not have the characteristic features of the condition. These more recent definitions include the International Consensus Criteria[32] (ICC, 2011) and the CCC (2003).[18] However, these definitions are sometimes used in combination with the Fukuda (1994) criteria to enable the comparison of historical data and outcomes across multiple studies.

4.3 World Health Organisation classification of ME/CFS

In the International Classification of Diseases version 11 (ICD-11) the World Health Organisation (WHO) classifies ME under: *08 Diseases of the nervous system* with the subcategory: *other disorders of nervous system:* 8E49 *post viral fatigue syndrome,* with the inclusions of *Benign Myalgic Encephalomyelitis* and *Chronic Fatigue Syndrome*.[33]

Fatigue syndrome was historically listed under ICD- 10 V: *Mental and Behavioural Disorders* with the subcategory: F48.0 *Neurasthenia*.

Although *Fatigue syndrome - neurasthenia* was considered by WHO as a separate condition to ME, the symptoms presented in the classification appeared similar.[34] Having fatigue syndrome included in categories of disorders of the nervous system as well as mental/behavioural disorders reflects the historical debate faced by ME/CFS patients, one in which the condition is classified as physiological and the other in which it is considered mental and behavioural. In ICD-11 *Fatigue syndrome – neurasthenia* has been removed from the mental health classification.

4.4 Burden of disease

4.4.1 Australian Burden of Disease and Injury Study

The Australian Burden of Disease and Injury Study (ABDS) is conducted every 10 years by the Australian Institute of Health and Welfare (AIHW) and is a measurement of the burden of disease experienced by Australians. Disability-adjusted life years (DALYs) are used to measure morbidity and mortality. DALYs are a cumulative measure of years of healthy life lost due to disease or injury and are aggregated at the population level to measure the gap between the ideal health of a population and the current health of a population.[35] The data collected in the ABDS are used to inform policy and planning.

Quality data on ME/CFS incidence and prevalence are scarce. In 2003, the ABDS included ME/CFS as a separate disease when considering incidence and prevalence estimates for the Australian population. Two possible presentations of ME/CFS described in the literature analysed by AIHW were:

a) Post-infective fatigue syndrome (30-40% of patient cases)

b) Protracted chronic fatigue syndrome (60-70% of patient cases).

Using data compiled for the 1993 ABDS (including estimated disability weight), AIHW concluded in 2003 that people with ME/CFS are symptomatic 90% of the time. Median symptom duration ranges from 99% recovery after two years in post-infective fatigue syndrome, to cases fluctuating at around 50-80% of their previous healthy state. The median duration of protracted chronic fatigue syndrome has been reported as seven years, with the Fukuda (1994) diagnostic criteria used for patient selection.[36] In comparison, international estimates for recovery indicate 17-64% of patients improve with treatment, but less than 10% of patients have full recovery to pre-morbid levels of functioning, and approximately 20% of patients may worsen overtime.[15,21]

This is in contrast to recent paediatric data, which indicate that the majority of young people (who seemed to be more likely to have infection as a trigger) had a mean duration of illness of five years with a range of 1-15 years. By five years, 38% reported recovery and by 10 years 68% reported full recovery.[16,17,37]

In the 2011 ABDS study, however, ME/CFS was excluded as a separate disease given the then outdated prevalence estimates used in the 2003 ABDS. Instead ME/CFS was included under 'other neurological diseases'.[38] These 'other neurological conditions' (including ME/CFS) were responsible for 9.8% of the total DALYs for neurological conditions in 2011.

4.4.2 Prevalence and burden of disease

As at 2002 when the RACP guidelines were being developed, ME/CFS was estimated to affect 0.2 - 1.0% of the Australian population, approximately 48,000 - 240,000 people.[1,2] Such prevalence data represent a snapshot of all diagnoses at the population level at a point in time. This is costly to measure and is typically dependent on measurement of occasions of service (OOS) at the primary care level. It is likely that ME/CFS is not reliably coded in these OOS, contributing to inaccuracies in the reported prevalence.

Based on one report from the USA, approximately 13% of patients diagnosed with ME/CFS maintain employment, 25% become housebound or bedbound, and 62% remain unemployed.[39] The results of a 2015 Australian patient survey reported by an Australian advocacy group provided similar results with 74% of respondents indicating ME/CFS had a strong impact on or stopped their participation in paid employment and 34% of respondents reported having no income at the time of the survey.[40]

Given the information in the above two sections, it would appear that the estimates of Australian prevalence and burden of ME/CFS would benefit from being updated. Even though the information is limited, patient groups believe there is a mismatch between the amount of research funded and burden of disease.

4.5 Community concerns[iii]

4.5.1 Graded Exercise Therapy, the PACE Trial and other options for physical activity

Options for physical activity and exercise for patients with ME/CFS range from mild and gentle physical activity through to more structured and rigorous exercise programs that are sequentially graded. Physical activity and exercise therapy treatments have received significant attention in the media, amongst ME/CFS research sectors and the wider community. Patients and advocates have a real concern about the harm caused by some exercise modalities. These options for physical activity are of interest and a controversial topic of debate within all sectors (research, patients and clinicians), given the variety of responses to this form of management, and its effectiveness. These are briefly discussed below.

Graded Exercise Therapy

Graded Exercise Therapy is considered a controversial treatment and there is some ambiguity in its application in the clinical care setting. The primary reported concern with recommending graded exercise therapy for ME/CFS patients is it causing post-exertional malaise (PEM), exacerbation of symptoms and unintended harm.[41,42,43,44] Many public consultation submissions expressed concern about the potential for harm from graded exercise therapy.

Some specialist clinicians and researchers maintain that graded exercise therapy is effective when correctly administered as a patient-centred management strategy, and substantiate this with a number of clinical trials.[45,46] However, these trials have been questioned by some patients, advocacy groups, academics, clinicians and Australian and international researchers. For example, the United States Agency for Healthcare Research and Quality stated in their 2016 Addendum on the diagnosis and treatment evidence for ME/CFS.[22,44,47]

"...By excluding the three trials using the Oxford (Sharpe, 1991) case definition for inclusion, there would be insufficient evidence of the effectiveness of graded exercise therapy on any outcome...missing from this body of literature are trials evaluating effectiveness of interventions in the treatment of individuals meeting case definitions for...ME/CFS." - Smith et al (2016) pp. 11-13[48]

iii Community is defined in this Report as the entire ME/CFS community including patients, carers, researchers and clinicians.

A Cochrane review of exercise therapy for ME/CFS is currently the subject of ongoing review, with an update posted on Cochrane's website in March 2019:

"Cochrane's editors and the review author team have jointly agreed that there will be a further period up to the end of May 2019, in which time the [review] author team will amend the review to address changes aimed at improving the quality of reporting of the review and ensuring that the conclusions are fully defensible and valid to inform health care decision making. The changes will also address concerns raised in feedback since the ...complaint. The amendment will not include a full update, but a decision about this will [be] made subsequently."

Concern about the potential for harm from graded exercise therapy was a common theme expressed in public consultation submissions, and the Committee acknowledged this as a reality for many patients. The Committee noted that GET should not be offered as a cure for ME/CFS but that it might have a role in a patient's overall management strategy, helping with any secondary anxiety, de-conditioning and stress.

One trial that has received significant attention is the UK PACE trial.

PACE Trial

In 2011, The Lancet published a randomised controlled trial by White et al (2011*): Comparing adaptive pacing therapy, cognitive behaviour therapy , graded exercise therapy and specialist medical care for treatment of ME/CFS*, referred to as the PACE trial. The PACE trial supported the use of cognitive behavioural therapy and graded exercise therapy in treating ME/CFS as the results implied a moderate improvement of outcome measures. Participants were recruited using the Oxford (1991) diagnostic criteria (*Attachment E*).[48,49] PEM is not a mandatory feature in the Oxford (1991) criteria and this has contributed to dispute over whether patients recruited using this criterion actually have ME/CFS.

The PACE trial has been the subject of sustained criticism. In March 2014, a freedom of information request was lodged with Queen Mary University of London (QMUL) asking for the release of patient level data. QMUL refused to release the data, citing confidentiality concerns. In October 2015, the UK information commissioner conducted a decision notice advising QMUL to release the withheld data. QMUL appealed; the appeal was dismissed in August 2016 and the data released.[50,51]

Re-analysis of the data by Geraghty (2017) suggested that the PACE trial team overstated claims of benefit for cognitive behavioural therapy and graded exercise therapy through methodological alterations made throughout the study that skewed outcomes. The PACE trial was also criticised for its exclusion of severe ME/CFS cases and the potential inclusion of those with fatiguing conditions other than ME/CFS.[52,53]

The UK Medical Research Council (MRC) Executive Chair released a statement in August 2018 following a letter calling for The Lancet to reanalyse the PACE trial data. MRC, as funder of the trial, rejected the view that the scientific evidence was unsound, stating:

"The PACE trial was funded following expert peer review, was overseen by an independent steering committee, and its published findings were also independently peer reviewed. The process through which PACE was funded, supervised and published therefore meets international standards for clinical trials." – MRC 28 August 2018.[54]

Physical activity and pacing

Patients have reported pacing to be a helpful approach to managing their illness.[55] Pacing is described as an energy conservation strategy that aims to keep ME/CFS patients within their safe limits of activity (cognitive and physical) so as not to trigger PEM.[41]

Some patients have found that they are able to incorporate physical activity as part of their pacing and management strategy.[41] Physical activity can range from massage, assisted stretching with resistance bands, building functional strength, through to gentle movement like yoga and Tai Chi.[56,57,58] As with all management strategies for ME/CFS, any sort of physical activity program needs to be tailored to the individual and sensitive to the patient's capacity, symptoms and energy limit.[59,60] In 2015, an Australian survey of 610 patients with ME/CFS reported that 89% of respondents felt worse after increased activity or

exercise. The survey reported that pacing (58%) and rest, including bedrest (60%), were the most effective strategies for managing the illness.[44,61] Some patients have adopted the use of heart rate monitors to find their 'safe level of activity' to ensure PEM is not triggered.[62,63]

4.5.2 Differing experiences of patients and clinicians

A review and meta-synthesis of qualitative studies on ME/CFS patients identified a disparity in views between patients, clinicians and researchers on the diagnosis and treatment of ME/CFS.[64]

Patient perspectives are critical to understanding the complexity of ME/CFS and patient interactions with health care services.[65] Patients have, however, described feeling dismissed, negatively stereotyped and stigmatised after attending health care services.[66] This was affirmed by many public consultation submissions. These attitudes can affect patients receiving a timely and accurate diagnosis and effective clinical care. Other barriers to accessing clinical care raised during public consultation included hypersensitivities to light, sound and smell, and difficulty finding a place to lie down to help manage orthostatic intolerance during a clinical appointment. Housebound, bedbound and rural patients have reported difficulties in accessing healthcare services, further impeding effective care.[15, 20,67,68]

Poor clinician-patient interaction can be seen as a form of epistemic injustice in which the patient experience is given little credibility, leading to delayed diagnosis or misdiagnosis and further harm. The IOM reports that approximately 84% of those afflicted with ME/CFS remain undiagnosed and that those diagnosed waited six years or more to receive a diagnosis. [17,69,70]

A 2005 UK survey indicated that only half of General Practitioner (GP) respondents believed that ME/CFS was a real condition.[71] These results are similar to those of an Australian survey of GPs conducted in 2000,[72] indicating medical education and training is a key priority in addressing barriers to effective health care.

4.5.3 National Disability Insurance Scheme and access to supportive services

Whilst not within the remit of NHMRC's statutory responsibilities, as part of the work to develop this Report, ONHMRC and the Department of Health have been informed of the reported exclusion of some patients severely affected by ME/CFS from accessing the National Disability Insurance Scheme (NDIS), the Disability Support Pension (DSP) and other supportive services. Access to support services like NDIS and DSP is an issue of significant concern to the Australian ME/CFS community and has been a major focus of advocacy efforts.

To date, there have been three submissions to the Joint Parliamentary Committee on the NDIS (by Emerge Australia, ME/CFS Legal Resources Australia and ME/CFS & the NDIS Facebook group),[73,74,75] as well as a national #MillionsMissing advocacy campaign. Advocates have raised concern about the lack of understanding of the condition by National Disability Insurance Agency (NDIA) assessors, and the rejection of claims of people who are significantly impaired. Patients have indicated that a requirement of NDIS is that ME/CFS patients undergo graded exercise therapy and/or cognitive behavioural therapy before they can access NDIS, DSP or supportive services. To access care through the NDIS and DSP patients need to show they have a significant disability. For these ME/CFS patients, graded exercise therapy may not be appropriate. The following summarises the submissions' proposed recommendations to NDIS:

- recognition of ME/CFS as a serious debilitating condition
- the condition should be listed on the NDIS under list B: neurological disorders
- that assessment guidelines for NDIA assessors be developed in collaboration with clinicians with expertise in management of ME/CFS and the ME/CFS community.

5. ME/CFS Advisory Committee

5.1 Purpose of the Committee

The ME/CFS Advisory Committee (the Committee) was established to advise NHMRC's CEO on current needs for research on ME/CFS and clinical guidance on its diagnosis and treatment. The Committee will advise on: the status of international and national research on ME/CFS, gaps in research, the status of clinical guidance available to doctors and health professionals and requirements and opportunities for improved clinical guidance.

ONHMRC has embarked on this project given its dual role in supporting health and medical research and developing evidence-based health advice for the Australian community. On behalf of the Committee, ONHMRC has consulted with Australian and international researchers and institutions across a variety of disciplines in the field of ME/CFS to explore opportunities for collaborative research and clinical guidance efforts to inform this Report.

The Terms of Reference and Committee membership details are at *Attachment G*.

The recommendations presented in this Report are the result of extensive discussions by the Committee. This Report is intended as a starting point to capture and prioritise research and clinical guidance options for consideration by NHMRC and relevant Australian government health agencies. The Committee recognises that some of the research recommendations fall outside the remit of NHMRC.

5.1.1 Public consultation

The Report was released for public consultation for a period of 60 days from 21 December 2018 to 18 February 2019 and over 250 public submissions were received. The Committee considered the public consultation comments in finalising the Report.

5.2 Committee principles underlying research recommendations

The following principles underpin the Committee's advice on research and clinical guidance recommendations for ME/CFS:

- Consumer Engagement
- Consistency
- Collaboration
- Capacity Building.

The Committee advises that addressing each principle is critical to ensuring progress in research on ME/CFS and development of any meaningful and effective clinical practice guidelines. These are described in more detail below.

5.2.1 Consumer engagement

The Committee recognises that patient and carer involvement is integral to research and clinical guideline development. Participation needs to occur at every level of research, bringing the patient experience to design, implementation and analysis. This aligns with the 2016 NHMRC and Consumers Health Forum of Australia joint *Statement on Consumer and Community Involvement in Health and Medical Research.* The purpose of this statement is to guide research institutions, researchers, consumers and community members in the active involvement of consumers and community members in all aspects of health and medical research.

NHMRC is currently drafting a handbook to guide the development of guidelines by NHMRC and other parties, and one important chapter of this handbook, the *Consumer Involvement Module,* aims to inform guideline developers of appropriate consumer engagement strategies throughout the process of developing a guideline. The involvement of consumers in guideline development is essential to producing meaningful and effective advice to improve the health and wellbeing of specific target groups. This is especially important in conditions like ME/CFS because patients may have a wide variety of experiences. Engagement of ME/CFS patients requires an understanding of the range and types of disability and limitations experienced by patients and flexibility to accommodate these to ensure meaningful participation. Consideration should be given to both physical and cognitive challenges posed by the illness, as well as illness severity. Accommodations could include, for example extra time, rest breaks, sensory accommodations (audio versions of written materials, low noise and light in the meeting environment), or the opportunity to lie down, and should be guided by patient need.

5.2.2 Consistency

Heterogeneity of symptoms and clinical presentation is a challenge for clinicians and researchers. The Committee considers a clear and consistent description of the condition will allow improved acceptance and clinical diagnosis as well as recruitment of subjects with comparable symptoms in future research. The Committee also recommends adopting consistent research data collection aligned with the National Institute of Neurological Diseases and Stroke's Common data elements (NINDS CDE). This will likely assist in better description and comparison of patient cohorts and subgroups.

Describing ME/CFS

The Committee acknowledged the lack of a clear and universally accepted description of ME/CFS. It should be noted that a description of an illness differs from the diagnostic criteria set for clinical purposes (where the intent is to make a diagnosis and engage with management) and from diagnostic criteria for research purposes (where the intent is to identify a homogenous patient group to test research hypotheses). The Committee recommends adopting the advice in the British Medical Journal article 'Best Practice on Chronic Fatigue Syndrome' [21] on defining and describing ME/CFS.

Box 1: Defining and describing ME/CFS

Describing ME/CFS

There are several diagnostic criteria for ME/CFS in common clinical usage. There is also variation and controversy in the use of the terms ME, CFS, and ME/CFS (often, but not always, used interchangeably by clinicians). Many patients consider the name 'chronic fatigue syndrome' overly simplistic, and pejorative. The term 'Myalgic encephalomyelitis' is also problematic, given the limited evidence for brain inflammation. ME/CFS is characterised by a sudden or gradual onset of persistent disabling fatigue, post-exertional malaise (PEM)/exertional exhaustion, unrefreshing sleep, cognitive and autonomic dysfunction, myalgia, arthralgia, headaches, and sore throat and tender lymph nodes (without palpable lymphadenopathy), with symptoms lasting at least 6 months. The fatigue is not related to other medical or psychiatric conditions, and symptoms do not improve with sleep or rest.

Variations in describing ME/CFS

Definitions of ME/CFS have evolved from a focus on fatigue and impairment as described in the US Centers for Disease Control (CDC) criteria to PEM/exertional exhaustion in ME/CFS as defined by the Canadian Consensus Criteria and systemic exertion intolerance disease (SEID) introduced in 2015 by the US National Academy of Medicine (then known as the Institute of Medicine [IOM]). SEID was defined based on an extensive review of the literature, and was introduced as an alternative term for ME/CFS to emphasise that dysfunction involves the entire body, and that it is aggravated by physical or cognitive exertion and other stressors. Diagnosis of SEID requires disabling fatigue, PEM, and unrefreshing sleep that are persistent, moderate

or severe in severity, and present at least 50% of the time, plus either cognitive or orthostatic intolerance with the same severity and frequency. Pain was not considered unique to ME/CFS and so was not included in the SEID criteria. Use of the term SEID is not currently widespread, and within this topic the nomenclature ME/CFS is used. These 3 definitions (CDC, Canadian Consensus Criteria, and National Academy of Medicine/IOM) have compatible criteria that focus on PEM, disability, sleep, pain, and cognition.

Characteristic features of ME/CFS

PEM is the most characteristic feature of ME/CFS according to the National Academy of Medicine/IOM criteria. PEM has been described as a group of symptoms following mental or physical exertion, lasting 24 hours or more. Symptoms of PEM include fatigue, headaches, muscle aches, cognitive deficits and insomnia. It can occur after even simple tasks (e.g., walking, or holding a conversation) and requires people with ME/CFS to make significant lifestyle changes to conserve their physical resources and mental concentration to stay competent in normal occupational, educational, and social settings. Patients are often limited to a few hours per day of productive endeavours, with the remainder of the time spent resting with slow and partial recovery from the disorganised thoughts, total body pain, malaise, and other features of their chronic fatigue state. Consideration of 'fatigue' as mental or physical tiredness is too simplistic to encompass the scope of impairment in ME/CFS, and belies the inadequacy of the vocabulary of fatigue.

There is a strong bias to the vocabulary of acute viral illness, such as influenza and poliomyelitis, because these were considered historical precedents of ME/CFS.

This information and these descriptions could be used by both clinicians and researchers, noting that descriptions will likely evolve as new evidence surfaces.

It is important to note that some Committee members indicated that PEM may not be unique to ME/CFS, as it is evident in some other fatiguing illnesses, including post-cancer fatigue, post-polio syndrome and multiple sclerosis.[76,77] Some Committee members, however, suggested that PEM experienced by ME/CFS patients has unique features that differ from PEM in other types of fatiguing illnesses, including what triggers the PEM.[78,79,80]

Diagnostic criteria

The Committee also recommended adopting consistent diagnostic criteria for clinical practice and for research. The Committee acknowledged that no single set of diagnostic criteria entirely encompasses the presentation of all ME/CFS symptoms. This is due in part to the absence of a diagnostic test and the unresolved pathophysiological basis of the condition.

To achieve consistency in research, the same criteria should be utilised nationally and should reflect international standards. This will allow for research collaboration and comparison of research findings, as well as stratification of patient cohorts.

As mentioned, as at 2014, the Fukuda (1994) criteria were the most frequently adopted criteria for use in research.[12] However, these criteria have been proposed to be overly broad in defining symptoms. This may lead to further lack of consistency, heterogeneity of patient cohorts and the potential for inclusion of patients who do not have ME/CFS, as these criteria do not have PEM as a mandatory symptom. In light of this, the Committee recommends the adoption of either the 2003 CCC or the 2011 International Consensus criteria (ICC), and the Paediatric Primer (2017) for child and adolescent patient selection for use in Australian research, whilst also recommending that NIH National Institute of Neurological Diseases and Stroke Common Data Elements (CDE) be collected to ensure that previous research studies and those using alternate diagnostic criteria can be readily compared.

5.2.3 Collaboration

Increasing national and international collaboration facilitates consistency in research design and builds ME/CFS research capacity. Collaboration also allows targeting of research gaps through the use of shared data, therefore improving research accuracy and accelerating progress.

5.2.4 Capacity building

Australian research into ME/CFS to date has been limited to small research teams with limited funding and capacity. The Committee feels that building research and researcher capacity is critical for ME/CFS. This could be facilitated through consistent funding and the collection of data and collaborative data sharing, helping to target research gaps and supporting the whole research journey from providing high quality funding applications through to carrying out sound scientific research and improving how research findings are disseminated.

5.3 Committee recommendations

NHMRC's strategic direction for health and medical research, described in its Strategy for Health and Medical Research, has three themes: to invest in high quality health and medical research and build research capability, to support the translation of health and medical research into clinical practice and to maintain a strong integrity framework for research and guideline development and promote community trust.

Given the above, the Committee recommends focussing on the following to improve ME/CFS research and clinical care:

1. Build **research quantity and capacity** through investment in high quality ME/CFS research
2. Support specific activities that will boost and add value to **health services research**
3. Develop **health advice**.

5.3.1 Strategic Focus 1: Build ME/CFS research quantity and capacity in Australia

Key points

- Encourage hypothesis generating research.
- Support new and emerging researchers in the field of ME/CFS.
- Encourage translatable research and community collaboration.
- Encourage collaborative funding initiatives both nationally and internationally.

Background

The Committee acknowledges research capacity as central to generating quality research, which can be translated into evidence-based health advice and inform health policy and decision-making. Some research on ME/CFS has been conducted within Australia; however, these research efforts are yet to significantly impact health policy and clinical practice.

The Committee recommends funding of multiple collaborative grants with a focus on addressing the current knowledge gaps in ME/CFS. Increased opportunities for funding will also help to build research capacity through support for the work of current and new researchers in the field, through topics such as:

- Understanding the pathophysiology of ME/CFS to identify mechanisms of the condition
- Discovery of potential biomarkers and development of diagnostic tests

- Development of evidence-based treatment
- Consumer engagement strategies to effectively address gaps in clinician and health providers' knowledge, awareness and education, broadening awareness of the condition.

Some of these opportunities are discussed below, whilst others are expanded on further in the Report.

5.3.1.1 Conduct a targeted call for research (TCR) on ME/CFS pathophysiology

A targeted call for research (TCR) is a one-time solicitation for grant applications to address a specific health issue. A TCR specifies the scope and objectives of the research to be proposed, application requirements and procedures, and the review criteria to be applied in the evaluation of applications submitted in response to the TCR. TCRs will stimulate and advance research in a particular area of health and medical science that will benefit the health of Australians.

The Committee advises that a ME/CFS TCR would allow for hypothesis-generating studies and would stimulate the Australian ME/CFS research field by bringing new, emerging, early and mid-career researchers into the field and allowing existing researchers to undertake substantial projects. A TCR specific to ME/CFS aetiology and pathophysiology could focus on one or more of the following areas:

- Neurology
- Metabolomics
- Neurophysiology (e.g. exercise provocation studies)
- Immunology
- Endocrinology
- Genomics
- Sleep physiology.

The Committee also recommends inclusion of a specific focus on patient groups often excluded from research studies including children and adolescents, and those severely affected by the condition.

Any TCR proposal will be provided to NHMRC's Research Committee for consideration and advice, including recommending a budget allocation from the Medical Research Endowment Account.

If Research Committee supports the TCR proposal and recommends it to NHMRC's CEO, ONHMRC or an expert group (whose members would not be able to apply for TCR funding given the conflict of interest) will develop TCR-specific information. This will provide detailed background to the call, scope, aims and objectives, desired outcomes, examples of research that will not be supported and the approved budget, forming the Grant Opportunity Guidelines.[iv]

5.3.1.2 Establish an Australian ME/CFS collaborative research consortium

Collaboration is one of the important principles underpinning successful biomedical research, and can facilitate consistency in research design and build capacity in ME/CFS research. Australian research into ME/CFS to date has been limited to small research teams with limited funding and capacity. In order to answer critical questions about the underlying disease mechanisms and pathophysiology of ME/CFS, collaborative research initiatives are required from multi-disciplinary teams. The Committee suggests establishing and funding an Australian research consortium, amalgamating various resources into one centralised, and most likely virtual, team to create effective links and foster the dissemination of research findings between researchers, health care providers and consumers.

The purpose of such a research consortium would be to:

- Build research capacity by attracting new and emerging researchers into the field and supporting career progression of already established researchers
- Facilitate consumer engagement in the design, conduct and implementation of research findings

iv On 27 March 2019, the Australian Government allocated $3 million to a targeted call for research through the NHMRC MREA, to help researchers develop a better understanding of the causes and mechanisms of ME/CFS.

- Increase knowledge and understanding of ME/CFS by conducting high quality research to understand pathophysiology, aetiology, biomarkers and diagnostic tools for ME/CFS
- Encourage sharing of population data and previous published research findings and unpublished research findings, including raw data, to ensure that consistent hypotheses can be generated, and research discoveries disseminated
- Provide collaborative opportunities for established researchers to exchange knowledge and identify gaps in research, as well as being a focus for centralised funding from philanthropic foundations
- Disseminate research findings to support, research translation and consumer awareness, including education of the community and health care providers in the diagnosis, treatment and management of ME/CFS.

5.3.2 Strategic Focus 2: Improve ME/CFS health services research

Key Points

- Report the Australian burden of disease including DALYs and quality-adjusted life years (QALYs) to inform policy recommendations.
- Describe the economic impact of ME/CFS on the Australian economy, including health disparities.
- Report on child and adolescent impact, including impact on parents and carers.
- Research models of care and service delivery, including effective translation of research findings into practice.
- Increase awareness of ME/CFS, to help inform policy on economic service accessibility and social support service accessibility.

Background

NHMRC supports and promotes the translation of knowledge created through research into clinical practice, health policy, health services and systems and public health. Health services research can examine issues such as how patients access care, their treatment and how their health concerns are managed. Determining the economic impact of ME/CFS, the cost of accessing care and the cost of health care services is particularly important for ME/CFS patients. Some patients have reported a dependence on family and social support services, given the debilitating impact of ME/CFS on a patient's capacity to support themselves financially. Analysis of the economic and social consequences of the condition will assist in addressing some of the broader complexities of the condition.

5.3.2.1 Health economic analysis

A health economics report conducted through some form of targeted call for research could describe the impact ME/CFS has on the Australian economy through aspects such as loss of income for sufferers and carers, use of social services and support and costs to the community of medical care and health care resources. The existing Australian health economic data for ME/CFS are several decades old.[v]

The Population Health Research Network (PHRN) is an initiative of the Australian Government as part of the National Collaborative Research Infrastructure Strategy (NCRIS). The PHRN provides researchers with the opportunity to access a nationwide data linkage infrastructure and specifically health data from the Australian population. The PHRN could be utilised to access data for ME/CFS prevalence estimates, hospital admissions, GP visits and patient diagnosis data and to extrapolate economic data including health services access and expenditure.

v On 27 February 2019, The Australian Government announced a grant opportunity to fund a ME/CFS health economics study of the impacts and costs associated with ME/CFS through the Medical Research Future Fund. Applications were open from 27 February 2019 until 10 April 2019.

However, the Committee notes that accurate collection of health data for ME/CFS may be challenging, as this diagnosis may not have been collected consistently, for reasons identified throughout this Report.

5.3.2.2 Research on models of care and service delivery

Health services research provides up to date evidence to inform high quality policy and service delivery. The Committee recommends translatable health services research that can improve models of primary and/or secondary care and service delivery for patients with ME/CFS. NHMRC encourages and promotes partnerships between researchers, clinicians, health consumers and policy makers across the full spectrum of health and medical research. This collaborative approach helps to deliver research outcomes that are needed by consumers and end users, and can be translated more effectively into practice and, ultimately, better health outcomes. Funding this research will also positively impact research and researcher capacity.

Research on models of care could focus on:

1. Collaborating with consumers on the best approaches to improve quality of health care delivery, including models for management of the condition across the spectrum of severity, and how to better support carers.
2. Improving multi-disciplinary models of ME/CFS care.
3. How best to educate health care providers about ME/CFS and its effective treatment or management.

5.3.3 Strategic Focus 3: Develop health advice

Key points:

- Provide clinicians with ME/CFS health care resources including clinical guidelines based on the latest evidence.
- Develop a clinical pathway within clinical guidelines for ME/CFS management and effective patient support.
- Collaborate nationally to improve clinician awareness of ME/CFS and to disseminate and implement clinical resources.

Background

Research creates knowledge that informs our understanding of health, disease and interventions, including how these interventions are used in treatment. Effective research translation involves the implementation of research evidence into everyday practice. This can be achieved through various streams, e.g. university medical education: both primary and allied health, continuing professional education for health professionals and through government agency research translation initiatives. NHMRC is committed to raising the standard of individual and public health through consistency in health standards, research and training. One of NHMRC's primary responsibilities is supporting and driving translation of research into clinical and population health policy and practice to ensure that Australia benefits from its investment in health and medical research. The Committee agrees a key way of addressing this for ME/CFS would be to improve health advice in the form of updated Australian ME/CFS clinical practice guidelines.

5.3.3.1 Australian ME/CFS clinical practice guidelines

As previously discussed, the RACP guidelines (2002) are the most recent Australian guidelines for the diagnosis and management of ME/CFS. Whilst they were developed at a time when little was known about how to manage the condition, the guidelines have informed clinical practice since 2002. These guidelines, however, have been criticised by some patients, advocacy groups, academics, some clinicians and some Australian and international researchers. The treatment recommendations made in the RACP guidelines, including graded exercise therapy and cognitive behavioural therapy, as well as the ambiguity around the management of the condition, have led to some patient mistrust, and a lowering of patient confidence in the guidelines and health care services more generally. Patient mistrust

and lack of confidence have also been observed in the UK and have stimulated the revision of the NICE 2007 ME/CFS clinical guidelines, with patient/consumer engagement a priority.

The Committee advises updating or developing new Australian ME/CFS clinical practice guidelines as well as developing General Practitioner educational material and patient engagement strategies. The currency of these resources should be maintained to reflect the latest high quality evidence; this may help to re-establish patient trust and confidence in health care practitioners. Under Section 9(1) of the *National Health and Medical Research Council Act 1992*, NHMRC can develop and issue clinical practice guidelines and under Section 14A can approve selected clinical practice guidelines developed by other organisations.

NHMRC guideline development options include developing them internally or by a third party. NHMRC endorses externally developed guidelines that meet the requirements outlined in the *Procedures and requirements for meeting the 2011 NHMRC standard for clinical practice guidelines.* At the time of writing this Report, ONHMRC had not received any indication from third party organisations willing to develop guidelines for ME/CFS, and as such, the Committee recommends NHMRC consider developing them internally.

5.3.3.2 Australian clinical pathway

The Committee advises including a 'best practice' clinical pathway based on the current evidence for diagnosis, treatment and management of ME/CFS. Effective clinical pathways provide consumers and clinicians with a framework of action for service delivery. They can facilitate interpretation of guidelines into a local health care context and help consumers navigate multidisciplinary teams and complex systems of care.

In the interim, the Committee recommends a range of resources for clinical use, currently available on the NHMRC webpage for this project.

5.3.4 Additional Committee recommendations

5.3.4.1 Develop Australian capacity through international collaboration

International engagement can improve both the quality of research undertaken in Australia, and the uptake of the latest international research in Australian health policy and practice. International collaborative activities are a key strategy for ensuring that Australia contributes to, shares in and benefits from, the work of the global research community. The Australian Government recognises this and supports international collaborative efforts through a wide variety of programs and initiatives across all sectors of research. While some activities target specific international relationships, others include international linkages developed at the working researcher level.

United States National Institutes of Health

NHMRC currently supports collaborative approaches to health and medical research internationally, through a comprehensive International Engagement Strategy. A letter of intent between NIH and NHMRC was issued in December 2014 '*to develop a coordinated program that will foster collaborative research focused on mutual interest and shared national priority.*' NHMRC currently has research collaboration initiatives with NIH in the areas of 'Brain Research through Advancing Innovative Neurotechnologies' (BRAIN), with cancer research collaboration currently under discussion. These initiatives are joint funding initiatives where both NIH and NHMRC co-fund research after the area of research is defined by the scientists in Australia and NIH. These existing models could be used as a framework for ME/CFS research collaboration.

Strategic use of funding to leverage the capability of established ME/CFS collaborative research centres (CRCs) in the US may be an appropriate option in the quest to understand what causes ME/CFS and to find biomarkers, as well as to research better treatment for the condition. Some Australian researchers working on ME/CFS are already collaborating nationally and internationally (see *Attachment B*).

The Committee advises that NHMRC leverage these relationships by co-funding Australian researchers to collaborate on research projects with NIH CRCs. To ensure autonomy and leadership of Australian researchers, NHMRC and NIH would jointly decide on what areas of ME/CFS research need focus and then support them through a co-funded research call.

5.3.4.2 Australian collaborative biobank

In the past, the limited research funding for ME/CFS has made it difficult to determine whether ME/CFS has subtypes or is instead a collection of potentially distinguishable disorders. Large studies with diverse symptoms are needed to fill in these knowledge gaps. Almost all studies conducted to date have compared ME/CFS patients to healthy control groups. Finding the cause of and cure for ME/CFS may also require research on a large number of ME/CFS patients, from which important subtypes can be identified (for example, variations in symptoms, response to physical and cognitive stressors, brain imaging, the microbiome, virology, immune function and gene expression). Biobanks could help with the conduct of these large scale studies to identify patient subtypes and to allow multiple research centres to access samples from patients, including those who are homebound. A high quality single biobank may offer cost and research efficiencies as well as assist collaboration across the different ME/CFS research fields.

The Committee has differing opinions on the value of research biobanks for Australia. Some Committee members advise expanding existing biobanks so as to fast-track a large scale study of ME/CFS. However, such a proposal needs careful consideration since a biobank is effectively a piece of research infrastructure, and consequently needs to be maintained with strong governance arrangements, ethics processes, and procedures for receiving and maintaining samples, sharing of data and so on. Considerable funds would also need to be guaranteed to maintain the biobank well into the future. NHMRC funds the direct costs of research and does not directly fund individual elements of research infrastructure.

Some members of the Committee are not in favour of prioritising a biobank. Issues such as costs, sustainability, location, purpose and methods, continuity, and intellectual property ownership were identified as concerns. Conversely, some members support setting up biobanks in collaboration with those that already exist in the UK.

The Mason Foundation held a stakeholder information session in May 2018 with researchers, clinicians and patients to investigate the viability of a ME/CFS biobank or patient registry in Australia. The report indicated that a small scale biobank was a viable option for investment if risks are managed. It recommends that the Mason Foundation provide a targeted grant for a research project that involves a biobank, where samples and data are made accessible to other researchers. By contrast, the report indicated that a medium scale biobank would be financially unsustainable unless ongoing funding was received.[81] During the finalisation of this Report the Mason Foundation announced a grant for a ME/CFS biobank and/or patient registry.[vi]

vi On 1 April 2019, the Mason Foundation opened a targeted project grant to build the capacity and scale of the ME/CFS research sector in Australia, which included the establishment of a ME/CFS biobank and/or patient registry. Further information is available at https://www.eqt.com.au/charities-and-not-for-profits/grants/medical-research-and-health.

In summary

The Committee recognises patient and carer involvement as integral to effective research and clinical guideline development for ME/CFS. Consumer engagement, consistency, collaboration and capacity building are four principles that underpin the Committee's advice and recommendations to NHMRC's CEO about research and clinical guidance. The Committee recommends building research quantity and capacity, improving health services research and developing health advice.

Creating collaboration opportunities and encouraging hypothesis generating research in Australia could support entry of new and emerging researchers in the field of ME/CFS. This may improve research design and implementation, enhance research translation, and improve the sector's competitiveness for major funding schemes.

Health services research, as described in this Report, could assist in gathering the most recent data available on prevalence and burden of disease figures. It could also improve ideas about how to deliver quality care, including access to primary and secondary health care, and how to support patients and their carers.

Updating current health advice and clinical practice guidelines may be an effective option to improve care. This will reflect the current evidence and assist in developing effective clinical pathways for clinicians and patients.

The Committee acknowledges the challenges and controversial issues faced by ME/CFS researchers, clinicians and the patient community. This Report endeavours to provide a balanced background and context to these challenges and controversies, whilst articulating potential opportunities for future research and improved clinical guidance for ME/CFS in Australia.

The recommendations presented in this Report are the result of extensive discussions by Committee members and, as such, are intended as a starting point for consideration by NHMRC and relevant Australian health care departments and agencies. The Committee acknowledges that some of the research recommendations fall outside the remit and capacity of NHMRC.

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Attachment A

Table 1: NHMRC Funding Streams – MREA

NHMRC Funding Streams – MREA	
Investigator Grants	Highest-performing researchers at all career stages will be provided funding for their salary (if required) and a significant research support package. (Consolidates previous fellowships and research support schemes)
Synergy Grants	Will provide $5 million per grant for outstanding multi-disciplinary research teams to work together to answer complex questions
Ideas Grants	Will support innovative and creative research projects, and be available to researchers with bright ideas at all career stages, including early and mid-career researchers
Strategic and Leveraging Grants	Will support research that addresses identified national needs. This will include an enhanced Targeted Calls for Research scheme and a dedicated funding stream for Clinical Trials and Cohort Studies. It also includes existing schemes such as Centres of Research Excellence, Development Grants, international collaborative schemes, and Partnerships for Better Health (Partnership Centres and Partnership Projects).
Department of Health funding	
Medical Research Future Fund (MRFF)	The Department of Health provides grants of financial assistance to support health and medical research and innovation.

Attachment B

Recent Australian ME/CFS research

Australian Researcher Teams	Study areas
Research Centre **Adelaide Chronic Fatigue Syndrome Research Group** Authors Dr Richard Burnet, Dr Barry Chatterton, Professor Jon Buckley, Dr Garry Scroop, Dr Bu Yeap, S Lim, T Ho, Dr Robert Gaffney	Research Focus • Gastric emptying • Total body potassium • Lactic acid response to exercise • Influence of pyruvate in lactic acid response to exercise • Metabolic response to incremental exercise
Research Centre **University of Adelaide** Authors Dr Susan Cockshell, Dr Jane Mathias	Research Focus • Cognitive deficits • Subjective and objective measures of cognitive functioning • Cognitive functioning related to everyday functioning and symptomatology
Research Centre **Australian National University (ACT), works in collaboration with Hudson Medical Research Institute at Monash university, Oxford University UK and Parenta Sciences and the CFS discovery group** Authors Dr Brett Lidbury, Dr Alice Richardson, Dr Mark Hedger, Dr Don Lewis, Dr David de Kretser	The ANU group specialise in the modelling of pathology, clinical and immune data by machine learning algorithms and advanced statistics, with the aim of identifying data patterns unique to ME/CFS patients, as diagnosed under the Canadian consensus Criteria. Therefore, rather than relying on traditional reference intervals for pathology markers, they can produce data networks reflecting ME/CFS. In addition to the need for a laboratory biomarker, these studies aim to provide decision support for GPs to allow screening within the 15-20 minutes of a standard consultation. Research Focus • Immunology • Orthostatic intolerance • Genetics
Research Area **Child and Adolescent research** Authors Dr Sarah Knight (Murdoch Children's Research Institute) Dr Kathy Rowe (The Royal Children's Hospital) Dr Brett Gordon (La Trobe University)	This is a selection of some significant Australian researchers contributing to the field of Child and Adolescent ME/CFS patients. Research Focus • Child health and Chronic fatigue syndrome • Paediatric and adolescent health • Exercise Physiology

Australian Researcher Teams	Study areas
Research Centre **Deakin University (VIC)** Authors Dr Michael Maes, Gay Morris, Professor Michael Berk	This team is researching neuroimaging abnormalities in ME/CFS, major depression and multiple sclerosis. Replicated experimental findings suggest that the use of high-resolution SPECT imaging may have the capacity to differentiate patients afforded a diagnosis of CFS from those with a diagnosis of depression. Research Focus • Neuroimaging • Mitochondrial dysfunction • Immune dysfunction
Research Centre **Griffith University (QLD): National Centre for Neuroimmunology and Emerging Diseases (NCNED)** Authors Professor Don Staines & Professor Sonya Marshall-Gradisnik, Dr Leighton Barnden, Dr Helene Cabanas, Dr Zack Shan, Professor Alfred Lam, Professor Donald Stewart	NCNED have published more than 32 papers in the field of ME/CFS and fatigue states since 2009. Eighteen of these papers were published in 2016 and 2017, and a number of papers published or in press in 2018. This research focuses on the functional changes found in specific calcium ion channel receptors and is working on developing technologies to further develop genetic markers of these ion channels for screening and diagnostic testing for ME/CFS. The team is also undertaking research on cerebral MRI imaging. Research Focus • Immunology • Genetics • Brain imaging
Research Centre **La Trobe University** Authors Professor Paul Fisher, Dr Sarah Annesley	Results from this team have so far found three key ideas about what is dysfunctional in ME/CFS cells: ME/CFS cells have a clear specific defect in mitochondrial energy production and energy metabolism; ME/CFS cells try to compensate for inefficient energy production in the mitochondria; Key cellular stress-sensing pathways in ME/CFS cells are activated and may cause compensatory changes in metabolism and mitochondrial energy generating capacity. Research Focus: • Mitochondrial dysfunction • Energy metabolism / production
Research Centre **University of Melbourne (VIC): Molecular Science and Biotechnology Institute (Bio21) and Victoria University** Authors Dr Chris Armstrong, Professor Neil McGregor, Dr Paul Gooley, Dr Don Lewis, Dr Henry Butt	The team have identified the association between metabolites and microbiota in faeces, blood and urine of ME/CFS patients. This group pioneered the use of metabolomics to study ME/CFS patients, finding energy, nitrogen, purine and oxidative metabolism issues. The metabolism findings have been found consistently across several other studies since then. Nuclear Magnetic Resonance (NMR) spectroscopy is another research focus of this group. Some of the findings have indicated that energy metabolism, chronic immune activation and oxidative stress are may be implicated in ME/CFS, with further longitudinal research being conducted on the gene expression and metabolic profiling aspects of ME/CFS. Research Focus: • Metobolomics • Genomics • Microbiomics

Australian Researcher Teams	Study areas
Research Centre **University of New South Wales (NSW)** Authors Professor Andrew Lloyd, A/Professor Ute Vollmer Conna, Dr Carolina Sandler, Dr Ben Barry, Dr Matthew Jones, Dr Erin Cvejic, Dr Sophie Li, Dr Jessica Beilharz, Ms Sally Casson, Mr Scott Fatt	The Fatigue Research Program and UNSW Fatigue Clinic was developed at the Fatigue Clinic at the University of New South Wales under the supervision of infectious diseases specialist, Prof Andrew Lloyd. The focus of the research has been studying leucocyte gene expression and symptom exacerbation patterns in response to exercise, randomised controlled trials to improve sleep-related symptom control and functional capacity, and autonomic nervous system function, as well as clinician-education resource development and evaluation. The UNSW Fatigue Clinic treatment program was developed to manage medically-unexplained fatigue syndromes including: chronic fatigue syndrome (CFS); post-infective fatigue syndrome (PIFS); and post-cancer fatigue (PCF). The intervention involves activity pacing, graded exercise therapy (GET), cognitive exercise therapy (CET), and cognitive behaviour therapy (CBT - for sleep, mood, and coping strategies). Research Focus • Autonomic functioning • Sleep • Physical activity • Cognitive function • Clinician education
Research Centre **The Queen Elizabeth Hospital** Authors Dr Reynolds Casse, Dr Peter Del Fante, Dr Leighton Barnden, Dr Richard Burnett, Dr Michael Kitchener, Dr Richard Kwiatek, Setayesh Behin-Ain S, Steve Unger, Dr Benjamin Crouch, Dr Anacleto Mernone, Dr Steve Chryssidis, Dr Garry Scroop	Research Focus • Cerebral blood flow • Longitudinal progression in changes in brain structure • Age comparisons in brain scans • Brainstem dysfunction and homeostasis • Upregulation of prefrontal myelination
Research Centre **South Australian Health and Medical Research Institute (SAHMRI)** Authors Dr Michael Musker, Dr Martin Lewis, Pamela Saunders	Research Focus • Cytokine expression over time • Cytokine levels and symptom severity, including during PEM • Cytokine levels in severely ill patients

Australian Researcher Teams	Study areas
Research Centre **University of South Australia (SA)** Authors Dr Max Nelson, Professor Jon Buckley, Dr Rebecca Thomson, Dr Kade Davison, Dr Katia Ferrar, Associate Professor Marie Williams, Dr Kylie Johnston, Mr Daniel Clark, Dr Ashleigh Smith, Dr Kade Davison, Dr Stephanie Reuter, AM Evans	Research looks at the use of active video games for people with ME/CFS to increase their physical activity levels. Physical activity promotion in this clinical population has been poorly and under-researched, and any exploration of alternative physical activity options for this population is much needed. Research Focus • PEM • Respiratory effort • Inflammatory indicators and physical activity • Pacing • Heart rate monitoring correlated with activity monitoring • CPET testing • Carnitine activity
Research Centre **University of Sunshine Coast (QLD)** Authors Associate Professor Suzanne Broadbent	This research focuses on Chronic Fatigue Syndrome/ME exercise management, intermittent and graded exercise, CFS/ME aquatic exercise rehabilitation and effects of exercise on lymphocyte and NK cell function. Research Focus • Exercise management, intermittent and graded exercise • Aquatic exercise rehabilitation • Exercise and the immune system
Research Centre **Victoria University (VIC)** Authors Dr Michelle Ball, Emeritus Professor Dorothy Bruck, Dr Henry Butt, Dr Don Lewis, Dr Sandra McKechnie and Dr Phillip Paull, Amy Wallis	The microbiota-gut-brain axis provides one possible pathway where dysfunction in communication between enteric microbiota, the gastro-intestinal system, and the brain may precipitate some ME/CFS symptoms. Sleep, neurocognitive and depressive symptoms are examined within this project, with recent microbiome research highlighting the potential etiological role of dysfunction in gut-brain communication. *This work is currently not funded and has been temporarily discontinued.* Research Focus • Gut microbial imbalance • Microbiomics
Research Area **University of Western Australia (WA)** Authors Professor Paul Fournier,	Professor Fournier specializes in the field of bioenergetics in exercise, health and disease. This discipline is concerned with not only the regulation of energy utilization, intake and storage, but also with the mechanisms whereby these processes are affected by exercise, nutrition, and metabolic disorders such as obesity and diabetes. Specifically research investigating the role of oxidative stress in muscle fatigue is linked to current hypotheses on ME/CFS. Research Focus • Muscle strength and oxygenation • Exercise biochemistry/ physiologist

Disclaimer: this is not an exhaustive list of all Australian research currently underway, it is intended to provide a snapshot of the types of research fields and areas of research being conducted by expert teams in Australia as at February 2019. This list does not represent the views or opinions of Committee members and is intended for information only.

Attachment C

NIH Collaborative Research Centres	Research undertaken
Cornell ME/CFS Collaborative Research Center	Investigating the biological mechanisms underlying ME/CFS by obtaining blood samples and conducting brain scans on individuals with ME/CFS before and after they undergo an exercise test designed to bring on symptoms of post-exertional malaise. Dr Hanson's team will use a wide range of tools and technologies to test the role of genes, inflammation and the immune system in this disease.
Center for Solutions for ME/CFS	Examining an existing collection of biological samples from people with ME/CFS and healthy controls for microbial agents, such as viruses and bacteria that may play a role in the disease. Dr. Lipkin's group will use cutting-edge technology to conduct comprehensive genetic analyses and to identify metabolites (small molecules that have a variety of functions in cellular processes) that are present in the samples, which may help in the development of diagnostic tests for ME/CFS.
Topological Mapping of Immune, Metabolomic and Clinical Phenotypes to Reveal ME/CFS Disease Mechanisms	Using novel tools to take a detailed look at how the immune system, the microbiome (our body's complete collection of microbes including bacteria and viruses) and metabolism (the chemical reactions that produce energy for the body) interact in ME/CFS. A greater understanding of those interactions may help researchers identify causes of the disease and lead to the development of therapies.
Data Management and Coordinating Center (DMCC) for the ME/CFS Collaborative Research Centers	Dr. Williams and his team will lead the DMCC that will bring together research data from the CRCs into one database. Dr. Williams' group will promote collaboration among the centers and the broader research community. They will provide state-of-the-art data processing systems and analytic instruments, as well as overseeing efforts to standardize data that is collected by the researchers.

In 2017, The U.S National Institutes of Health (NIH) awarded over $7 million for four grants comprising a consortium of the following research centres. The collaborative centres (CRC) will each conduct independent research but will also collaborate on several projects, forming a network to help advance knowledge on ME/CFS. The data will be managed by the Data Management and Coordinating Center (DMCC) and will be shared among researchers within the CRCs and more broadly with the research community (https://www.nih.gov/news-events/news-releases/nih-announces-centers-myalgic-encephalomyelitis-chronic-fatigue-syndrome-research).

Attachment D

International ME/CFS research centres

Research Teams	Study areas
Research Centre **Bateman Horne Center** Salt Lake City, USA Researchers Dr Lucinda Bateman, Dr Suzanne Vernon	The Bateman Horne Center of Excellence is leading the way in the medical advancement and treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) and Fibromyalgia. Bateman Horne Center is squarely targeted on bringing these diseases to the mainstream. An active and specialized medical centre with an innovative research program which focuses on the discovery of biomarkers to improve treatment and diagnosis. • Identification and diagnosis for all patients • Patient participation in research • Bateman Horne Centre – Biomarker Research Project • Immunology and biomarkers
Research Centre **Brain Health Research Centre,** University of New Zealand, Otago, NZ Researchers Professor Warren Tate and Team (complements the work being studied at Stanford University), in collaboration with Dr Rosamund Vallings	Professor Tate's group is now focusing on measuring mitochondrial function utilizing a new technology with a 'Seahorse XF Analyzer'. It enables a new energy parameter, 'The Bioenergetic Health Index', to be measured in the cells of a fresh blood sample taken from a subject. The Seahorse analyzer measures properties of energy delivery that can show whether mitochondria are under 'oxidative stress • Mitochondrial function and energy delivery • Biochemical pathways and general metabolism
Research Centre **Children's Center Chronic Fatigue Clinic** John Hopkins University, Baltimore, USA Researchers Dr Peter Rowe (Director), Dr Colleen Marden, Dr Maria Roma, Dr Marissa Flaherty, Dr Samantha Jasion, Dr Erica Cranston, Dr Megan Lauver, Dr Kevin Fontaine, Dr Malini Moni, Dr Carol Thompson	Dr Rowe directs the Chronic Fatigue Clinic at Johns Hopkins Children's Center and was the first to provide data linking CFS and orthostatic intolerance, a condition marked by the body's inability to adequately cope with abrupt changes in posture. People with orthostatic intolerance develop light-headedness, fatigue and cognitive problems with prolonged standing, often associated with marked increases in heart rate, profound drops in blood pressure or both. • CFS & Adolescent medicine • Postural orthostatic tachycardia syndrome (POTS) • Orthostatic intolerance

Research Teams	Study areas
Research Centre **Department of Biomedicine** University of Bergen, Norway Researchers Dr Karl Johan Tronstad, Professor Olav Mella, Dr Øystein Fluge, Dr Per M. Ueland and team.	Immune suppression research: Five Norwegian hospitals are now collaborating on a clinical trial aiming to confirm or refute whether Rituximab can be useful in the treatment of ME/CFS patients. Through these clinical studies, the research group are aiming to uncover possible treatment methods, while simultaneously working to shed light on the underlying symptom mechanisms in ME/CFS. Biochemical research: More than 200 patients have been included in the studies after thorough medical assessment according to internationally accepted (Canadian) criteria. Based on the material collected in a biobank, the research group has conducted a comprehensive and detailed mapping of the metabolism in 200 patients and 100 healthy controls. • Immune system function • Metabolic analyses • Biochemical changes in blood • pyruvate dehydrogenase (PDH) enzyme inhibition • mitochondrial dysfunction • muscle energy production
Research Centre **Centre for Community Research** DePaul University - ME/CFS Research Team, USA Researchers Dr Leonard A. Jason, Dr Ben Katz, Madison Sunnquist, Dr Joseph Cotler, Shaun Bhatia, Dr Marcie Zinn, Mark Zinn, Carly Holtzman, Julia Terman, Chelsea Torres, Helen Bedree, Katie Ramian, Catherine Dudun, Sharlene Avila	Dr Jason is a leader in the field of ME/CFS research, he has published over 800 articles and 100 book chapters on ME/CFS and other topics. His team at DePaul university are currently working on better understanding the etiology of Myalgic Encephalomyelitis (ME) and chronic fatigue syndrome (CFS) among college students, as well as ME and CFS pediatric epidemiology. • Development of the DePaul symptom questionnaire • Post exertional malaise studies • Instrument to assess PEM in ME/CFS patients • Qualitative analysis of ME/CFS • Energy envelope theory • Patient perceptions of ME/CFS
Research Centre **Infectious Diseases and Geographic Medicine – ME/CFS initiative** Stanford University, USA Researchers Dr Jose Montoya, Dr Katie Vigano, Dr Amity Hall, Kikuno Gilbride, Diana Nufuente, Tullia Lieb, Donn Garvert, Tyson Holmes, Katya Lavine, Alyssa Aguilar	This groups programmatic goals include conducting translational research, treating patients, and training the next generation of ME/CFS physician-scientists. • Identify biomarkers associated with chronic unexplained illnesses, including ME/CFS, with the aim of translating that knowledge into early diagnoses and effective treatments • Immunology and infectious disease triggers

Research Teams	Study areas
Research Centre **Institute of Neuro-immune Medicine (INIM)** Nova Southeastern University, Florida USA Researchers Dr Nancy Klimas, Dr Alison Bested, Dr Mariana Morris, Dr Elizabeth Balbin, Jose Chen, Devra Cohen, Fanny Collado, Jeffry Cournoyer, Sabrina Fernandez, Lisa Hue, Monica Lazaro	Current research focus at the Institute for Neuro Immune Medicine (INIM) includes Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) and Gulf War Illness (GWI). Investigators, clinicians and educators are committed to applying scientific advances to promote efficiency, enhance patient care and improve clinical utility. This advancement is done through clinical, laboratory, computational and integrative cardiovascular immunological research, all of which are conducted at the INIM by renowned researchers in their respective fields. The team are also working on conducting a Multi-site research study on behalf of the Centers for Disease Control and Prevention (CDC) to better understand the nature of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) with the ultimate goal of improving quality of care available to ME/CFS patients Research Focus • Clinical, laboratory, computational and integrative cardiovascular immunological research • ME/CFS Genetic studies • Metabolic pathway dysfunction to identify biomarkers • Clinical nutrition profiling and nutritional biomarkers
Research Centre **Institute of Medical Immunology, Charite – Universitatsmedizin** Berlin, Germany Researchers Dr Carmen Scheibenbogen (also collaborates with the Euromene biomarker project), Dr Madlen Lobel, Dr Kristin Strohschein, Carolin Giannini, Uwe Koelsch, Sandra Bauer, Cornelia Doebis, Sybill Thomas, Nadine Unterwalder, Volker von Baehr, Petra Reinke, Michael Knops, Leif G. Hanitsch, Christian Meisel, Hans-Dieter Volk	The team's findings suggested evidence for a deficient Epstein-Barr Virus (EBV)-specific B- and T-cell memory response in CFS patients and suggest an impaired ability to control early steps of EBV reactivation. In addition the diminished EBV response might be suitable to develop diagnostic marker in CFS. • Immunology • Autoimmunity • Immune abnormalities in response to EBV
Research Centre **ME/CFS Collaborative Research Center, Cornell University** USA Researchers Dr Maureen Hanson, Dr Stephane Bentolila, Dr Myat Lin, Dr Ludovic Giloteaux, Dr Arnaud Germain	This team sequenced the mitochondrial DNA from a cohort of ME/CFS patients and healthy individuals, using DNA extracted from white blood cells stored in the biobank developed by the Chronic Fatigue Initiative. • Mitochondrial sequencing • Metabolism and gene regulation • Hypotheses on mitochondria and autoimmunity

Research Teams	Study areas
Research Centre **Nevada Center for Biomedical Research** Partners with research centres in US, Belgium and Australia Researchers Dr Kenny De Meirleir, Kenneth Hunter Jr, Petar Lenart, Ron Pardini	Research Focus • Genome-wide studies • Identification of autoimmune markers for ME
Research Centre **Nightingale Research Foundation** Ontario, Canada Researchers Dr Byron Hyde, Dr Sonia Neubauer, Dr John Chia	The Nightingale Research Foundation is a Canadian registered charitable organization dedicated to the study and treatment of Myalgic Encephalomyelitis (M.E.) and related illnesses. They have been investigating M.E. patients since 1984. Thousands of case studies have formed the basis of their research into the causes and treatment for symptoms, and have led to a continual enhancement of diagnostic protocols. They are now integrating the knowledge gained from this case-based research. Research Focus • Conducts patient based research toward an ME/CFS definition • Understand the underlying cause • Promote public awareness and advance technical data collection • Support and encourage public education
Research Centres - JAPAN **1. Osaka City University – Department of Metabolism, Endocrinology and Molecular medicine** **2. Osaka City University – Department of Physiology** **3. RIKEN Centre for Life Science Technologies, Hyogo Japan** Researchers Dr Inaba Nakatomi, Dr Mizuno Nakatomi, Dr Wada Ishii, Dr Tazawa Tanaka, Dr Takahashi Fukuda, Dr Kataoka Watanabe, Dr Yamaguti and Dr Onoe	Research Focus • Brain imaging studies

Research Teams	Study areas
Research Centre **Stanford ME/CFS Collaborative Research Center** Stanford University Medicine, USA Researchers Dr Ronald Davis, Dr Mark Davis (collaborates with the Open Medicine Foundation), Dr Mike Snyder, Dr Xiao Wenzhong, Dr Craig Heller, Dr Robert Phair, Dr Lars Steinmetz, Dr Laural Crosby, Dr Rahim Esfandyarpour, Dr Fereshteh Jahaniani, Dr Mohsen Nemat-Gorgani, Dr Peidong Shen, Dr Gozde Durmus, Julie Wilhelmy, Dr Robert Naviaux MD, Dr William Robinson MD, Dr Curt Scharfe MD, Dr Lucinda Bateman MD, David Kaufman MD, Dr Linda Tannenbaum, Kimberly Hicks	• Immunological basis for ME/CFS • HLA genes and Autoimmunity • Multi-omic and big data studies – molecular biomarkers • Supports collaborative medical research for treatment and diagnostic markers • Encourage the patient community to actively engage in their health care • Support health education about chronic complex disease • Advance translational research about chronic complex disease into clinical practice
Research Centre **Uppsala University** Sweden Researchers Dr Jonas Bergquist (OMF is funding this research)	Dr. Bergquist is measuring proteins in cerebrospinal fluid and blood plasma from a small cohort of Swedish ME/CFS patients. • Steroid hormonal dysregulation • Autoantibodies and Autoimmunity • Proteomics and neuro-inflammatory and chronic pain

Disclaimer: this is not an exhaustive list of all International research currently underway; it is intended to provide a snapshot of the types of research fields and areas of research being conducted by expert teams internationally as at February 2019. This list does not represent the views or opinions of Committee members and is intended for information only.

Attachment E

Chronology of criteria used for ME/CFS

Centers for Disease Control and Prevention (CDC or Fukuda et al 1994) diagnostic criteria[i]

Symptom	Evaluation
1. Fatigue	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 • Results in substantial reduction in previous levels of occupational, educational, social or personal activities
2. 4 or more of the following symptoms	all of which must have persisted or recurred during 6 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, multi joint pain without joint swelling or redness • Headaches of a new type, pattern or severity • Unrefreshing sleep • Post exertional malaise (PEM) lasting more than 24hrs

Oxford Guidelines Criteria for research (Sharpe et al 1991)[ii]

Symptom	Evaluation
1. Fatigue	(a) A syndrome characterized by fatigue as the principal symptom. (b) A syndrome of definite onset that is not life-long. (c) The fatigue is severe, disabling, and affects physical and mental functioning. (d) The symptom of fatigue should have been present for a minimum of 6 months during which it was present for more than 50% of the time.
2. Other symptoms may be present	Particularly: myalgia, mood and sleep disturbance.

Canadian Consensus Criteria (CCC) diagnostic criteria – Clinical working case definition (Carruthers et al, 2003)[iii]

Symptom	Evaluation
	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. Further: The illness must persist for at least six months. It usually has a distinct onset, although it may be gradual. Preliminary diagnosis may be possible earlier. Three months is appropriate for children.
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 other 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 fasciculation's 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:	a) Autonomic Manifestations: orthostatic intolerance neurally mediated hypotension (NMH), postural orthostatic tachycardia syndrome (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. b) 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. c) Immune Manifestations: tender lymph nodes, recurrent sore throat, recurrent flu-like symptoms, general malaise, new sensitivities to food, medications and/or chemicals.

International Consensus Criteria (ICC) diagnostic criteria - Myalgic Encephalomyelitis (Carruthers et al, 2011)[iv]

Symptom	Evaluation
	Myalgic encephalomyelitis is an acquired neurological disease with complex global dysfunctions. Pathological dysregulation of the nervous, immune and endocrine systems, with impaired cellular energy metabolism and ion transport are prominent features. Although signs and symptoms are dynamically interactive and causally connected, the criteria are grouped by regions of pathophysiology to provide general focus. A patient will meet the criteria for post-exertional neuroimmune exhaustion (A), at least one symptom from three neurological impairment categories (B), at least one symptom from three immune/gastro-intestinal/genitourinary impairment categories (C), and at least one symptom from energy metabolism/transport impairments (D).
A. Post-exertional neuroimmune exhaustion (PENE) - Compulsory	This cardinal feature is a pathological inability to produce sufficient energy on demand with prominent symptoms primarily in the neuroimmune regions. Characteristic areas follows: 1. Marked, rapid physical and/or cognitive fatigability in response to exertion, which may be minimal such as activities of daily living or simple mental tasks, can be debilitating and cause a relapse. 2. Post exertional symptom exacerbation: e.g. acute flu-like symptoms, pain and worsening of other symptoms. 3. Post exertional exhaustion may occur immediately after activity or be delayed by hours or days. 4. Recovery period is prolonged, usually taking24h or longer. A relapse can last days, weeks or longer. 5. Low threshold of physical and mental fatigability (lack of stamina) results in a substantial reduction in pre-illness activity level.

Symptom	Evaluation
B. Neurological Impairments	**1. Neurocognitive impairments** a. Difficulty processing information: slowed thought, impaired concentration e.g. confusion, disorientation, cognitive overload, difficulty with making decisions, slowed speech, acquired or exertional dyslexia b. Short-term memory loss: e.g. difficulty remembering what one wanted to say, what one was saying, retrieving words, recalling information, poor working memory **2. Pain** a. Headaches: e.g. chronic, generalized headaches often involve aching of the eyes, behind the eyes or back of the head that may be associated with cervical muscle tension; migraine; tension headaches b. Significant pain can be experienced in muscles, muscle-tendon junctions, joints, abdomen or chest. It is non inflammatory in nature and often migrates. e.g. generalized hyperalgesia, widespread pain (may meet fibromyalgia criteria), myofascial or radiating pain **3. Sleep disturbance** a. Disturbed sleep patterns: e.g. insomnia, prolonged sleep including naps, sleeping most of the day and being awake most of the night, frequent awakenings, awaking much earlier than before illness onset, vivid dreams/nightmares b. Unrefreshed sleep: e.g. awaken feeling exhausted regardless of duration of sleep, day-time sleepiness **4. Neurosensory, perceptual and motor disturbances** a. Neurosensory and perceptual: e.g. inability to focus vision, sensitivity to light, noise, vibration, odour, taste and touch; impaired depth perception b. Motor: e.g. muscle weakness, twitching, poor coordination, feeling unsteady on feet, ataxia
C. Immune, gastro-intestinal and genito-urinary Impairments At least one symptom from three of the following five symptom categories	**1. Flu-like symptoms** may be recurrent or chronic and typically activate or worsen with exertion. e.g. sore throat, sinusitis, cervical and/or axillary lymph nodes may enlarge or be tender on palpitation **2. Susceptibility to viral infections** with prolonged recovery periods **3. Gastro-intestinal tract**: e.g. nausea, abdominal pain, bloating, irritable bowel syndrome **4. Genitourinary:** e.g. urinary urgency or frequency, nocturia **5. Sensitivities** to food, medications, odours or chemicals Notes: Sore throat, tender lymph nodes, and flu-like symptoms obviously

Symptom	Evaluation
D. Energy production/transportation impairments: At least one	**1. Cardiovascular**: e.g. inability to tolerate an upright position - orthostatic intolerance, neurally mediated hypotension, postural orthostatic tachycardia syndrome, palpitations with or without cardiac arrhythmias, light-headedness/dizziness **2. Respiratory**: e.g. air hunger, laboured breathing, fatigue of chest wall muscles 3**. Loss of thermostatic stability**: e.g. subnormal body temperature, marked diurnal fluctuations; sweating episodes, recurrent feelings of feverishness with or without low grade fever, cold extremities **4. Intolerance of extremes of temperature**
E. Paediatric considerations	Symptoms may progress more slowly in children than in teenagers or adults. In addition to post exertional neuroimmune exhaustion, the most prominent symptoms tend to be neurological: headaches, cognitive impairments, and sleep disturbances. **1. Headaches**: Severe or chronic headaches are often debilitating. Migraine may be accompanied by a rapid drop in temperature, shaking, vomiting, diarrhoea and severe weakness. **2. Neurocognitive impairments**: Difficulty focusing eyes and reading are common. Children may become dyslexic, which may only be evident when fatigued. Slow processing of information makes it difficult to follow auditory instructions or take notes. All cognitive impairments worsen with physical or mental exertion. Young people will not be able to maintain a full school programme. **3. Pain** may seem erratic and migrate quickly. Joint hypermobility is common.

Institute of Medicine (IOM) - Beyond Myalgic encephalomyelitis / Chronic Fatigue Syndrome: Redefining an illness (Report guide for Clinicians) (IOM, 2015)[v]

Symptom	Evaluation
Systemic Exertion Intolerance Disease (SEID)	Diagnosis requires that the patient have the following three symptoms:
Fatigue **Post-exertional malaise,* and** **Unrefreshing sleep***	1. A substantial reduction or impairment in the ability to engage in pre-illness levels of occupational, educational, social, or personal activities, that persists for more than 6 months and is accompanied by fatigue, which is often profound, is of new or definite onset (not lifelong), is not the result of ongoing excessive exertion, and is not substantially alleviated by rest. 2. prolonged exacerbation of a patient's baseline symptoms after physical/ cognitive/ orthostatic stress; may be delayed relative to the trigger 3. Feeling unrefreshed despite sleeping many hours and other sleep disturbances
1. Cognitive impairment* **or** **2. Orthostatic intolerance**	At least one of the two following manifestations is also required: 4. Problem with thinking exacerbated by exertion, effort, or stress or time pressure 5. Symptoms worsen upon assuming and maintaining upright posture and are ameliorated, though not necessarily abolished, by recumbency * Frequency and severity of symptoms should be assessed. The diagnosis of ME/CFS (SEID) should be questioned if patients do not have these symptoms at least half of the time with moderate, substantial, or severe intensity.

i. Fukuda, K. Straus, SE, Hickie, I, Sharpe, M, Dobbins, JG, Komaroff, A et al, 1994. 'The Chronic Fatigue Syndrome: A comprehensive Approach to its definition and Study,' *Annals of Internal Medicine,* vol. 121, is. 12, pp. 953-959.

ii. Sharpe, MC, Archard, LC, Banatvala, JE et al, 1991. 'A Report – Chronic fatigue syndrome: Guidelines for research.' Journal of the Royal Society of Medicine, vol. 84, pp. 118 – 121.

iii. Carruthers, BM, Van de Sande, MI, De Meirleir, KL et al, 2003. 'Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Clinical Working Case Definition, Diagnostic and Treatment Protocols,' Journal of Chronic Fatigue Syndrome, vol. 11, is. 1, pp. 7-36

iv. Carruthers, BM, Van de Sande, MI, De Meirleir, KL et al, 2011. 'Myalgic encephalomyelitis: International consensus criteria.' Journal of Internal Medicine, vol. 270, is. 4, pp. 327-338.

v. IOM (Institute of Medicine). 2015. Beyond Myalgic encephalomyelitis/chronic fatigue syndrome: Redefining an illness. Washington, DC: The National Academies Press.

Attachment F

Table 2: IOM Committee recommendations

IOM Committee recommendations
Recommendation 1: *"Physicians should diagnose ME/CFS if diagnostic criteria are met following an appropriate history, physical examination, and medical work-up. A new code should be assigned to this disorder in the International Classification of Diseases, Tenth Revision (ICD-10), that is not linked to "chronic fatigue" or "neurasthenia."*
Recommendation 2: *"The Department of Health and Human Services should develop a toolkit appropriate for screening and diagnosing patients with ME/CFS in a wide array of clinical settings that commonly encounter these patients, including primary care practices, emergency departments, mental/behavioural health clinics, physical/occupational therapy units, and medical subspecialty services (e.g., rheumatology, infectious diseases, neurology)."*
Recommendation 3: *"A multidisciplinary group should re-examine the diagnostic criteria set forth in this report when firm evidence supports modification to improve the identification or care of affected individuals. Such a group should consider, in no more than 5 years, whether modification of the criteria is necessary. Funding for this update effort should be provided by non-conflicted sources, such as the Agency for Healthcare Research and Quality through its Evidence-based practice centres process, and foundations."*
Recommendation 4: *"The IOM committee recommends that this disorder be renamed "systemic exertion intolerance disease" (SEID). SEID should replace Myalgic encephalomyelitis/Chronic fatigue syndrome for patients who meet the criteria set forth in this report."*

Attachment G

NHMRC Advisory Committee on Myalgic Encephalomyelitis and Chronic Fatigue Syndrome

(s39 Advisory Committee)

Terms of Reference

The NHMRC Myalgic Encephalomyelitis and Chronic Fatigue Syndrome Advisory Committee (the Committee) will advise the Chief Executive Officer of NHMRC on the research and clinical guidance requirements for Australia of Myalgic Encephalomyelitis (ME) and Chronic Fatigue Syndrome (CFS).

To provide this function, the Committee will advise on:

1. the status of national and international research into ME and CFS
2. gaps in research on ME and CFS. This will include but not be limited to research on the immunology, psychology, microbiology and virology of the conditions, as well as any health services research
3. the status of clinical guidance on ME and CFS available to doctors and health professionals
4. requirements and opportunities for improved clinical guidance
5. any other issue on ME and CFS that the NHMRC Chief Executive Officer may request advice
6. submissions received through the public consultation process

The Committee will be effective for the period 31 October 2018 to 30 April 2019 and will report to the Council and Chief Executive Officer of NHMRC.

Name	Expertise of ME/CFS Advisory Committee Member
1. Royal Australasian College of Physicians (RACP)	
Professor Kwun Fong **MBBS, PhD, FAPSR, FThorSoc**	• Thoracic and Sleep Physician at The Prince Charles Hospital (TPCH) and Professor with the University of Queensland School of Medicine. • Clinical Manager of the Pulmonary Malignancy Unit and Director of the UQ Thoracic Research Centre which undertakes molecular, genomic and translational research in lung diseases at TPCH. • Deputy Chair of Medical Services Advisory Committee (MSAC) • Co-Editor of the Cochrane Lung Cancer Review Group and Deputy Editor for the Journal of Thoracic Diseases. • NHMRC Practitioner Fellow and was former Chair of NHMRC Research Translation Faculty Cancer Steering Group
2. Royal Australian College of General Practitioners (RACGP)	
Dr Gary Deed **MBBS, FACNEM, MRACGP**	• Medical Practitioner and Chair of Diabetes Specific Interest Network RACGP • Has major interests in Clinical support for people with diabetes, multi-morbidities, autism and cancer therapies, with specific interest in fatigue assessment and management • Co-editor of "General Practice management of type 2 diabetes" – RACGP/Diabetes Australia • Educational support and consultancy in diabetes.
3. Researchers	
Professor Rachel Ankeny **BA, MA, PhD, Grad Cert Online Learning**	• Professor, School of Humanities, University of Adelaide • Has major interests in Ethics, policy development, food, biotechnology and has been on numerous Ethics Committees • Co-authored chapter "Three Approaches to Chronic Fatigue Syndrome in the United Kingdom, Australia and Canada: Lessons for Democratic Policy" • Co-founder and organising member of the Society for Philosophy of Science in Practice.
Associate Professor Suzanne Broadbent **BE, B. Exercise Science, PhD**	• Exercise Scientist & Accredited Exercise Physiologist • Program Lead - Clinical Exercise Science, School of Health and Sports Sciences, University of the Sunshine Coast • Current research interests include ME/CFS immune responses and rehabilitation; chronic liver disease exercise and dietary effects on immune function, physical capacity and life expectancy and exercise prescriptions for cancer patients.

Name	Expertise of ME/CFS Advisory Committee Member
Professor Andrew Lloyd AM **MBBS, PhD, FRACP**	• An infectious diseases physician, and an epidemiology, virology and immunology researcher • Principal investigator on several high profile clinical cohorts (HITS-p, SHARP-p) and clinical trials (SToP-C), and also leads laboratory-based immunovirological studies in hepatitis C. • Leads the Viral Immunology Systems Program (VISP) in the Kirby Institute for Infection and Immunity in Society at the University of New South Wales. • With funding support from NMHRC and the Centres for Disease Control, USA, he led the establishment of the Dubbo Infection Outcomes Study (DIOS), which confirmed the link between chronic fatigue states and several acute infectious diseases • Chair, Steering Committee, Immunovirology Research Network and Deputy Director of Australian Centre for HIV and Hepatitis Virology.
Professor Sonya Marshall-Gradisnik **BSc, PhD, Grad Cert Higher Education**	• Director of National Centre for Neuroimmunology and Emerging Diseases (NCNED), based at Griffith University • Her research is focused towards identifying biomarkers of CFS/ME for translation into the clinical environment. • Head Reviewer and Chairperson for NIH Centre for Research Excellence Applications, for CFS/ME. • Only Australian appointed to the International Association for Chronic Fatigue Syndrome Board of Directors, the peak international advising body for the clinical management and research for CFS.
Dr Katherine Rowe **MBBS, MD, MRACP, FRACP, MPH, DipEd**	• Senior Consultant Physician at the Royal Children's Hospital, Melbourne • Research interests include: developmental assessment; the impact of externalizing behaviour problems and auditory processing difficulties on children's learning outcomes; and the educational/epidemiological implications of *Attention-Deficit/ Hyperactivity Disorder* (AD/HD) and *Chronic Fatigue Syndrome* (CFS) in children and adolescents. • Academic appointments in the Department of Paediatrics of The University of Melbourne, consisting of teaching, clinical and research responsibilities • Extensive clinical and research experience in the management of children and adolescents with behavioural and learning difficulties (ADD; AD/HD), as well as those with CFS. • Part of the RACP working party developing clinical practice guidelines for CFS and has been an invited international representative for National Institutes of Health Special Emphasis Panel and Centres for Disease Control committees for Common Data Elements for ME/CFS and a reviewer for the NIH 'Beyond Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome: Redefining an illness' • Part of the International Committee for the Case Definition of Chronic Fatigue Syndrome, Chronic Fatigue Syndrome Service review Advisory Group.

Name	Expertise of ME/CFS Advisory Committee Member
7. Consumer Representatives	
Ms Simone Eyssens **Psychologist, ME/CFS consumer advocate** **Nominated by Emerge Australia President, Sally Missing**	• Has severe ME/CFS, and has been mostly bedbound since 2014 • One of the founding members and one of the administrators, of #MEAction Network Australia, the Australian chapter of the international #MEAction Network. • Worked in both the clinical and organisational fields of psychology, having worked with the military, disability and aged care agencies, employee assistance programs, in corporate training and academic lecturing, as well as having her own private practice • Supports Emerge Australia in its advocacy work • Set up a website for Melbourne ME/CFS researchers, Chris Armstrong & Neil McGregor, to help them promote their work.
Ms Sally Missing **BA, Masters Health Admin** **Simone's support person and/ or proxy in the event that she is unable to attend meetings due to her illness**	• Former President of Emerge Australia (non-profit organisation) supporting people with ME/CFs and associated conditions • A focus on secondary prevention of chronic illness and engagement of vulnerable communities • Established and re-designed a number of HARP (Hospital Admission Risk Program) programs in community health settings.
Ms Penelope McMillan **BSc (Psychology), Teacher**	• President, ME/CFS Australia (SA) and in that role, co-author of the submission to the NHMRC for a Targeted Call for Research for ME/CFS • Director on the board of ME/CFS Australia Ltd • Trained consumer advocate with Health Consumers Alliance of SA • Health consumer, Consumer and Community Engagement Committee, South Australian Health and Medical Research Institute, including consumer representative with the current Cochrane priority review of consumer engagement strategies • Public sector psychologist, involving individual assessment, counselling and therapy; group work; staff training; management consulting; research • Teacher, including school principal; preschool, primary and adult teaching; parent education; writing distance education modules; action research; program evaluation.