Myalgic Encephalomyelitis / Chronic Fatigue Syndrome Advisory Committee

Report to the NHMRC Chief Executive Officer

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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. 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, and lack of supportive care.

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[1]. 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

[1] *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.

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.

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*).

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.

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*.

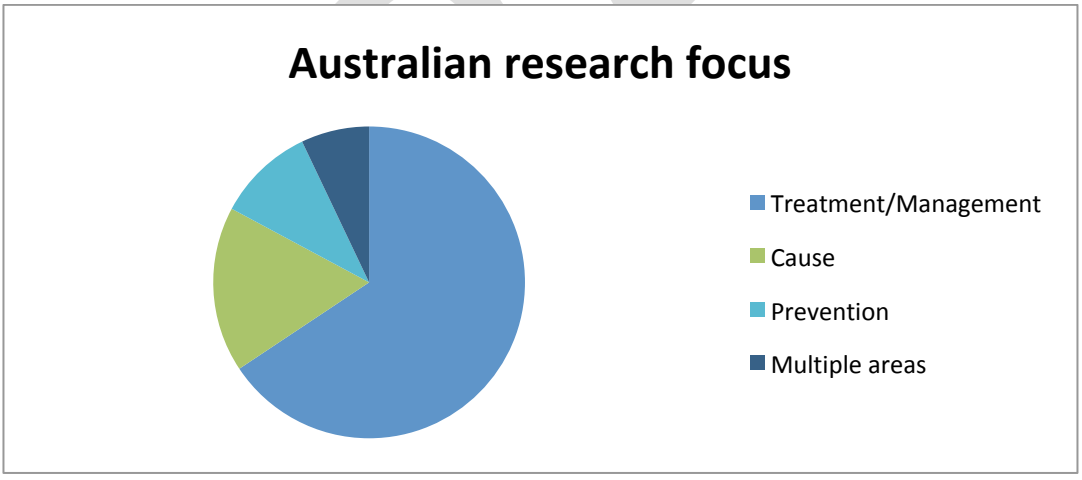

Figure 1: Australian Research Focus - Data sourced from the Mason Foundation Report – ME/CFS Research Mapping – Final Report (NOUS group, 2016). [5]

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 for Health Research (CIHR)

The Canadian Institutes for 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 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, 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 created 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 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) andthe Canadian Consensus Criteria (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 ideal health of a population versus 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 chronic 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 50-80% recovery after 7 years in protracted chronic fatigue syndrome, when using the Fukuda (1994) diagnostic criteria for patient selection.[36]

This is in contrast to recent paediatric data, which indicated that the majority of young people (who seemed to be more likely to have infection as a trigger) reported recovery after 4-5 years with a range of 1-15 years. By 5 years, 60% reported recovery and by 12 years 88% reported recovery.[16, 17]

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.'[37] 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.[38] 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.[39]

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

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 harms 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. The primary reported concern with recommending graded exercise therapy for ME/CFS patients is the onset of post-exertional malaise (PEM) and the risk of worsening symptoms.[40,41,42,43]

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

"…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]

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*). [47,48] 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. [49, 50]

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. [51,52]

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.[53]

Physical activity and Pacing

Patients have reported pacing to be a helpful approach to managing their illness.[54] 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.[55,56,57] 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.[58,59] In 2015, an Australian survey of 610 patients with ME/CFS reported that 89% of respondents felt worse after increased activity or exercise and that pacing was an effective strategy to manage this.[44,60] Some patients have adopted the use of heart rate monitors to find their 'safe level of activity' to ensure PEM is not triggered.[61,62]

4.5.2 Gaps in awareness–clinical perspectives

A review and meta-synthesis of qualitative studies on ME/CFS patients identified a disparity between patients, clinicians and researchers on the diagnosis and treatment of ME/CFS.[63] Patient perspectives are, however, critical to understanding the complexity of ME/CFS and patient interactions with health care services.[64]

Patients describe feeling dismissed and stigmatised after attending health care services.[65] 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 and further harm. [66,67]

Clinicians are trained to diagnose conditions with observable objective data (signs) and ME/CFS challenges this approach given its subjective description (symptoms). A UK survey (2005) indicated that only half of General Practitioner (GP) respondents believed that ME/CFS was a real condition. [68] These results are similar to those of an Australian survey of GPs conducted in 2000.[69]

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 (DoH) have been informed of the reported exclusion of some patients severely affected by ME/CFS from accessing the National Disability Insurance Scheme (NDIS) and other supportive services. Access to support services like NDIS 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),[70,71,72] 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 or supportive services. To access care through the NDIS patients need to show they have a significant disability. For these ME/CFS patients, graded exercise therapy may not be appropriate. The following is a summary of the submissions' proposed recommendations to NDIS:

1. Recognition of ME/CFS as a serious debilitating condition.
2. The condition should be listed on the NDIS under list B: neurological disorders.
3. 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.

For Terms of Reference and Committee membership details see: *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 both NHMRC and relevant Australian government health agencies. Some of the Committee's research recommendations fall outside the remit of NHMRC. However, NHMRC will endeavour to bring the identified needs in this report to the attention of appropriate Australian health agencies through the Council of NHMRC, noting that NHMRC has limited capacity to fund all recommendations put forward by the Committee.

5.1.1. Public consultation

The Committee recognises the importance of input from the ME/CFS community before finalising the report. As such this draft report will undergo public consultation to ensure that the views of the general public as well as ME/CFS patients, carers, clinicians and researchers are captured and considered.

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 such 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.

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 more reproducible recruitment 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 description 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 is not unique to ME/CFS, as it is evident in some other fatiguing illnesses, including post-cancer fatigue, post-polio syndrome and multiple sclerosis.[73, 74]

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.[13] 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 the 2003 Canadian Consensus Criteria (CCC) 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.

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) Building **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.**

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) and the Paediatric Primer (2017) for child and adolescent patient selection and collect common data elements (CDEs).
Strategic focus 2: 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 and maximise the uptake of Australian ME/CFS clinical practice guidelines.
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.

5.3.1. Strategic Focus 1: Building ME/CFS Research Quantity and Capacity in Australia

Key points

- Encourage hypothesis generating research.
- Support new and emerging researchers into 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 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.

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, an expert group (whose members would not be able to apply for TCR funding given the conflict of interest) will develop call-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.

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 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

- 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: 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.

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.

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: Developing 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 re-development of the NICE 2007 ME/CFS clinical guidelines, with patient/consumer engagement a priority.

The Committee advises updating Australian ME/CFS clinical practice guidelines as well as developing General Practitioner educational material and patient engagement strategies. These 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 (Attachment H) *'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, both NHMRC and NIH would jointly decide on what areas of ME/CFS research need focus and then support that 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 on 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 recently held a stakeholder information session 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 (see: *Attachment I*).

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 both 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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