Summary paper for Mason Foundation Stakeholder Information Session: Investigating the viability of an Australian ME/CFS biobank or patient database

Background

The Judith Jane Mason & Harold Stannet Williams Memorial Foundation ('the Mason Foundation')[1] is a charitable trust managed by Equity Trustees Limited that supports medical and scientific research on myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and Alzheimer's disease. The Mason Foundation currently funds research through a competitive grants program supported and overseen by a National Medical Advisory Panel.

The Mason Foundation is seeking to increase the impact of its research investments in ME/CFS and has engaged Nous Group (Nous) to investigate the viability of establishing an ME/CFS biobank and/or a patient registry/database (patient database) in Australia. This follows previous work by Nous which found most stakeholders' broadly support the idea of a biobank and/or a patient database but that further work was required to determine if these are viable research investments.

Nous has undertaken this project is to inform the Mason Foundation's decisions on ME/CFS research funding, including whether to fund the establishment of an Australian ME/CFS biobank and/or a patient database for ME/CFS. Regardless of any decision to fund a database or biobank, the Mason Foundation will continue to allocate a portion of its funds to the research grants program.

This summary paper presents the project findings and draft recommendations of the Nous project.

Overview of process and methodology

This project to investigate the viability of a biobank builds upon previous projects to map the ME/CFS research landscape and explore stakeholder views on the establishment of an ME/CFS biobank. These projects involved literature reviews on ME/CFS research and biobanking in Australia and internationally and interviews and workshops with key stakeholders, including ME/CFS consumers, researchers and biobank experts.

This previous work established that stakeholders and biobank experts generally agree that it is feasible to establish a biobank and/or patient database in Australia and that these options had potential to advance ME/CFS research and could attract new researchers to the field. However, in a 2017 workshop, stakeholders and biobank experts confirmed that further work was required to see whether there would be sufficient market demand for a sustainable ME/CFS biobank in Australia.

Nous' methodology for this current project has been designed to assess viability of a potential patient database and biobank investment options that draw on learnings from previous projects. Nous established an Expert Advisory Committee (EAC) for the project, made up of members of the Mason Foundation National Medical Advisory Panel and experts in biobanking and health research. The EAC has provided input and advice on the project methodology, analysis and findings at key points in the project.

The project is being conducted from January to May 2018. It involves desktop research, stakeholder interviews, a survey of researchers, a limited cost-benefit analysis and a teleconference information session for ME/CFS stakeholders.

The key steps of the project are summarised in Figure 1 (overleaf).

[1] Equity Trustees Wealth Services Limited is the sole trustee for the Mason Foundation. It is responsible for managing the trust in accordance with the intent and terms of the Mason Foundation deed. In this report, the Mason Foundation refers to Equity Trustees as the manager of the trust.

Figure 1 | Summary of Nous methodology

						
Establish an Expert Advisory Committee for the project with biobank experts and members of the Mason Foundation Medication Advisory Panel	**Conduct desktop research** on market need, scope options and cost and benefit drivers of a potential ME/CFS biobank and develop scoping paper	**Test the findings** from the desktop research with the expert advisory committee (EAC) and a selection of stakeholders in phone interviews	**Conduct survey of researchers** that study ME/CFS and other related fields to understand market need for a biobank and patient database	**Conduct limited cost-benefit analysis and test the preliminary findings**, with the EAC, and incorporate feedback into the draft report	**Hold a stakeholder information session** via teleconference to discuss the findings with ME/CFS consumers, researchers and biobank experts	**Finalise findings & recommend-ations** for the Mason Foundation on whether it should fund the establishment of an ME/CFS biobank

Findings

A summary of the project findings is provided in Table 1. The findings are structured based on four options for future research investments. These options are based on the scope options that were tested with stakeholders at the Mason Foundation workshop in 2017. These options were further refined in consultation with the EAC for this project. The four options are not mutually exclusive. The Mason Foundation has indicated it will continue to fund a research grants program regardless of whether it decides to invest in other options.

Nous investigated the viability of each option, to help inform the Mason Foundation's future decision making on optimal research investments. The findings are based on qualitative analysis of the literature review, stakeholder interviews, survey of researchers and limited cost-benefit analysis. Nous has tested the findings with the EAC at various points in the project.

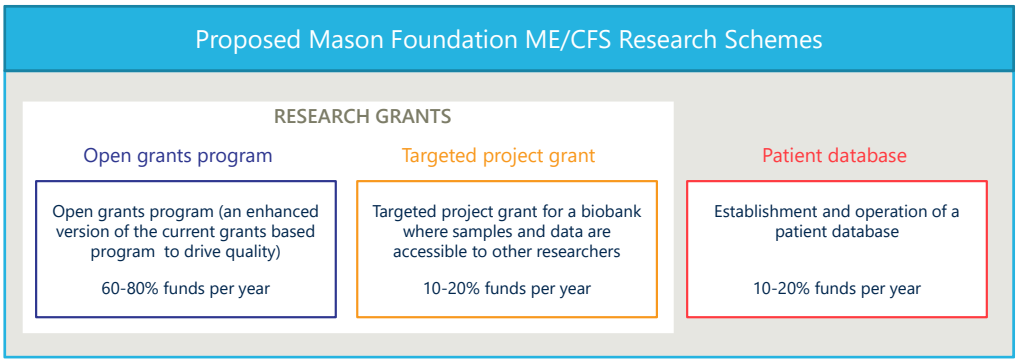
Table 1 | Summary of project findings

	Base case: Current grants program	Option 1: Patient database	Option 2: Small scale-up biobank focused on single research question	Option 3: Medium scale biobank
Overall finding	**There are opportunities to improve the current grants program to increase focus on quality research.**	**Option 1 is the most viable option for new investment; it offers a potentially substantial benefit to research with lower costs and lower risks than other options.**	**Option 2 is a viable option for investment if risks are managed.**	**Option 3 would have significantly more cost than benefit over 10 years; this option is unlikely to be viable in Australia at this stage.**
Description	The base case is the Mason Foundation's current research grants program	A clinical patient database with 500-1,000 participants	A biobank focused on one research question / project in which the samples are specifically collected for that project; established in an existing biobank facility; potential to scale up at a later stage	A biobank similar in scale, sample types and costs of the UK ME/CFS Biobank and established in an existing facility
Market need	There is sufficient demand for the Mason Foundation's current grants program; some researchers raise concern over the opportunity cost of investing in other options	There is sufficient market demand for a patient database; this option was more popular than a biobank in the survey of researchers	There is mixed support for a biobank; some stakeholders are supportive provided it is found to be viable; a small number oppose the idea	There is insufficient demand to sustain an ME/CFS biobank of this scale in Australia at this stage
Costs and benefits	There are minor administrative costs and notable benefits as this is the only competitive grants program that funds ME/CFS research in Australia; the quality of proposals and subsequent research is inconsistent	The patient database has a lower cost than other options; benefits are potentially substantial but smaller than for a biobank; this option is unlikely to be financially sustainable without some ongoing funding	The costs of a scale up biobank are moderate (provided it is established in an existing institution), but it would provide substantial benefit for the researchers that use it; this option is unlikely to be financially sustainable without some ongoing funding	This option has major establishment costs, which mean benefits would not outweigh costs in the medium to long-term. There is also a risk that the biobank is underutilised, negating potential benefits; this option is unlikely to be financially sustainable without some ongoing funding

Draft recommendations

The draft recommendations for the project are summarised in Table 2 below.

Table 2 | Draft recommendations

	Draft recommendation
Overall	**1. The Mason Foundation should enhance its future ME/CFS research through allocation of funding across three schemes:** 
Current grants program	**2. The Mason Foundation should enhance its current grants program by:** 2.1. Funding a smaller number of larger research grants over a longer time period with a focus on highly reputable and promising researchers 2.2. Allocating a proportion of funds each year to: • Researchers who have never or are not currently conducting research on ME/CFS (to attract more researchers to the field) • Early career researchers • Research proposals that involve domestic or international research collaborations • Research proposals that utilise a patient database (should one be established) • Research proposals that focus on research priority areas for ME/CFS, including: ○ understanding the pathology of the illness ○ developing a diagnostic test for patients ○ improving how health professionals currently diagnose and manage ME/CFS ○ severe cases of ME/CFS, and ○ emerging research priorities.
Patient database	**3. The Mason Foundation should run a tender process for the establishment of a clinical patient database for ME/CFS research.**
Scale-up biobank	**4. The Mason Foundation should provide a targeted grant for a research project that involves a biobank, where samples and data are accessible to other researchers.**
Moderate biobank	**5. The Mason Foundation should not proceed with funding the establishment of a medium-sized biobank for ME/CFS research at this stage.**

ME/CFS Research Mapping Final Report

Final Report

9 November 2016

Bold ideas | Engaging people | Influential, enduring solutions

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Executive summary

The Judith Jane Mason & Harold Stannet Williams Memorial Foundation ('the Mason Foundation')[1] engaged Nous Group ('Nous'), an independent management consulting firm, to undertake a review of the research landscape for myalgic encephalomyelitis/chronic fatigue syndrome ('ME/CFS') in Australia and internationally. The purpose of the review was to better understand the current ME/CFS research landscape, including gaps and priority areas of research, and identify opportunities for future investments in ME/CFS research that could maximise positive impact for ME/CFS patients.

This report presents:

- findings on the current state of ME/CFS research in Australia and internationally
- findings on the strengths, gaps and challenges for ME/CFS research
- analysis of opportunities for the Mason Foundation to maximise investments in ME/CFS research and improve the grant process
- recommendations for the Mason Foundation's future ME/CFS research investments.

A summary of the key themes and issues identified in each of these areas is contained below.

The current state of ME/CFS research in Australia and internationally

ME/CFS research is growing steadily but remains limited both in Australia and internationally.

Within Australia, the majority of ME/CFS publications over the past ten years have originated from New South Wales and Victoria. There are a small number of key institutions and researchers, however active and effective networks are limited and more difficult to discern. There are also a small number of clinical trials in Australia, which all examine biological interventions. In terms of focus, Australian research tends to focus on management of CFS and applies an immunological basis. Universities and the Mason Foundation fund the majority of Australian research on ME/CFS, with no funding from the National Health and Medical Research Council ('NHMRC') or Australian Research Council ('ARC') in the past decade. This is contrary to the international experience, where equivalent government institutions in the UK and USA have provided a small but regular supply of funding for ME/CFS research.

The document review and stakeholder consultations indicate that the UK, USA and Norway are the key international players in ME/CFS research; however Australia is also an important player, contributing around seven per cent of publications globally. Between 2011 and 2015 the volume of ME/CFS research internationally has increased by approximately 20 per cent (based on a review of 694 peer-reviewed articles on PubMed), with articles published in a range of medium and low impact journals.

The focus of Australian and international research is mostly similar, but there are some important differences, with international research more likely to have a psychological focus. As noted above, governments are more active in funding ME/CFS research than the Australian government – indicating either a difference in quality and/or level of support between Australian and international research.

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Strengths, gaps and challenges for ME/CFS research

In Australia and internationally, there are strengths but also gaps and challenges in the current state, which need to be considered for future investment decisions. There is a reasonable knowledge of the epidemiology of ME/CFS and pockets of strong research that can be built on. However key gaps relate to the quality, focus and consistency of ME/CFS research. There are also broader ME/CFS gaps and challenges, with a connection to the research state. These include difficulty in attracting clinical researchers to the field, lack of understanding of ME/CFS within the medical profession and sub-optimal collaboration between researchers.

Opportunities for the Mason Foundation to maximise investments in ME/CFS research and improve the grant process

The current state mapping and stakeholder consultations undertaken for this project have identified a number of opportunities for the Mason Foundation to re-think current approaches to increase the value and impact of funded research for patients and the ME/CFS sector. These opportunities fall into two categories:

1. **Opportunities for the focus of Mason Foundation funding to operate more strategically – *what is funded.*** Mason Foundation funding is currently spread across multiple research areas and hypotheses. In prioritising future investment, the Mason Foundation will need to consider whether it can generate greater impact through a narrower research focus. This may be through identified priority areas or leveraging existing knowledge, or through other means, such as supporting collaboration or building capacity either at a sector (i.e. through the establishment of a biobank or shared resources) or individual level (i.e. through supporting new researchers to join the field).
2. **Opportunities for the Mason Foundation to improve their grants process – *how the funding process operates***. The review identified a range of opportunities to enhance the value of the current grants process, and to ensure future investment decisions maximise positive impact. This included: use of eligibility criteria as a lever to promote collaboration; directed investment to build on the established evidence base; a more holistic approach to understanding research quality and impact; and the introduction of core and desired criteria to the application process. There were also opportunities identified to consider a broader use of funding to support education and awareness raising initiatives.

It is important to note that most stakeholders were not opposed to a radical re-orientation of the Mason Foundation's current approach, provided it furthered the aim of positively impacting on individuals suffering from ME/CFS.

Recommendations

Table 1 overleaf provides a summary of Nous' recommendations emerging from this review. A detailed list of recommendations, together with advice regarding timeframes, is contained in Section 4 of this report.

Table 1: Summary of recommendations

No.	Recommendation
Recommendations on focus areas for research investment	
1.	**The Mason Foundation/Equity Trustees should consider the following focus areas for future investments in ME/CFS research:** 1.a. Directing grant funding to current gaps in ME/CFS research, in particular: • understanding the pathology of the illness • developing a diagnostic test for patients • research aimed at improving how health professionals currently diagnose and manage ME/CFS • research that includes patients with severe ME/CFS. 1.b. Supporting PhD and post-doctoral researchers, to encourage new entrants into the sector. 1.c. Supporting research collaborations between international and Australia-based researchers, including large-scale multi-country projects.
2.	**Based on the consideration of the focus areas for future investment (recommendation 1), the Mason Foundation/Equity Trustees should identify specific areas for research investment for the 2017 grant round.**
3.	**The Mason Foundation/Equity Trustees should investigate the opportunity to develop a biobank of shared resources for ME/CFS researchers.**
4.	**The Mason Foundation/Equity Trustees should consider investing in the establishment of a biobank of shared resources for ME/CFS research** (based on the investigation conducted under recommendation 2).
Recommendations to improve the grant process	
5.	**The Mason Foundation/Equity Trustees should identify who is eligible to apply for funding on the 2017 grant round, including whether international researchers that partner with Australian researchers are eligible.**
6.	**The Mason Foundation/Equity Trustees should support new and existing research and allocate a specific proportion of funding to each (e.g. 40 per cent to new research and 60 per cent to existing research).**
7.	**The Mason Foundation/Equity Trustees should consider requiring applicants to use only the Canadian Consensus Criteria or Fukuda criteria in funded research.**
8.	**The Mason Foundation/Equity Trustees should consider use and communication of a research quality and impact framework to help applicants demonstrate impact of past research and potential value of proposals, and to track (subject to feasibility) the impact and influence of funded research.**
9.	**The Mason Foundation/Equity Trustees should consider the following core criteria for the 2017 grant round:** • **Scientific credibility:** the proposal includes a strong hypothesis, endorsed methodology and publication plan. • **Demonstrates impact**: the proposal identifies evidence that the research is likely to have a positive impact on ME/CFS sufferers. • **Translation:** the proposal identifies how the research will be translated into clinical practice, policy, public education or further research.
10.	**The Mason Foundation/Equity Trustees should consider the following desirable criteria for the 2017 grant round:** • **Capacity building**: the proposal has a capacity building element, such as supporting early career researchers, scholarships or attracting new clinical researchers to the field. • **Collaboration:** the proposal involves meaningful collaboration between researchers within Australia or internationally.
11.	**In addition to the recommendations listed above, the Mason Foundation/Equity Trustees may wish to consider supporting public education and awareness raising initiatives for patients, doctors and researchers.** However, the Mason Foundation/Equity Trustees would need to consider whether these initiatives are within the scope of the terms of trust.

1 Introduction

1.1 Background

ME/CFS is a complex illness and is poorly understood by the research community. It is a multi-system condition that crosses neurological, psychological and immunological disciplines. ME/CFS affects a range of individuals and causes considerable ill health and disability. While the precise prevalence is unknown, it is estimated that at least one person in 2,500 is affected in Australia.[2] Despite the damaging impact of ME/CFS, the etiology of ME/CFS is yet to be understood by the research community. There is no definitive diagnosis, no cure and no agreed management plan.

The Mason Foundation is a charitable trust. Its goal is to achieve enduring, positive impact in the area of ME/CFS and Alzheimer's disease through funding medical research into the causes, prevention and/or management of these diseases. In relation to ME/CFS, the Mason Foundation currently funds medical and scientific research through three streams: early career researcher grants, proof of principle grants and innovation grants. The findings from this project will be important in guiding future decisions on the best approach to achieve the Mason Foundation's goals.

1.2 Purpose

The Mason Foundation engaged Nous to undertake a review of the ME/CFS research landscape in Australia and overseas. The purpose of the review was to:

- map the current ME/CFS research landscape, including gaps and priority areas of research
- identify opportunities for future investments in ME/CFS research that maximise positive impact for ME/CFS patients.

Recommendations from the review are expected to inform the Mason Foundation's future ME/CFS research investments as well as the design of the 2017 grant program.

1.3 Report structure

The report presents findings on the current ME/CFS research landscape and recommendations for future research investments. It presents:

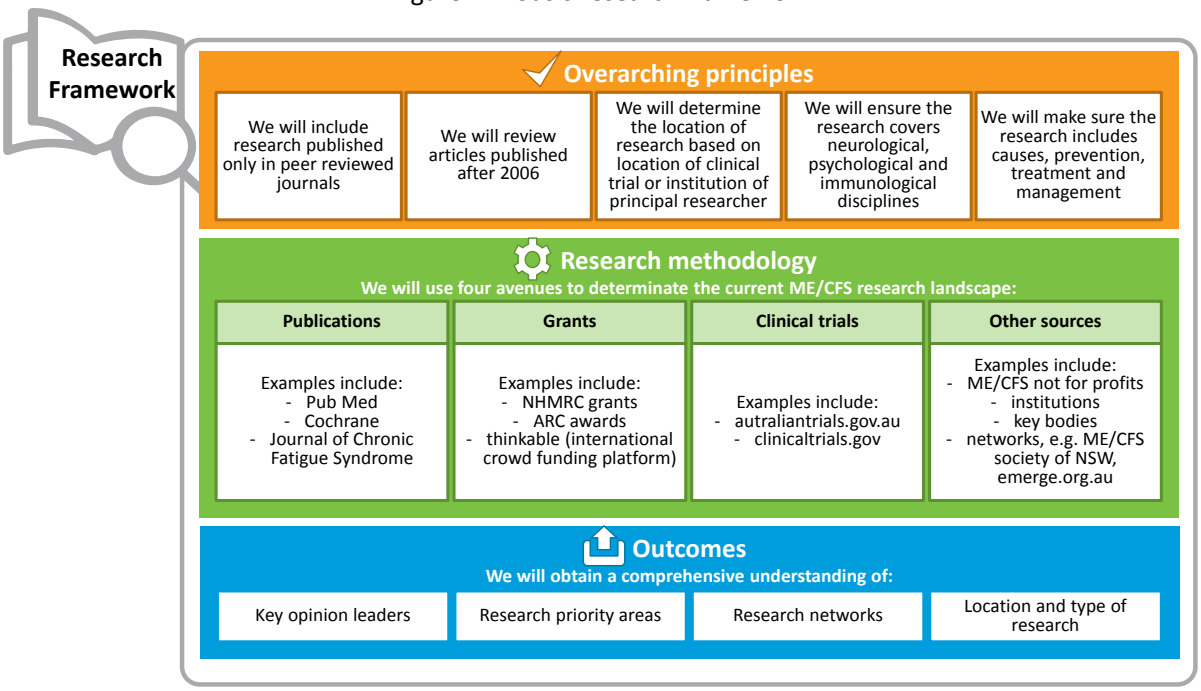
- findings on the current state of ME/CFS research in Australian and internationally
- findings on the strengths, gaps and challenges for ME/CFS research
- analysis of opportunities for the Mason Foundation to maximise investments in ME/CFS research and improve the grant process
- recommendations for the Mason Foundation's future ME/CFS research investments.

[2] ME/CFS Society of New South Wales (2016) http://www.me-cfs.org.au/faqs/ (accessed 24.09.16).

1.4 Research framework and methodology overview

Nous developed a research framework to guide the review (see Figure 1). The framework included overarching principles for conducting the review, a high level research methodology and the expected outcomes of the review.

Figure 1: Nous's research framework



The original focus for this project was to understand and map the current state of ME/CFS research in Australia and internationally to identify gaps and priority areas for research. During the project, the Mason Foundation and Nous identified a need to also understand the opportunities for the Mason Foundation to improve its current grants funding process. This included exploration of possible criteria to guide future funding decisions.

The methodology for the review is outlined in Appendix A. Nous conducted the project between September and November 2016. The project included a desktop review of 134 research records, electronic data scraping of 694 publications from the PubMed website and a limited number of stakeholder interviews. Nous identified six key lines of enquiry to guide the review:

Table 2: Key lines of enquiry

1. What is the current state of ME/CFS research in Australia?	**2. What is the current state of ME/CFS research internationally?**	**3. How does the Mason Foundation currently allocate grants?**	**4. What are the opportunities for ME/CFS research that maximises potential for positive impact?**	**5. What criteria can the Mason Foundation use to make investment decisions?**	**6. How can the findings from this project inform future redesign of the grants process?**

There are some limitations with the methodology and analysis. These are outlined in Appendix A.

2 Findings

This section outlines findings from the document review and stakeholder consultations on the current state of ME/CFS research. It maps the research landscape in Australia and internationally and identifies strengths, gaps and challenges for ME/CFS research.

2.1 Current state of ME/CFS research in Australia

ME/CFS research is growing steadily but remains limited in Australia (which is a similar finding to the current state of research internationally – see section 2.2). There are four overarching findings on the Australian research landscape:

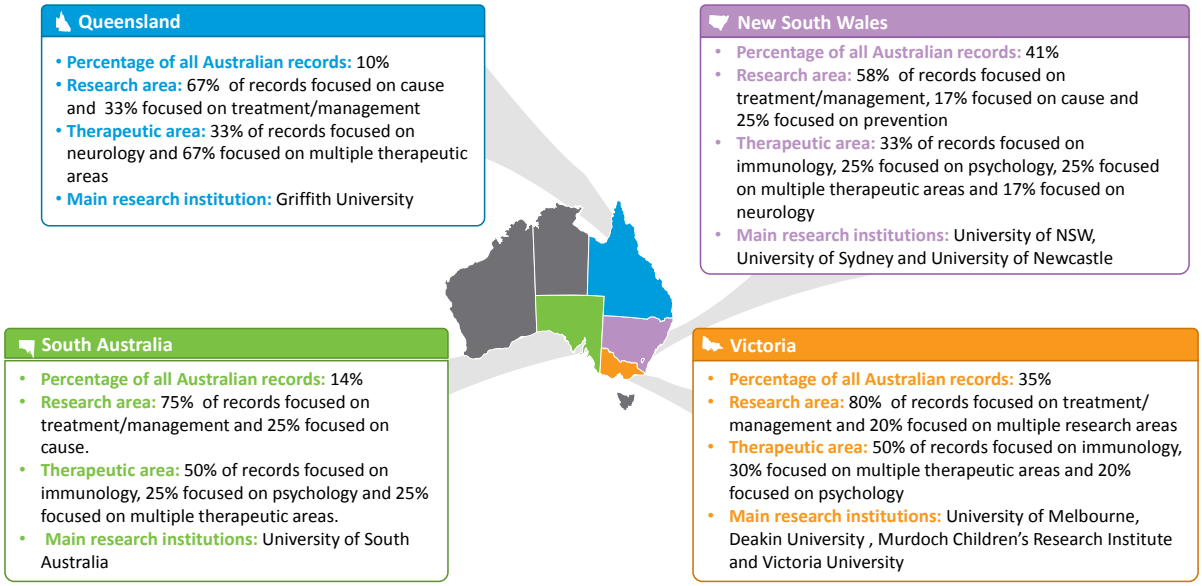
1. The majority of ME/CFS publications in Australia over the past ten years have originated from New South Wales and Victoria.
2. Australian research tends to focus on management of ME/CFS from an immunological hypothesis, although there are several studies on exercise and cognitive-based therapies.
3. There are a small number of clinical trials in Australia, which all examine biological interventions.
4. Universities and the Mason Foundation fund the majority of Australian research on ME/CFS, with no funding from NHMRC in the past decade.

The following pages discuss each of these points in turn.

2.1.1 The majority of ME/CFS research in Australia over the past ten years have originated from NSW and Victoria

Around three quarters of all Australian-based records that Nous reviewed were from New South Wales (41 per cent) and Victoria (35 per cent) (see Figure 2). Queensland and South Australia accounted for 10 per cent and 14 per cent of records respectively. The document review did not include records from the ACT or Western Australia, based on the search criteria and methodology for the review (see Appendix A). However, stakeholders reported that a small number of researchers were also active in these states. Figure 2 provides information on the proportion, focus and key institutions involved in ME/CFS research in each state.

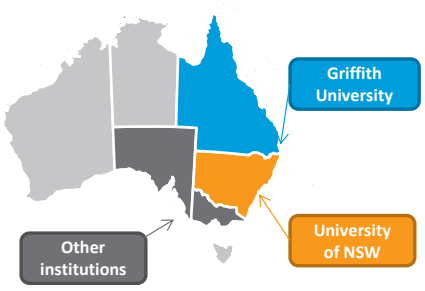
Figure 2: Key information on research records by state[3]



There are a small number of key institutions and individuals involved in ME/CFS research in Australia, but no discernible research networks (based on the stakeholder consultations and document review). Of the main research institutions involved in ME/CFS research, Griffith University tended to focus on cause and immunology while the University of New South Wales tended to have a mixed focus on neurology, psychology and treatment/management (based on stakeholder interviews and the document review). Figure 3 provides further information on the research areas of key institutions and opinion leaders in Australia.

[3] This is based on all Australian records that were subject to a detailed reviewed. This includes publications, clinical trials, grants and other sources (mainly consumer websites).

Figure 3: Key ME/CFS research institutions and key opinion leaders in Australia[4]



Griffith University

- **Research centre:** National Centre for Neurology and Emerging Diseases
- **Key opinion leaders:** Sonya Marshall-Gradisnik; Donald Staines; Samantha Johnston
- **Research areas:** Natural Killer (NK) cell cytotoxicity and signalling dynamics; T- and B-cell phenotypes profiles and cytokine production; genomic and proteomic profiling and gene expression; epidemiological analysis and current diagnosis criteria

University of NSW (Fatigue Clinic)

- **Research centre:** The Fatigue Clinic
- **Key opinion leaders:** Andrew Lloyd; Ute Vollmer-Conna; Erin Cvejic; Sophie Li
- **Research areas:** Exercise programs; activity pacing; cognitive and mindfulness-based therapies; gene expression and metabolic profiling; ME/CFS education for health professionals; sleep and pain

Other institutions and key opinion leaders

- **Institutions and key opinion leaders:** University of Melbourne (Henry Butt, Neil McGregor, Paul Gooley); University of South Australia (Stephanie Reuter Lange , Katia Ferrar); Murdoch Children's Research Institute (Sarah Knight); University of Sydney (Ron Grunstein, Ian Hickie); University of Newcastle (Tim Roberts)
- **Research areas:** Metabolomics profiling (Melbourne University & University of Newcastle); post exhaustive malaise, physical activity (University of South Australia); paediatric ME/CFS (Murdoch Children's Research Institute); phenotyping and neuromarkers (University of Sydney)

2.1.2 Australian research tends to focus on management of ME/CFS from an immunological hypothesis, although there are several studies on exercise and cognitive-based therapies

Overall, 66 per cent of research records in Australia focused on management, while 5 per cent focused on cause and 5 per cent had a mixed focus. The therapeutic area of Australian-based records was most likely to be immunology (38 per cent of all records), followed by psychology (21 per cent) and neurology (10 per cent). The remaining 31 per cent of Australian records focused on multiple therapeutic areas.

An analysis of key words of research records shows that while most research has an immunological focus, there continues to be a notable amount of research on exercise programs and physical activity as treatment (see Figure 4).

Of the five most common key words for Australia research records (excluding sleep), three reflect an immunological hypothesis (metabolic, mitochondria and autonomic functioning) and two reflect a psychological hypothesis (exercise programs and activity pacing).

This indicates that despite the overall focus on immunology in ME/CFS research, there is still a notable amount of research on exercise and activity-based therapies. There also continues to be research on cognitive and mindfulness-based therapies which reflect a psychological focus.

[4] The assessment of key researchers was informed by the document review and stakeholder consultations, and so is influenced by the perspectives of those individuals.

Figure 4: Key words for Australian research records[5]

It is important to note that many researchers who study psychological and exercise-based therapies recognise a biological cause for ME/CFS (based on stakeholder consultations and the document review). They hold that such therapies are legitimate management options for a disease which is likely neurological or immunological in origin.[6] In contrast, other researchers and consumer groups argue against psychological and exercise-based therapies (based on stakeholder consultations and the document review). They hold that ME/CFS research should only focus on investigating a biological cause and biological treatment options. Many also report that exercise-based therapies can be harmful, particularly for people with severe ME/CFS.[7] This is an area of strong contention among researchers and consumer groups in Australia and internationally.[8]

2.1.3 There are a small number of clinical trials in Australia, which all examine biological interventions.

Over the past ten years, the majority of clinical trials in Australia have had an immunological basis. They examined a range of biological interventions for treating and managing ME/CFS. Table 3 (overleaf) lists key information on all ME/CFS clinical trials registered in Australia over the past ten years.

Most Australia-based clinical trials are in the early phases of research. Of the six clinical trials registered with the NHMRC over the past ten years, one was a Phase I trial and three did not list a phase, indicating they were exploratory studies. Phase I trials are designed to test a new intervention for the first time to evaluate safety.[9] Only two trials were in Phase II or Phase III. These phases are designed to further study

[5] This is based on Australian records that were subject to a detailed review. Nous identified key words for each record reviewed, as not all records included a list of key words (e.g. grants and clinical trials). The size of the word indicates how frequently the word appeared as a key word, with larger words indicating a higher frequency of appearance. This analysis is intended to give a broad impression of the overall research landscape, but given the small sample size subject to a detailed review, it cannot be used to accurately identify the proportion of research focused on specific research areas.

[6] White, P.D. et al (2011) 'Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trials.' *The Lancet*, Vol. 377, Issue 9768, p823-836.

[7] Rehmeyer, J (2016), 'Bad science misleads millions with chronic fatigue syndrome. Here's how we fought back,' *Stat*, 12 September 2016, https://www.statnews.com/2016/09/21/chronic-fatigue-syndrome-pace-trial/ (accessed 20.10.2016).

[8] Friedberg, Fred (2016), 'Cognitive-based therapy: why is it so vilified in the chronic fatigue syndrome community?' *Fatigue: Biomedicine, Health and Behaviour*, Vol. 3, Issue 3, pp127-131.

[9] NHMRC (2016), "Phases of Clinical Trials", https://www.australianclinicaltrials.gov.au/what-clinical-trial/phases-clinical-trials (accessed 24.10.16).

an intervention that had already been tested with a larger group. Generally, an intervention can be approved for public use after its safety and efficiency is confirmed in a Phase III trial.[10]

Table 3: ME/CFS clinical trials in Australia (2006 – 2016)[1]

Title	Study type	Phase	Funder	Lead institution	Research area	Therapeutic focus
Active clinical trials						
Mitochondrial agents in the treatment of chronic fatigue syndrome: a 20-week, open-label, intervention trial	Interventional (Non-randomised trial)	Phase II	University of Melbourne	University of Melbourne	Treatment/ management	Immunology
An association between changes in the intestinal microbial flora and the alteration of sleep in Chronic Fatigue Syndrome: A pilot open label trial with use of the antibiotic erythromycin	Interventional (Non-randomised trial)	n/a	Commercial sector (Bioscreen Australia)	University of Victoria	Treatment/ management	Immunology
Assessment of Fatty Acid/Carnitine Homeostasis in Patients with Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (ME/CFS)	Observational (Assessment with healthy controls)	n/a	Mason Foundation	University of South Australia	Treatment/ management	Immunology
The influence of modafinil on the post-exercise exacerbation of symptoms in patients with chronic fatigue syndrome	Interventional (Double-blinded placebo-controlled study)	Phase III and IV	Mason Foundation	University of NSW	Treatment/ management	Psychological
Concluded clinical trials						
A study to evaluate the safety, tolerability, pharmacokinetics and analgesic efficacy of oral CMX-020 in healthy male and female subjects (2015)	Interventional (Double-blind, randomised, placebo controlled trial)	Phase I	Commercial sector (Cytometix Australia)	Cytometix Australia Pty Ltd	Treatment/ management	Immunology
The use of a natural medicine, S-Adenosylmethionine (SAM-e) in the treatment of Fibromyalgia (2007)	Interventional (Double-blind, randomised, placebo controlled trial)	n/a	Commercial sector (Nutrition Care Pharm-aceuticals)	Deakin University	Treatment/ management	Immunology

2.1.4 Universities and the Mason Foundation fund the majority of Australian research on ME/CFS, with no funding from NHMRC in the past decade

In the past ten years, Australian-based researchers have mostly relied on funding from universities or the Mason Foundation. The Mason Foundation typically provides between $500,000 and $600,000 in grant funding for ME/CFS research per year. In a temporary arrangement (whilst awaiting the findings of

[10] Ibid.

the Nous report) for this year's funding round, grants of up to $100,000 for 12 month projects have been made available. In previous years the Mason Foundation has provided three different types of grants for ME/CFS research:

1. **Early career researcher grants** – once-off grants of up to $60,000 for new researchers who have completed their PhD within the past five years.
2. **Proof of principle grants** – once-off grants of up to $80,000 intended to help researchers strengthen their position for attracting more significant competitive funding through sources such as the NHMRC.
3. **Innovation grants** – grants of up to $300,000 over three years (with a maximum of $100,000 in any one year) for projects that involve multi-disciplinary teams and are exploring novel concepts and innovative approaches.

Table 4 lists the research projects funded by the Mason Foundation in 2015. They covered a range of therapeutic areas, with most focusing on management and only two focused on cause.

Table 4: Mason Foundation research grants in 2015

Title	Research area	Therapeutic focus	Lead institution
Sleeping, but your heart's not in it: Decreased heart rate variability during slow wave sleep in chronic fatigue syndrome	Cause	Neurology	University of NSW
Personalized mindfulness-based therapy to optimize autonomic functioning in patients with chronic fatigue syndrome	Management	Psychology, neurology	University of NSW
A longitudinal study of gene expression and metabolic profiling changes that occur in Chronic Fatigue Syndrome.	Management	Immunology	University of Melbourne
Confirmation of a central nervous system origin for CFS symptoms	Cause	Neurology	Griffith University
Can amino acid supplementation reduce fatigue in CFS patients? A randomized double-blind placebo-based trial	Management	Immunology	University of Newcastle
Optimising exercise programs for chronic fatigue syndrome	Management	All/multiple	Monash University
Measuring and improving activity pacing in chronic fatigue syndrome.	Management	All/multiple	University of NSW
A randomised controlled trial of online continuing education for health professionals to improve the management of CFS.	Management	All/multiple	University of NSW
Extreme phenotyping in patients with non-restorative sleep (NRS): Is there a "neuromarker" for CFS/SEID?	Management	Neurology	University of Sydney
The development of an international patient registry to improve the clinical definition, diagnosis and management of ME/CFS	Management	Neurology	Griffith University
Active video gaming to increase physical activity in adults with chronic fatigue syndrome	Management	All/multiple	University of South Australia

Universities also provide funding to their research staff for ME/CFS research. This research covers a range of disciplines, including immunology, neurology, psychology, pediatric and adolescent health and exercise physiology. The main universities that have funded ME/CFS research are:

- Deakin University
- Griffith University
- Monash University
- Murdoch Children Research Institute (affiliated with the University of Melbourne)
- University of Melbourne
- University of NSW
- University of South Australia
- University of Sydney
- Victoria University.

In addition to university and Mason Foundation funding, researchers occasionally receive funding from hospitals, foundations, commercial entities and other institutes. Biopharmaceutical companies, for example, have funded a small number of clinical trials in Australia.[11] However, this forms a small proportion of overall funding for ME/CFS research in Australia.

Overall, there is very limited funding available for ME/CFS research in Australia. The NHMRC and ARC have not funded any ME/CFS research in the past ten years. Stakeholders indicate that this is due to a number of reasons. The NHMRC is a highly competitive grant process which requires a very high standard of scientific rigor. ME/CFS research may lack the maturity and scientific rigor to compete against more established research areas, particularly given that the etiology of the disease is still relatively unknown. Consumer groups say that some research institutions still hold biases around the scientific credibility of ME/CFS research.

This is contrary to the international experience, where equivalent government institutions in the UK and USA have provided a small but regular supply of funding for ME/CFS research (see Section 2.2.4 for further discussion on international research funding). Given that these institutions also have stringent funding criteria, this could suggest that some researchers in the UK and USA are engaging in higher quality research than their Australian counterparts. However, stakeholders and consumer groups argue that this also indicates that there is more overall support for ME/CFS research in these countries than Australia.[12]

2.2 Current state of ME/CFS research internationally

The international ME/CFS research sector is steadily growing but remains small overall. Australian researchers are aware of and tracking international progress. This is accompanied by a push from stakeholders for the sector to reach consensus on case definitions, to ensure research can be leveraged and applied consistently on a global scale (see Section 3.2 for a further discussion on case definitions).

There are five overarching findings on the international research landscape:

[11] Ibid.

[12] Logan, Elizabeth (2016) 'Australian Health Dept. answers questions on ME,' *Emerge Australia*, 28 January 2016, http://emerge.org.au/australian-health-dept-answers-questions-on-me/#.WBaC2U-7qpo (accessed 1.10.16).

1. International research is most concentrated in the UK, USA and Norway, although Australia is also a key player.
2. The volume of ME/CFS research has moderately increased, with articles published in a range of medium and low impact journals.
3. The focus of Australian and international research is mostly similar, but there are some important differences, with international research more likely to have a psychological focus.
4. As in Australia, there is a small and dispersed picture of research networks, institutions and key opinion leaders. They are mostly based in the UK, USA and Norway.
5. Overseas governments are more active in funding ME/CFS research than the Australian government.

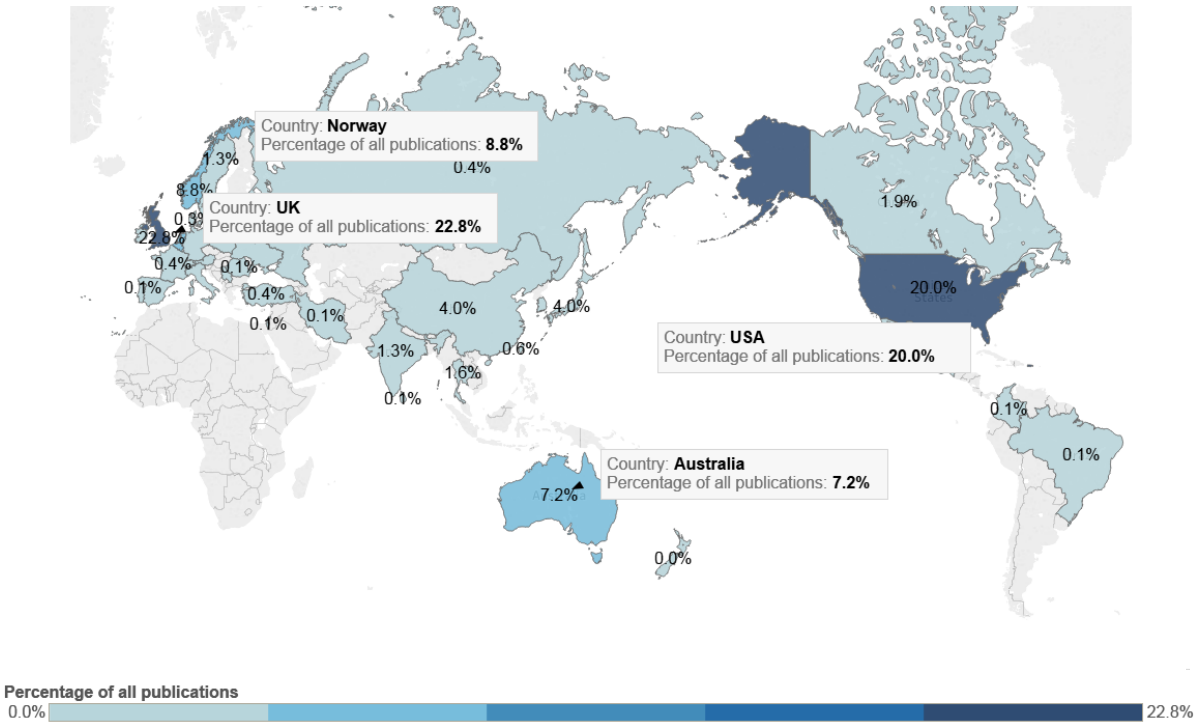
The following pages discuss each of these points in turn.

2.2.1 International research is most concentrated in the UK, USA and Norway, although Australia is also a key player

The document review and stakeholder consultations indicate that the UK, USA and Norway are the key international players in ME/CFS research. Nous reviewed 694 peer-reviewed articles on ME/CFS from the PubMed database published in the past five years.[13] Of these, around 23 per cent originated from the UK, 20 per cent from the USA and 9 per cent from Norway (see Figure 5, overleaf).

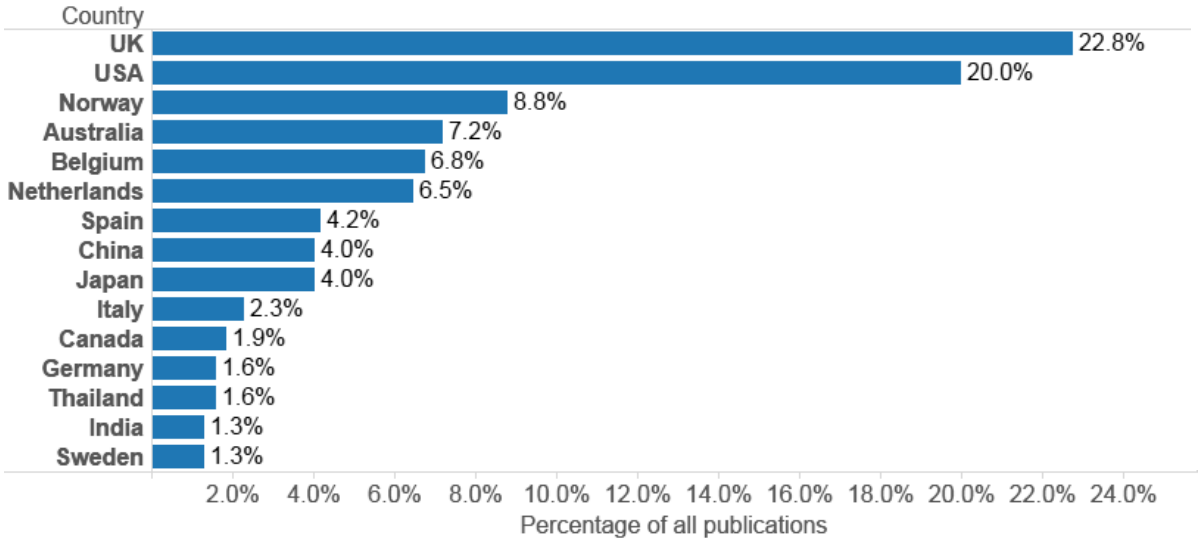
[13] Nous electronically scraped 694 peer-reviewed articles published from the PubMed online research database. The articles had "myalgic encephalomyelitis" or "chronic fatigue syndrome" in the title and were published between 2011 and 2016. The articles originated from 37 different countries (based on location of first author).

Figure 5: Proportion of research publications for all countries (Jan 2011 – Oct 2016)[14]



Australia is also a key player in the international research community for ME/CFS, accounting for approximately 7 per cent of these publications (see Figure 6). On a per capita basis, Belgium, Norway and Australia have published the most ME/CFS articles in the past five years.

Figure 6: Proportion of research publications by country (Jan 2011 – Oct 2016)[15]



Note: This graph excludes countries that accounted for less than 1 per cent of total publications.

[14] This is based on the 694 peer-reviewed articles web-scraped from the PubMed online research database (see above, Note 13).
[15] Ibid.

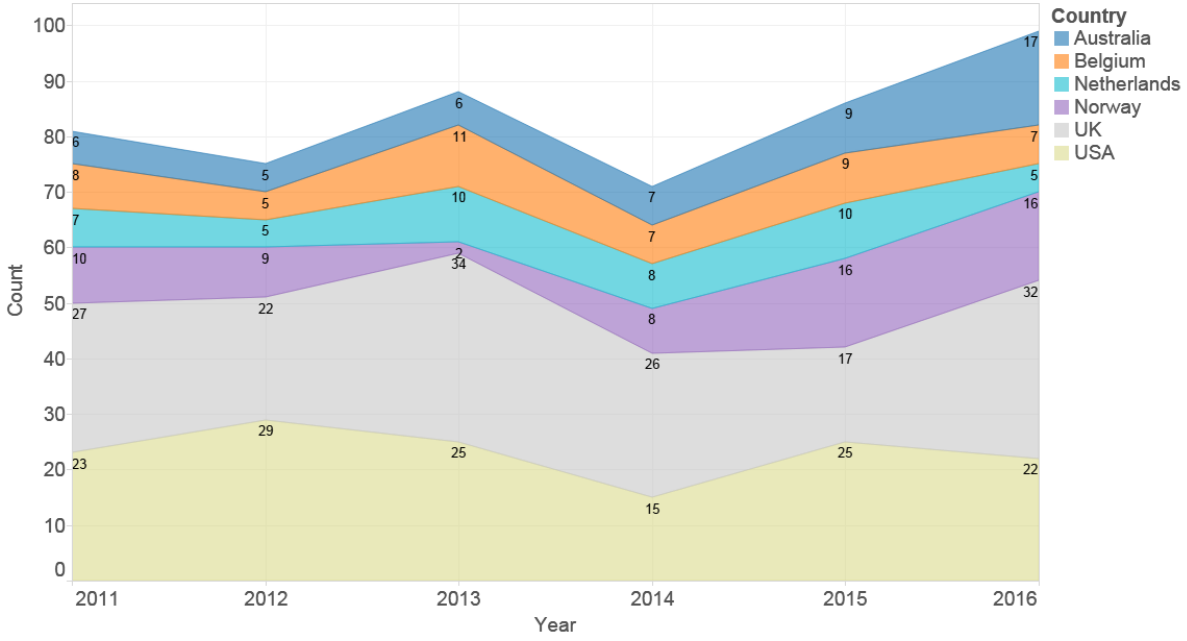
2.2.2 The volume of ME/CFS research has moderately increased, with articles published in a range of medium and low impact journals

Overall, the number of articles on ME/CFS published per year grew by approximately 20 per cent between 2011 and 2015 (based on a review of 694 peer-reviewed articles across all countries).

Among the top six countries that produce ME/CFS research, growth varied considerably (see Figure 7). Between 2011 and 2016, Australia experienced the highest average yearly growth, at 23 per cent, followed by Norway, at 10 per cent.[16] The UK's average yearly growth in number of articles published was 3 per cent over the same period.

The USA, Belgium and the Netherlands experienced a slight decrease in the number of articles published. Between 2011 and 2016, the average yearly growth in the number of articles published was -1 per cent for the USA, -3 per cent for Belgium and -7 per cent for the Netherlands.[17] However, these countries still accounted for a large proportion of overall ME/CFS research.

Figure 7: Number of ME/CFS articles published per year by country (Jan 2011 – Oct 2016)[18]



Note: The top six countries with the most publications are included in this graph.

Across all countries, articles were published in a mixture of medium and low impact journals, as measured by the impact factor index.[19] This index cannot be relied upon to measure research quality but does provide an indication of the translational impact of a journal. While there is no universal agreement on what constitutes a high impact factor, the National Institute of Health reports that journals with an

[16] The average yearly growth is calculated based on the compound annual growth rate (CAGR) for the period 2011 to 2016. For 2016, this is based on articles published between January and September, and therefore the actual growth rate for 2016 is likely to be higher.

[17] Ibid.

[18] This is based on the 694 peer-reviewed articles web-scraped from the PubMed online research database (see above, Note 13).

[19] Impact factor is a measure of the frequency with which the average article in a journal has been cited in a particular year. A higher number indicates that the journal has a higher impact based on number of citations. Impact factors are calculated yearly starting from 1975 for those journals that are listed in the Journal Citation Reports (National Institute of Health (2016) "High Impact Journals," https://tools.niehs.nih.gov/srp/publications/highimpactjournals.cfm (accessed 11.10.16)).

impact factor of 10.24 or more are high impact.[20] Among the top six countries that produce ME/CFS research, Australia, the UK and the Netherlands were more likely to publish articles in medium impact journals. Of the top five journals that mostly commonly published ME/CFS research in these countries, the highest impact factor was 6.22 (see Table 5).

Table 5: Impact factor[21] for the most common journals of publication by country (Jan 2011 – Oct 2016)[22]

UK

Journal	Impact factor
Psychol.Med	**6.16**
PLoS.One	**3.23**
BMJ.Open	**2.57**
BMC.Fam.Pract	**2.16**
J.Health.Psychol	**1.88**

USA

Journal	Impact factor
J.Transl.Med	**3.99**
PLoS.One	**3.23**
Fatigue	**2.98**
BMC.Neurol	**2.48**
J.Health.Psychol	**1.88**

Norway

Journal	Impact factor
Cochrane.Database.Syst.Rev	**6.22**
PLoS.One	**3.23**
Biopsychosoc.Med	**2.57**
BMJ.Open	**2.27**
Tidsskr.Nor.Laegeforen	**0.02**

Netherlands

Journal	Impact factor
Psychol.Med	**6.16**
Behav.Res.Ther	**4.45**
J.Psychosom.Res	**3.27**
Eur.J.Pediatr	**1.98**
Tijdschr.Psychiatr	**0.24**

Belgium

Journal	Impact factor
J.Intern.Med	**6.06**
Clin.Rheumatol	**2.60**
Disabil.Rehabil	**1.99**
J.Rehabil.Res.Dev	**1.32**
Acta.Clin.Belg	**0.37**

Australia

Journal	Impact factor
J.Intern.Med	**6.06**
Med.Sci.Sports.Exerc	**4.46**
Transl.Med	**3.99**
Clin.Epidemiol	**2.17**
J.Paediatr.Child.Health	**1.12**

Note: For each country, the first five journals were selected based on a list of the number of publications per journal. The Journals are listed in order of impact factor, not in order of number of publications.

2.2.3 The focus of Australian and international research is mostly similar, but there are some important differences, with international research more likely to have a psychological focus

The current research base internationally is strongest in disease management. Of the international records reviewed, 57 per cent focused on management of the disease while 34 per cent focused on cause and 1 per cent focused on prevention. A very small number of publications address prevention. This is consistent with the Australian landscape.

As in Australia, international clinical trials are primarily focused on management of ME/CFS. Of these trials, 42 per cent consider management from a psychological discipline and 46 per cent from an immunological discipline. The greatest numbers of clinical trials have occurred in the USA and Norway.

In contrast to Australia, international research is more likely to focus on the psychological hypothesis of ME/CFS. This review found 43 per cent of all research records (encompassing publications, grants and clinical trials) were of a psychological basis, as opposed to only 21 per cent of Australian records. Internationally, clinical trials were slightly less likely to have a psychological focus than publications (42 per cent of all clinical trials and 48 per cent of publications could be classified as psychology).

[20] Ibid.
[21] Ibid.
[22] This is based on the 694 peer-reviewed articles web-scraped from the PubMed online research database (see above, Note 13).

A word analysis of international research records identified sleep, cognitive behaviour therapy, quality of life and adolescents as common focus areas (see Figure 8). Of these, sleep and cognitive behaviour therapy are typically associated with a psychological hypothesis. Quality of life implies a focus on research addressing the management of the disease.

Interestingly, despite a relatively even split in clinical trials between psychology and immunology, this did not translate into publications, with only 21 per cent of international publications classed as immunology. This suggests a potential shift in the focus of current research internationally but a time lag that means this research has not yet translated to publications.

Figure 8: Key words for international research records[23]

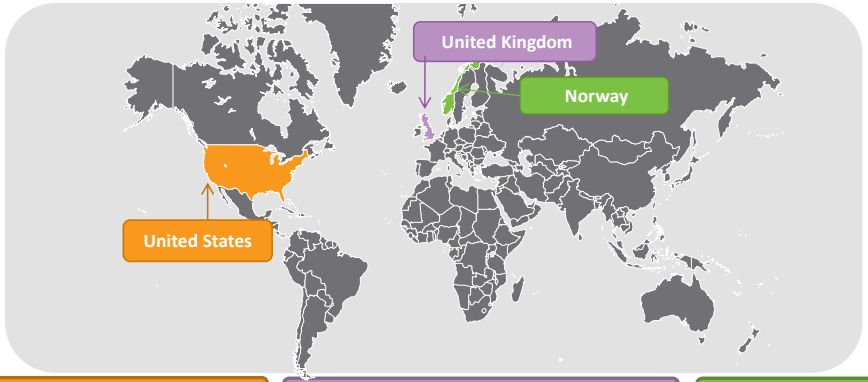
2.2.4 As in Australia, there is a small and dispersed picture of research institutions and key opinion leaders. They are mostly based in the USA, UK and Norway

Like Australia, there are a small number of disparate institutions and key opinion leaders involved in ME/CFS research internationally. They are mostly based in the UK, the USA and to a lesser extent, Norway. A recent report on ME/CFS research funding found that while there are a few key players, ME/CFS funding for the most part is distributed in small grants to multiple different institutions and researchers.[24] Figure 9 outlines the main institutions and researchers that emerged from the stakeholder consultations and document review, including the aforementioned report on CFS/ME research funding.

[23] This is based on international records that were subject to a detailed reviewed. Nous group identified key words for each record reviewed. The size of the word indicates how frequently the word appeared as a key word. This analysis is intended to give a broad impression of the overall research landscape but given the small sample size subject to a detailed review, it cannot be used to accurately identify the proportion of research focused on specific research areas.

[24] Giles Radford and Sonya Chowdhury (2015) *ME/CFS Research Funding: An overview of activity by major institutional funders included on the dimensions database*, UberResearch and Action for M.E., London, https://www.actionforme.org.uk/uploads/pdfs/mecfs-research-funding-report-2016.pdf (accessed 17.10.16)

Figure 9: Key international institutions and individuals[25]



United States

- **Institutions:** US National Institute of Health, University of Miami, Cornell University, Nova Southeastern University
- **Key researchers:** Robert Naviaux (University of California, San Diego), Maureen Hanson and Dikuma Shungu (Cornell University), Daniel Peterson (clinician), Leonard A. Jason (DePaul University), Nancy Klimas and Michael Howard Antoni (University of Miami)

United Kingdom

- **Institutions:** UK CFS/ME Research Collaborative (CMRC), Bristol University, University of Newcastle , Queen Mary University of London
- **Key researchers:** Esther Crawley (Bristol University), Peter White (Queen Mary University of London), Julien Newton (University of Newcastle)

Norway

- **Key institutions:** Haukeland University Hospital in Bergen
- **Key researchers:** Øystein Fluge and Olav Mella (Haukeland University Hospital in Bergen) (Rituximab trials)

2.2.5 Overseas governments are more active in funding ME/CFS research than the Australian government

According to a recent report on ME/CFS research funding, between 2006 and 2015 more than 49 million pounds in research grants was awarded internationally for ME/CFS research. The report found that this figure was significantly lower than funding allocated to comparable illnesses over the same period. 21.1 million pounds was awarded to US-based researchers while 10.2 million pounds was awarded to UK-based researchers.[26]

In the USA, the majority of grants were funded by the National Institute of Health (32 grants in total between 2006 and 2015). In the UK, over half of grants were funded by government institutions. From 2006 to 2011, 20 grants were funded in total in the UK, with 12 grants funded by the Medical Research Council, six by the National Institute of Health Research and one by the Chief Scientist of Scotland.[27] In comparison, the Australian Government has not funded any ME/CFS research over the same period through its main research funding institutions (the NHMRC and ARC). This indicates that:

- UK and US research is of a higher quality than Australian research, as it is able to meet the funding criteria of national research institutions and compete with other research proposals; and/or
- there is more support for ME/CFS research from the US and UK governments than there is from the Australian Government.

[25] The assessment of key researchers was informed by the document review and stakeholder consultations, and so is influenced by the perspectives of those individuals.

[26] Giles Radford and Sonya Chowdhury (2015) *ME/CFS Research Funding: An overview of activity by major institutional funders included on the dimensions database*, UberResearch and Action for M.E., London, https://www.actionforme.org.uk/uploads/pdfs/mecfs-research-funding-report-2016.pdf (accessed 17.10.16)

[27] Ibid.

These two findings were supported in stakeholder interviews.

Other funders of ME/CFS research overseas included universities, independent research institutes, biomedical and biopharmaceutical companies, consumer organisations and charitable foundations and trusts, such as the Wellcome Trust.[28]

2.3 Strengths, gaps and challenges in the current ME/CFS research landscape

In Australia and internationally, there are strengths but also gaps and challenges in the current state, which need to be considered for future investment decisions. Nous identified three overarching strengths, gaps and challenges in the current ME/CFS research landscape:

1. There is a reasonable knowledge of the epidemiology of ME/CFS and pockets of strong research that can be built on.
2. Key gaps relate to the quality, focus and consistency of ME/CFS research.
3. There are also broader ME/CFS gaps and challenges, with a connection to the research state.

These are discussed in turn in the following pages.

2.3.1 There is a reasonable knowledge of the epidemiology of ME/CFS and pockets of strong research that can be built on

Stakeholders suggest that, despite definitional issues, there is a reasonable sense of the prevalence, burden, quality of life impact and functional impact of ME/CFS. However, progress in understanding the epidemiology of the disease has been limited by a lack of a common definition and diagnostic criteria for ME/CFS.

Stakeholders emphasised that there is strong research occurring in ME/CFS. Many of these examples, both in Australia and internationally, have been mapped in Section 2.1. However, in most instances these are small scale research projects, confined to a limited patient cohort, and cross-border recognition has varied. These pockets of strengths do however provide areas and research methodologies on which to build. For the Mason Foundation, this could mean both building on these existing strengths, and encouraging Australian researchers to leverage or collaborate with international areas of strength.

2.3.2 Key gaps relate to the quality, focus and consistency of ME/CFS research

Nous identified four key gaps in current ME/CFS research:

1. The quality and impact of current research is low

The majority of ME/CFS research is not published in high impact journals. There are only four active clinical trials related to ME/CFS in Australia. The NHMRC has not funded any ME/CFS research in the past ten years. This is despite strong advocacy from consumer groups to the Australian Government to increase funding for ME/CFS research (as discussed in Section 2.1.4). The lack of NHMRC funding

[28] Ibid.

indicates that ME/CFS research does not have same standard of research quality and maturity as research in other medical fields. This was acknowledged by most stakeholders, who recognised the competiveness of NHMRC grants. Some stakeholders also indicated that this may reflect broader biases against the scientific credibility of ME/CFS research.

Most stakeholders indicated that research grants currently funded by the Mason Foundation are generally too small to have influence on a global scale. This is a result of small scale funding and the limited potential size of patient cohorts within Australia. Hence, further replication and upscaling of studies is needed to have an impact on patients.

2. There are research gaps in relation to the cause of ME/CFS

The vast majority of research is directed at management and treatment. This is despite an international recognition among researchers that there is a need to better understand the pathophysiology of the illness to order to develop the most impactful management and treatment options.

Stakeholders generally agreed that while some research should continue in the area of disease management, there is a need to significantly increase the proportion of ME/CFS research on understanding the cause and pathophysiology of the disease.

3. Severely ill or bed-bound ME/CFS sufferers are often overlooked in research studies

According to stakeholders, there is only one Australian study currently working with a severe ME/CFS cohort. A major five-year study on the efficacy and safety of cognitive based therapy and graded exercise therapy recently came under heavy criticism after a Freedom of Information request revealed that no severe sufferers were included in the research cohort.[29] Stakeholders reported that this group was often excluded in research studies because they tend to be house-bound and therefore costly and difficult to engage in smaller scale, lower funded research.

4. A lack of consensus regarding research direction and hypothesis is diluting efforts and investment

There is a high divergence of opinion both across and between researchers and consumers. There is agreement among researchers that future research could focus on understanding the pathology of the illness (before understanding the treatment) and consensus on diagnostic criteria. As is the case in Australia (see Section 2.1.2), there is a strong divide internationally between a psychological model and biological model of the disease, with some institutions and consumer groups objecting to research supporting cognitive based therapy and graded exercise therapy (as associated with a historical psychological hypothesis and linked with potentially harmful outcomes for patients).

2.3.3 There are also broader ME/CFS gaps and challenges, with a connection to the research state.

Nous identified three key challenges in current ME/CFS research:

1. It is difficult to attract clinical researchers to the sector

Lack of funding, research prestige and clinical 'controversy'/lack of consensus deter clinical researchers from entering the field. This challenge is also recognised by consumers, who would support efforts to

[29] Rehmeyer, J (2016), 'Bad science misleads millions with chronic fatigue syndrome. Here's how we fought back,' *Stat*, 12 September 2016, https://www.statnews.com/2016/09/21/chronic-fatigue-syndrome-pace-trial/ (accessed 20.10.2016).

encourage others to move into the ME/CFS research field, including research funding for early career researchers.

2. There remains a lack of awareness and understanding of ME/CFS among the medical profession

Medical education is an area of need, with stakeholders citing issues of misdiagnosis and stigma. This was highlighted in relation to Australia, but we suspect it is an issue internationally. Better medical education, leading to more effective and productive interactions at the point of care, would have a considerable direct positive influence on patients.

3. While there are existing collaborations, this remains a much needed area of improvement

Small networks exist, both within Australia and internationally. There are differences of opinion in terms of how effectively grant funding can be used to promote collaboration. There needs to be a clear purpose of and commitment by researchers to collaboration, as funding collaboration for the sake of collaboration will not generate outcomes. Where appropriate, there should also be reciprocal arrangements with international organisations.

3 Opportunities for future ME/CFS investments

The current state mapping and stakeholder consultations undertaken for this project have identified a number of opportunities for the Mason Foundation to re-think current approaches to increase the value and impact of funded research for patients and the ME/CFS sector. These opportunities fall into two categories:

1. Opportunities for the focus of Mason Foundation funding to operate more strategically – ***what*** *is funded.*
2. Opportunities for the Mason Foundation to improve their grants process – ***how*** *the funding process operates*.

This section details the opportunities that have emerged, and Nous' recommended response for the Mason Foundation. **Section 4** then considers prioritisation of these recommendations, and proposes a timeframe for action.

It is important to note that most stakeholders were not opposed to a radical re-orientation of the Mason Foundation's current approach, provided it furthered the aim of positively impacting on individuals suffering from ME/CFS.

3.1 There are opportunities for the focus of Mason Foundation funding to operate more strategically

Current Mason Foundation funding is spread across multiple research areas and hypotheses. In prioritising future investment, the Mason Foundation will need to consider whether it can generate greater impact through a narrower research focus. This may be through identified priority areas or leveraging existing knowledge, or through other means, such as supporting collaboration or building capacity.

3.1.1 More directed funding could support faster progress in identified priority areas

While the Mason Foundation funds grants for proof of concept, innovation and early-career research projects, it does not currently mandate or prioritise specific focus areas of funded research. This approach maximises flexibility in decision making for the foundation and opportunities for researchers. However, it may also have drawbacks. This includes dispersing a relatively small amount of funding across multiple and sometimes conflicting areas, reduced ability to compare research outcomes in a common area, and potentially continuing to fund already proven or disproven hypotheses. Collectively, these factors may result in slower progress than a more directed and consistent approach.

The current state mapping and stakeholder consultations identified four priority areas of research that would benefit from more directed investment:

1. **Understanding the pathophysiology of ME/CFS**

   Mapping of the current ME/CFS research landscape both in Australia and internationally revealed a substantial bias towards research focused on the management and treatment of ME/CFS. As a result, there is considerably less understanding across the sector as to the

underlying cause of the condition. Better understanding of the pathophysiology of ME/CFS was also identified as a key priority by stakeholders.

There was some concern that a focus on research into the cause of ME/CFS was of less direct benefit and positive impact for consumers (as opposed to research focused on treatment, which can more quickly translate into policy and practice change). However there is a more common, contrasting, and in Nous' view, stronger position that identifying and understanding cause is critical to developing the most effective treatments.

2. **Development of a diagnostic test**

   Stakeholders also identified a priority need to develop a diagnostic test for ME/CFS to counter current issues of misdiagnosis and improve the experience of ME/CFS sufferers with the primary healthcare system. This issue was particularly important for consumer groups.

3. **Fund research on misdiagnosis**

   Connected to the above, misdiagnosis and lack of medical practitioner knowledge and understanding of ME/CFS is of particular concern to consumers**.** The Mason Foundation could specifically fund research to better understand the state of medical knowledge about ME/CFS and factors behind current misdiagnosis. This would support the design of specific education interventions to resolve the problems identified.

4. **Inclusion of patients with severe ME/CFS in research and trials**

   There is a current gap in research either specifically addressing, or including, patients with severe ME/CFS. Many of these patients are typically bed-ridden and so are often unavailable to participate in research trials undertaken in health services. Small-scale projects often lack the resource budget for home visits. There is an opportunity to make specific or additional funds available for projects to cater for inclusion of patients with severe ME/CFS in research and trials.

	Recommendation

1.a.	**The Mason Foundation/Equity Trustees should consider the following focus areas for future investments in ME/CFS research:**
	◦ Directing grant funding to current gaps in ME/CFS research, in particular:
	  ◦ understanding the pathology of the illness
	  ◦ developing a diagnostic test for patients
	  ◦ research aimed at improving how health professionals currently diagnose and manage ME/CFS
	  ◦ research that includes patients with severe ME/CFS.

3.1.2 The Mason Foundation could play a more active role in supporting capability building and international collaboration

There are three distinct opportunities for the Mason Foundation to support capacity building and research collaborations:

- Encouraging and supporting individual researchers and growing the field.
- Directly supporting collaborative efforts – both in Australia and internationally.
- Developing a shared resource that builds the capacity of the sector overall.

Each is discussed in turn.

3.1.2.1 The Mason Foundation could build sector capability through targeted support and development of new researchers

Nous' current state mapping and stakeholder consultations confirmed that the current ME/CFS landscape, particularly in Australia, is small, and it is difficult to encourage new players to the field. Particular challenges for ME/CFS researchers include stigma attached to the condition, a lack of prestige attached to researching it, division within the existing research sector, and the lack of NHMRC grant funding (based on stakeholder consultations and the document review). One option for the Mason Foundation is to dedicate a certain amount of funding to supporting PhD and post-doctoral researchers, to encourage new entrants into the sector. This could be administered as part of the Mason Foundation's existing "Early Career Researcher" grants category and support both young and emerging researchers, and researchers entering from other fields.

	Recommendation
1.b.	**The Mason Foundation/Equity Trustees should consider the following focus areas for future investments in ME/CFS research:** • Supporting PhD and post-doctoral researchers, to encourage new entrants into the sector.

3.1.2.2 The Mason Foundation could more directly support collaborative efforts – both in Australia and internationally

The benefits of collaborative research are undisputed. Collaboration provides both the opportunity for multi-disciplinary work, exposure to new ideas and thinking, potentially for larger scale research, and also opportunities for efficiency and resource sharing in a cost-constrained environment. This is particularly important in a small and underfunded field such as ME/CFS.

Two opportunities for supporting collaboration were identified:

1. **Fund establishment of (or support continuation of an existing) international collaborative network, and support Australian researchers to be involved in international networks**. All stakeholders consulted agreed there would be benefits in increased collaboration, particularly internationally. They did however caution against funding collaboration for the sake of collaboration, or forcing collaborative efforts without the buy-in of the researchers involved.
2. **Contribute to large-scale, multi-country research projects**. One of the key challenges identified with current Australian ME/CFS research is that research is currently operating on a small scale, both due to funding and also restricted sample sizes of patients. Supporting Australian researchers to participate in large-scale, multi-country research would lead to more impactful research outcomes. This support could be provided in conjunction with other international funders. For instance, the Mason Foundation could explore agreements where contributed funding is matched by international funders (noting that this project has not tested the international appetite for such a co-funding arrangement).

It is noted that establishment of a biobank as discussed in section 3.1.2.2 below, would also have the potential benefit of supporting international collaboration through mutual access to international biobanks and potential for larger scale international research projects.

	Recommendation
1.c.	**The Mason Foundation/Equity Trustees should consider the following focus areas for future investments in ME/CFS research:** • Supporting research collaborations between international and Australia-based researchers, including large-scale multi-country projects.

	Recommendation
2.	**Based on the consideration of the focus areas for future investment (recommendation 1), the Mason Foundation/Equity Trustees should identify specific areas for research investment for the 2017 grant round.**

3.1.2.3 Development of a shared resource could build capability at a sector level

There is an opportunity for the Mason Foundation to explore establishment of a ME/CFS biobank and shared information resource in Australia. This could be an open resource to boost capability at a sector level and be accessible for all researchers (public and private) in the sector, assuming baseline eligibility criteria were met.

This is a more ambitious option, and would not necessarily be something that the Mason Foundation set up alone. There would also be the opportunity to explore development in collaboration with an existing international biobank (for example, operate as the Australian post of an established bank).

The potential benefits of such an approach include:

- development of an underpinning / foundational resource that benefits all researchers in the ME/CFS sector
- enabling researchers to access a larger amount of specimens – increasing ability for larger scale research projects at lower cost
- use of specimens with a common case definition would promote transferability of research findings
- potential to encourage other field researchers to bring skills to ME/CFS research sector
- opportunity for collaboration with international researchers who may wish to access the biobank
- opportunity for collaboration with international biobanks to increase access to specimens and resources for Australian researchers.

There are also a number of areas that would require further consideration:

- Establishment of a biobank would require a substantial proportion of the Mason Foundation's annual funding quota. The risks of re-directing this funding (particularly in the context of a small research community where the Mason Foundation is the primary funder) would need to be carefully considered.
- Many ME/CFS patients are strongly opposed to any research involving cognitive based therapy or graded exercise therapy – therefore they may be opposed to providing a sample if they think it could be used for this purpose.
- There would be a need to agree on a common case definition for specimen inclusion (i.e. the Canadian Consensus criteria or Fukuda criteria).
- There would need to be rigorous protocols in place for collection, transport and storage of samples, and a thorough consideration of ethical issues.
- There is a strong divide in research priorities among Australian researchers and they may be unwilling to work with each other and share resources in this way.
- There would be a need for ongoing commitment or a transition plan to ensure the resource is sustainable.

The UK ME/CFS Biobank provides a useful case study and lessons learnt (see Figure 10).

Figure 10: Case study: The UK ME/CFS Biobank[30]

What is it	The UK ME/CFS Biobank functions as an open resource for clinical and biomedical research into ME/CFS, and in particular for research leading to the discovery of biomarkers for the diagnosis, prognosis, and stratification (sub-grouping) of cases. It currently stores samples from over 500 donors. It promotes transparent, multidisciplinary research informed by and for the benefit of people with ME/CFS.
Mission	The UK ME/CFS Biobank mission is to "conduct high quality, ethical investigations into ME/CFS and to create an open biobank resource enabling translational research for the clinical and biomedical understanding of the illness, fostering cooperation and collaboration between researchers and thereby enhancing the opportunity for breakthrough discoveries."
Establishment	The UK ME/CFS Biobank was launched in August 2011. The project is led and managed by CureME at the London School of Hygiene & Tropical Medicine, and it was officially made available to external researchers on 12 May, 2016. The project was initially funded by Action for ME, the ME Association, ME Research UK and considerable private donations. It is currently operating with funding from the US National Institutes of Health.
Priority research areas	All research proposals intending to use samples from the UK ME/CFS Biobank must be developed in line with the Biobank's mission and will the following focus areas are prioritised: • testing or generating new hypotheses on the mechanisms (pathophysiology) of ME/CFS; • improving diagnosis (biomarkers) and phenotyping; and/or • basic science, e.g. pharmacological in vitro studies potentially leading to clinical trials on therapeutic approaches.
Case definition	For inclusion in Biobank research there must be compliance with the Canadian Consensus Criteria or CDC '94 (Fukuda) criteria.
Access to samples	The CURE-ME team at the London School of Hygiene & Tropical Medicine use some of the samples for their funded research. Additionally, there is a peer review process for applications from external researchers for use of samples. Researchers must have a proven track record, be at an established institution and present a sound scientific rationale for the proposed study. The Biobank was only made available to external researchers in May 2016.
Involvement of consumers / patients	A principle of the Biobank is participatory research, so people with ME/CFS and their representatives are involved in setting the research agenda through consultation and discussions.

Interestingly, a key future priority for the UK ME/CFS biobank is "establishing an international network of biobanks with consistent procedures so that researchers have access to different cohorts and we use our limited resources as effectively and efficiently as possible."[31] This could be a good opportunity for the Mason Foundation to explore further, and leverage the process and administrative work already done in the UK.

There are also a number of lessons learnt from biobanks in other fields, and resources available to guide establishment of 'best-practice' biobanks.[32]

[30] CureMe (2016)"About Us," London School of Hygeine and Tropical Medicine, http://cureme.lshtm.ac.uk/about-us/ (accessed 25.10.16).
[31] Ibid.
[32] For example, the WA Department of Health has published Guidelines for human biobanks, genetic research databases and associated data:

	Recommendation

3.	**The Mason Foundation/Equity Trustees should investigate the opportunity to develop a biobank of shared resources for ME/CFS researchers.**
	This could involve the following steps:
	• Set up a meeting between key researchers to discuss the feasibility of establishing a biobank, including:
	  ◦ whether the Mason Foundation should support the establishment of a new biobank or collaboration with an existing international biobank (for example, by establishing an Australian outpost to an international bank)
	  ◦ the shared information resources that would be included in the biobank and potential benefits to ME/CFS research
	  ◦ the resources (money and personnel) required to establish a biobank
	  ◦ implementation risks
	  ◦ the governance arrangements for the biobank.
	• Conduct desktop research on the establishment and functioning of biobanks in ME/CFS and other medical fields.
	• Determine the best approach for the Mason Foundation to fund the biobank, including possible co-funding or partnership arrangements with research institutions or international biobanks.

	Recommendation
4.	**The Mason Foundation/Equity Trustees should consider investing in the establishment of a biobank of shared resources for ME/CFS research** (based on the investigation conducted under recommendation 2).

3.2 This project identified a range of opportunities for the Mason Foundation to improve their grants process

Stakeholder consultations identified a range of opportunities to enhance the value of the current grants process, and to ensure future investment decisions maximise positive impact, including:

- use of eligibility criteria as a lever to promote collaboration
- increase in value through a focused process to build on the established evidence base
- a more consistent case definition to increase applicability of research findings
- the need for a more holistic approach to understanding research quality and impact
- introduction of core criteria into the application process to improve quality of applications
- introduction of desired criteria into the application process to encourage broader benefits of research
- broader use of funding to support education and awareness raising indicatives.

http://ww2.health.wa.gov.au/~/media/Files/Corporate/general%20documents/Population%20Health%20Genomics/OPHG_guidelines_for_human_biobanks.ashx

3.2.1 Eligibility criteria could be considered as a lever to promote collaboration

Current eligibility for Mason Foundation grants is limited to Australian researchers. Given the challenges in securing quality research proposals, and the benefits associated with international collaboration, it would be useful for the Mason Foundation to consider whether international researchers that partner with Australian researchers are eligible. Any decision on this criterion needs to be communicated clearly and early to potential applicants to ensure they have time to investigate opportunities for meaningful collaboration with international partners, and likewise for international partners to approach Australian researchers.

	Recommendation
5.	**The Mason Foundation/Equity Trustees should identify who is eligible to apply for funding on the 2017 grant round, including whether international researchers that partner with Australian researchers are eligible.**

3.2.2 There is opportunity to increase value through a focused process to build on the established evidence base

There is a need to balance support for new and established research hypotheses. This is relevant to all areas of ME/CFS research, including the priority areas identified above in Section 3.2.1. Continued small scale investment in completely new areas of research will have variable success on an individual project level, and the collective impact and influence of successful research will be limited by scale and dispersion of efforts.

It follows that it could be more influential for the Mason Foundation to direct a greater proportion of funding to proposals that build on and leverage the existing evidence base, and hence are more likely to translate into policy and practice change in the short-term. This could be by way of a formula or ratio to balance research investment between new ideas, and building on established work.

	Recommendation
6.	**The Mason Foundation/Equity Trustees should support new and existing research and allocate a specific proportion of funding to each (e.g. 40 per cent to new research and 60 per cent to existing research).**

3.2.3 A more consistent case definition would increase applicability of research findings

One of the barriers to impact of ME/CFS research is the fact that there is no single universally agreed case definition. This limits the applicably of research outcomes. While this is an international challenge, the problem would be assisted at least in Australia if the Mason Foundation required a more consistent use of case definitions for ME/CFS across its funded research.

It will be difficult for the Mason Foundation to determine and dictate use of only one definition (this has not been achieved by the international research community) however it may be possible to limit to two. The key Australian researchers are divided between the Canadian Consensus Criteria and Fukuda criteria. The UK ME/CFS biobank similarly accepts specimens and research proposals that comply with either the Canadian Consensus Criteria or Fukuda criteria. As such it would appear feasible for the

Mason Foundation to consider limiting funding to researchers who propose to use one of the Canadian Consensus Criteria or Fukuda criteria.

	Recommendation
7.	**The Mason Foundation/Equity Trustees should consider requiring applicants to use only the Canadian Consensus Criteria or Fukuda criteria in funded research.**

3.2.4 There is need for a more holistic approach to understanding research quality and impact

Developing more effective and holistic approaches to measuring research impact is a topical issue of interest and investigation within the literature and by universities and major research funders in Australia (including the NHMRC) and internationally. The Mason Foundation can leverage this existing work in considering its own processes and the role of demonstrating impact in funding applications and awards.

Nous has conducted a scan of relevant literature and approaches taken by major institutions. The key findings are as follows:

- **There is strong consensus that measuring research impact needs to go beyond the traditional 'academic metrics'**

  Altmetrics, or alternative metrics, are new measures that take into account online reader behaviour, network interactions with content, and social media (i.e. the number of times a paper has been tweeted, 'liked' on Facebook, covered by the media or blogs, downloaded, cited on Wikipedia or bookmarked online). Altmetrics offer researchers a way to showcase the impact of papers that have not yet gathered many citations, and to demonstrate public engagement.[33] There are a series of purchasable tools available that measure both traditional metrics and altmetrics (for example Altmetric[34] and Impact Story[35]). These tools are targeted both at researchers seeking to demonstrate impact, and funders seeking to understand how funded research has been received, disseminated and where it is having an influence.

- **Quantitative metrics are relevant to understanding quality, but should not be the sole influencer in funding decisions**

  Quantitative metrics (both traditional academic and altmetrics) are attractive in assessing research impact as they provide a clear measure that can be consistently interpreted, and data can be easily aggregated and analysed. However it is increasingly recognised that these metrics do not pick up the translational and broader health, societal and economic impacts of research, and hence should not be unduly emphasised in funding decisions.[36]

[33] Kwok, R. (2013) Research impact: Altmetrics make their mark, *Nature, 500,* 491-493, http://www.nature.com/naturejobs/science/articles/10.1038/nj7463-491a (accessed 24.09.2016).

[34] Altmetric (2016) 'Who's talking about your research,' https://www.altmetric.com/ (accessed 24.09.2016).

[35] Impactstory (2016) 'Discover the online impact of your research,' www.impactstory.org (accessed 24.09.2016).

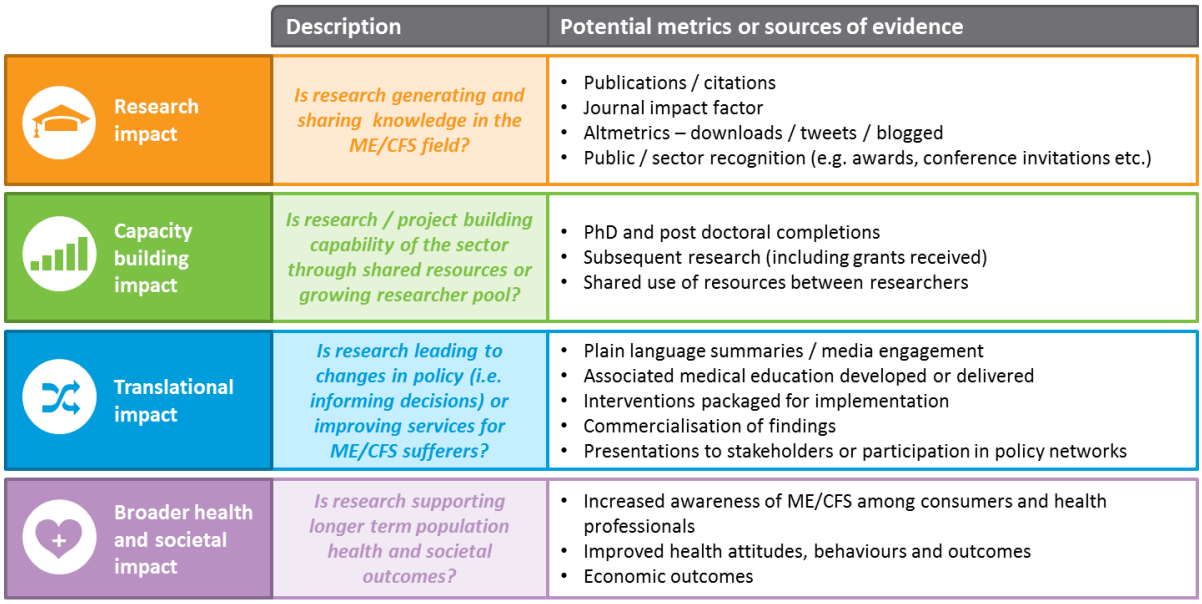
[36] NMHRC endorses the Declaration of Research Assessment, which provides that organisations should not use journal-based metrics, such as Journal Impact Factors, as a surrogate measure of the quality of individual research articles, to assess an individual scientist's contributions, or in hiring, or funding.

- **A holistic framework for measuring impact could be used to inform the Mason Foundation's grants review and funding process**

  There are a series of frameworks for measuring impact emerging in the literature that the Mason Foundation can draw on when exploring opportunities to improve its grants process. These frameworks are expressed in different ways but contain similar core components. Figure 11 illustrates a proposed framework for assessing research quality and impact. This framework could be used both to inform funding decisions (i.e. to demonstrate previous achievements and understand potential research impact) and to track the actual influence of Mason Foundation funded research post-publication to better understand value for investment.

  The Mason Foundation will need to further investigate the feasibility of tracking influence of funded research. In the first instance this may require a minimum investment in a citation or alternative metric tracking product. Understanding translation would be a more involved process. It would be sensible to further explore what approaches or products currently funded researchers are using to understand the influence and impact of their publications. It may not be necessary for the Mason Foundation to invest in additional processes, instead it may be more feasible to work with funded researchers to gather this information or require post publication information as a condition of funding.

Figure 11: Framework for assessing quality and impact[37]



[37] Adapted from: Cohen G, et al. Does health intervention research have real world policy and practice impacts: testing a new impact assessment tool. *Health Research Policy and Systems* (2015) **13**:3. Available online at: http://health-policy-systems.biomedcentral.com/articles/10.1186/1478-4505-13-3 (accessed 24.09.16); Buykx , P. et al, 'Making evidence count': A framework to monitor the impact of health services research. *Aust. J. Rural Health* (2012) 20, 51–58; Banzi, R. et al, Conceptual frameworks and empirical approaches used to assess the impact of health research: an overview of reviews, *Health Research Policy and Systems* (2011), 9:26. Available online at: http://www.health-policy-systems.com/content/9/1/26 (accessed 24.09.16).

	Recommendation
8.	**The Mason Foundation/Equity Trustees should consider use and communication of a research quality and impact framework to help applicants demonstrate impact of past research and potential value of proposals, and to track (subject to feasibility) the impact and influence of funded research.**

3.2.5 Core criteria could be introduced to improve quality of applications

Three factors were identified as core requirements to improve the quality of research proposals received by the Mason Foundation, and hence improve the quality and impact of funded research:

1. **There is a need to ensure scientific credibility:** Research funding could be prioritised by focusing on scientific credibility, encompassing a strong hypothesis, an endorsed methodology and a clear publication plan.
2. **Research needs to be more sophisticated in demonstrating impact:** Funded researchers could better demonstrate evidence of impact of previous research, or impact of the proposed methodology in other locations or similar fields. Section 3.2.4 above discusses the need for a holistic understanding and assessment of research impact and proposes a potential impact assessment framework for the Mason Foundation's use going forward. There would also be benefit in more robust tracking of Mason Foundation funded research impact and influence post publication.
3. **Translation:** Research proposals could more clearly identify how the research will be translated into clinical practice, policy, public education or further research. This could include incorporating or identifying opportunities for sharing and educating the medical profession on findings (e.g. presentations at conferences and seminars, training or online learning modules or apps). Funded research could also include a proposed plan for public awareness raising and educational activities. Demonstrating translational impact is also a component of the proposed potential impact assessment framework outlined in Section 3.2.4.

	Recommendation
9.	**The Mason Foundation/Equity Trustees should consider the following <u>core</u> criteria for the 2017 grant round:** • **Scientific credibility:** the proposal includes a strong hypothesis, endorsed methodology and publication plan. • **Demonstrates impact:** the proposal identifies evidence that the research is likely to have a positive impact on ME/CFS sufferers. • **Translation:** the proposal identifies how the research will be translated into clinical practice, policy, public education or further research.

3.2.6 Desirable criteria could be introduced to promote broader benefits and influence of research

In addition to the core criteria above, there are two other areas in which the Mason Foundation grants process could be improved to better promote broader benefits of research, and increase the likelihood that funded research will influence the national and international landscape. These are:

1. **Capacity building**: Funded research could be required to demonstrate a capacity building element, in terms of supporting early career researchers, scholarships or attracting new clinical researchers to the field. This would positively impact on the sector by growing and diversifying the pool of ME/CFS researchers in Australia.
2. **Collaboration:** Stakeholders agreed that that effective and valuable collaboration occurs through joint working on specific research projects. The Mason Foundation can support this type of collaboration through encouraging and rewarding research proposals that involve meaningful collaboration between researchers within Australia or internationally.

While clearly beneficial, it is not always relevant or practical to require evidence of capacity building or collaboration on every research project. As such, it is more appropriate for these to be considered desirable rather than necessary or core criteria for Mason Foundation grant funding.

	Recommendation
10.	**The Mason Foundation/Equity Trustees should consider the following desirable criteria for the 2017 grant round:** • **Capacity building**: the proposal has a capacity building element, such as supporting early career researchers, scholarships or attracting new clinical researchers to the field. • **Collaboration**: the proposal involves meaningful collaboration between researchers within Australia or internationally.

3.3 An additional option is to support ME/CFS awareness raising, although this may be outside the scope of funded research

Nous identified the need to improve awareness and understanding of ME/CFS among patients, health professionals, researchers and the general public. Stakeholder consultations and the document review indicate there continues to be misconceptions of the epidemiology of the illness. There also appear to be misconceptions and/or a low understanding of the nature, rationale and quality of research on ME/CFS.

While outside the scope of funded research, the Mason Foundation could explore opportunities to support education and awareness raising. This could be for a range of cohorts, including patients, health professionals, researchers and/or the general public. This education could play an important role in improving the overall understanding of the common research findings, and address some key issues for research studies, such as poor quality caused by inconsistent case definitions and recruitment.

	Recommendation
11.	**In addition to the recommendations listed above, the Mason Foundation/Equity trustees may wish to consider supporting public education and awareness raising initiatives for patients, doctors and researchers.** However, the Mason Foundation/Equity Trustees would need to consider whether these initiatives are within the scope of the terms of trust.

4 Summary of recommendations

This section summarises the recommendations identified and discussed in Section 3 above and provides a proposed order and timeframe for implementation (see further Figure 12).

In addition, we recommend that the Mason Foundation and Medical Advisory Panel should consider the findings of this report in their assessment of applications under the 2016 grant round. In particular, they should consider opportunities for funding projects that include a focus on:

- understanding the pathophysiology and cause of ME/CFS;
- developing a diagnostic test for ME/CFS;
- improving capacity among medical professionals to diagnose and treat ME/CFS; and/or
- meaningful collaboration with other Australian or international researchers.

The Mason Foundation and Medical Advisory Panel should also consider the proposed quality and impact assessment framework in considering proposals, to determine if this will be a useful tool in the future.

We note that while we recommend the Mason Foundation and Medical Advisory Panel consider the findings of this report in their review process, these focus areas and process opportunities were not communicated to applicants during the submission process, so cannot act as a substitute for or overwhelmingly influence the current grants funding process.

Figure 12: Summary of recommendations

No.	Recommendation	Timeframe
Recommendations on focus areas for research investment		
1.	**The Mason Foundation/Equity Trustees should consider the following focus areas for future investments in ME/CFS research:** 1.a. Directing grant funding to current gaps in ME/CFS research, in particular: ◦ understanding the pathology of the illness ◦ developing a diagnostic test for patients ◦ research aimed at improving how health professionals currently diagnose and manage ME/CFS ◦ research that includes patients with severe ME/CFS. 1.b. Supporting PhD and post-doctoral researchers, to encourage new entrants into the sector. 1.c. Supporting research collaborations between international and Australia-based researchers, including large-scale multi-country projects.	Dec 2016 – Feb 2017
2.	**Based on the consideration of the focus areas for future investment (recommendation 1), the Mason Foundation/Equity Trustees should identify specific areas for research investment for the 2017 grant round.**	Feb – March 2017

No.	Recommendation	Timeframe

3.	**The Mason Foundation/Equity Trustees should investigate the opportunity to develop a biobank of shared resources for ME/CFS researchers.**
	This could involve the following steps:
	• Set up a meeting between key researchers to discuss the feasibility of establishing a biobank, including:
	  ◦ whether the Mason Foundation should support the establishment of a new biobank or collaboration with an existing international biobank (for example, by establish an Australian outpost to an international bank)
	  ◦ the shared information resources that would be included in the biobank and potential benefits to ME/CFS research
	  ◦ the resources (money and personnel) required to establish a biobank
	  ◦ implementation risks
	  ◦ the governance arrangements for the biobank.
	• Conduct desktop research on the establishment and functioning of biobanks in ME/CFS and other medical fields.
	• Determine the best approach for the Mason Foundation to fund the biobank, including possible co-funding or partnership arrangements with research institutions or international biobanks.
		July – Sept 2017

4.	**The Mason Foundation/Equity Trustees should consider investing in the establishment of a biobank of shared resources for ME/CFS research** (based on the investigation conducted under recommendation 2).	Oct - Dec 2017
Recommendations to improve the grant process		
5.	**The Mason Foundation/Equity Trustees should identify who is eligible to apply for funding on the 2017 grant round, including whether international researchers that partner with Australian researchers are eligible.**	March - June 2017
6.	**The Mason Foundation/Equity Trustees should support new and existing research and allocate a specific proportion of funding to each (e.g. 40 per cent to new research and 60 per cent to existing research).**	March - June 2017
7.	**The Mason Foundation/Equity Trustees should consider requiring applicants to use only the Canadian Consensus Criteria or Fukuda criteria in funded research.**	March - June 2017
8.	**The Mason Foundation/Equity Trustees should consider use and communication of a research quality and impact framework to help applicants demonstrate impact of past research and potential value of proposals, and to track (subject to feasibility) the impact and influence of funded research.**	March - June 2017

No.	Recommendation	Timeframe
9.	**The Mason Foundation/Equity Trustees should consider the following <u>core</u> criteria for the 2017 grant round:** • **Scientific credibility:** the proposal includes a strong hypothesis, endorsed methodology and publication plan. • **Demonstrates impact**: the proposal identifies evidence that the research is likely to have a positive impact on ME/CFS sufferers. • **Translation:** the proposal identifies how the research will be translated into clinical practice, policy, public education or further research.	March - June 2017
10.	**The Mason Foundation/Equity Trustees should consider the following <u>desirable</u> criteria for the 2017 grant round:** • **Capacity building**: the proposal has a capacity building element, such as supporting early career researchers, scholarships or attracting new clinical researchers to the field. • **Collaboration:** the proposal involves meaningful collaboration between researchers within Australia or internationally.	March - June 2017
Additional options		
11.	**In addition to the recommendations listed above, the Mason Foundation/Equity trustees may wish to consider supporting public education and awareness raising initiatives for patients, doctors and researchers.** However, the Mason Foundation/Equity Trustees would need to consider whether these initiatives are within the scope of the terms of trust.	Jan – Dec 2017

Appendix A Methodology

Nous conducted the project between September and November 2016. There were four main elements of the project:

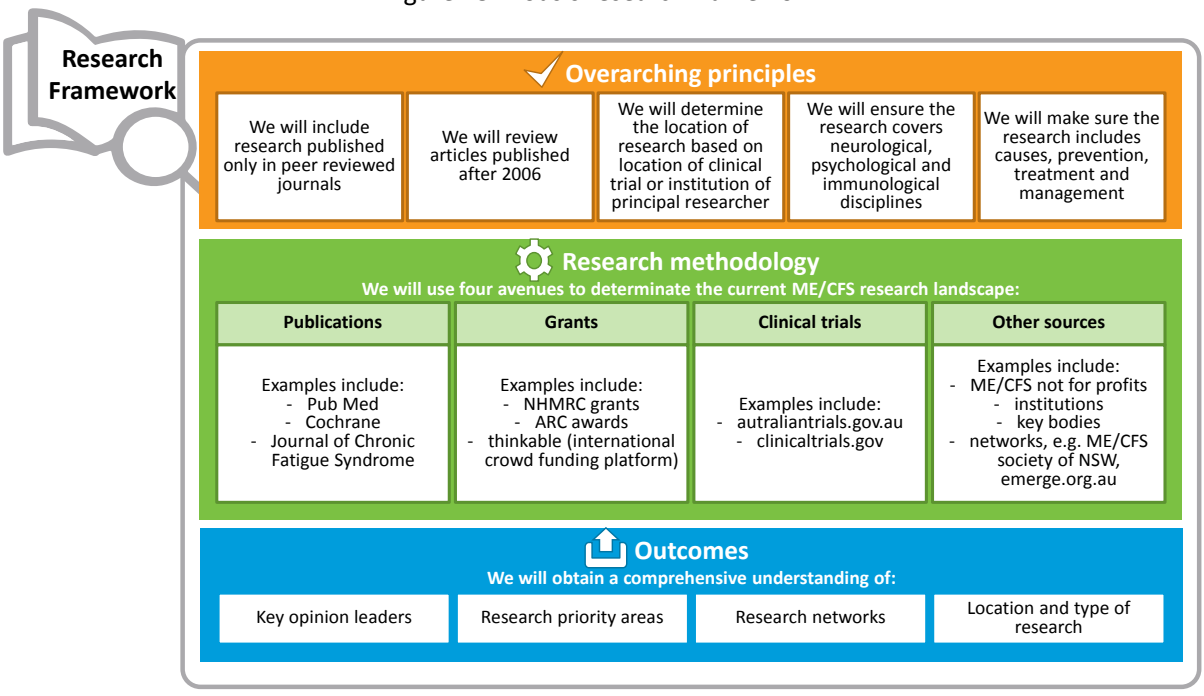
1. Research framework
2. Key lines of enquiry
3. Document review and electronic data scraping
4. Limited stakeholder consultations

Each of these is discussed in turn. Limitations in the methodology and analysis are discussed at the end of this Appendix.

A.1 Research framework

Nous developed a research framework to guide the review and identify the scope of research (see Figure 13). The framework included overarching principles for conducting desktop research, a high level research methodology and expected outcomes from the review.

Figure 13: Nous's research framework



A.2 Key lines of enquiry

Nous identified overarching research questions and six key lines of enquiry for the review (see Table 6). The key lines of enquiry informed the document review, electronic data scraping and stakeholder consultations. They guided the analysis of qualitative and quantitative data as well as the synthesis of key findings.

Table 6: Key lines of enquiry

Research question	Key lines of enquiry
What is the current research landscape for ME/CFS in Australia and overseas? **Given the current landscape, in what areas of ME/CFS research should the Mason Foundation invest in to maximise positive impact for ME/CFS patients?**	1. What is the current state of ME/CFS research in Australia?
	2. What is the current state of ME/CFS research internationally?
	3. How does the Mason Foundation currently allocate grants?
	4. What are the opportunities for ME/CFS research that maximises potential for positive impact?
	5. What criteria can the Mason Foundation use to make investment decisions?
	6. How can the findings from this project inform the future redesign of the grants process?

A.3 Document review and electronic data scraping

Nous conducted two separate processes to collect information on ME/CFS research: a document review and electronic data scraping. These are described below. Nous triangulated information from these processes with information from the stakeholder consultations to ascertain the current ME/CFS research landscape in Australia and internationally.

Document review

The purpose of the desktop review was to generate an understanding of the current research state, in terms of volume and type of research, and the key players involved. We applied the following criteria to research databases to search for records to review.

Search criteria:
Search terms: "chronic fatigue syndrome" or "myalgic encephalomyelitis" in the title
Search dates: 2006 – 2016 (including current research and clinical trials)
Search refinements: peer-reviewed publications only (this was applied to research publications only)

We also reviewed records provided by the Mason Foundation (namely successful Mason Foundation grant applications), identified by stakeholders and found through web searches.

Nous reviewed 134 records in total. Table 7 outlines the number of records reviewed and the approach used to select records to review.

Table 7: ME/CFS research records reviewed

Category	Approach	Number of records reviewed
Publications	• Reviewed all articles found on the EBSCO database using the above search criteria • Reviewed key research reviews • Reviewed a random selection of articles from the *Journal of Chronic Fatigue Research*	**84**
Grants	• Reviewed all successful Mason Foundation grants for 2015 • Searched the ARC and NHMRC websites but found no records • Conducted general research on international grant funding	**13** (includes an article that analysed 99 ME/CFS research grants)
Clinical trials	• Reviewed all active and completed trials registered on the clinicaltrials.gov and australiantrials.gov.au websites • Reviewed all active and completed trials registered with the ANZCTR	**30**
Other sources	• Reviewed key consumer websites in Australia and internationally • Conducted general research on ME/CFS as well as research quality and impact	**7**

For each record, Nous recorded key information based on the research framework. This included:

- location of research
- key researchers and institutions
- research focus (cause, management/treatment or prevention)
- therapeutic area (immunology, neurology or psychology)
- key words (where the record had no key words in the abstract, Nous identified a list of key words from the record).

Electronic data scraping

Nous used R Software to electronically scrape information on publications on ME/CFS from the PubMed database. Nous scraped information from 694 peer-reviewed articles published over the past five years between 2011 and 2016. This included the article title, date, authors and country.

Nous used this information to develop visual maps of the volume and location of ME/CFS research across the world using Tableau software.

A.4 Limited stakeholder interviews

Nous conducted four interviews with seven stakeholders in Australia. The Mason Foundation selected the list of stakeholders to be interviewed. They included researchers from two Australian universities and three consumer representatives.

The interview questions focused on the current state of ME/CFS research in Australia and overseas, and opportunities for future ME/CFS research in Australia. The interviews generated important qualitative information to inform our understanding of the ME/CFS research landscape and priority areas for future research investments.

Methodology limitations

There were four key limitations in the methodology and subsequent analysis:

1. **The level of detail and insight generated through the desktop review was limited to what could be gleaned through quantitative analysis.** This is particularly relevant when considering the quality and impact of research, and how Australia compares internationally. The desktop review generated useful information to inform the process for allocating future research investments, but could not subjectively identify or assess which opportunities are best suited to the Mason Foundation.
2. **There were limitations with the quantitative analysis.** Not all research records clearly or consistently identify research focus areas or therapeutic areas. Many research records also combined focus areas and/or therapeutic areas. Mapping of the current state of research was limited to common 'subject area' headings.
3. **Only a small and select group of stakeholders were interviewed.** This was due to the limited scope and size of the review. Insights from these stakeholder consultations were based on a limited number of views and should be further explored with a wider group of stakeholders in order to be validated.
4. **The electronic data scraping collected information on around half of all the records available on PubMed under the search criteria**. This was due to incomplete information in the PubMed records and limitations in the code used to scrape the data. However, Nous is confident that a large enough selection of articles was selected across years and locations to provide a good indication of the distribution of ME/CFS research internationally.