Defining future ME/CFS research

2022

The ME/CFS Priority Setting Partnership

The Top 10+ ME/CFS research priorities

Priority 1	What is the biological mechanism that causes post-exertional malaise (symptoms caused or made worse by physical, mental or emotional effort, which can be delayed) in people with ME/CFS? How is this best treated and managed?
Priority 2	Which existing drugs used to treat other conditions might be useful for treating ME/CFS, such as low dose naltrexone, or drugs used to treat Postural Orthostatic Tachycardia Syndrome (POTS)?
Priority 3	How can an accurate and reliable diagnostic test be developed for ME/CFS?
Priority 4	Is ME/CFS caused by a faulty immune system? Is ME/CFS an autoimmune condition?
Priority 5	Are there different types of ME/CFS linked to different causes and how severe it becomes? Do different types of ME/CFS need different treatments or have different chances of recovery?
Priority 6	Why do some people develop ME/CFS following an infection? Is there a link with long-COVID?
Priority 7	What causes the central and peripheral nervous systems (brain, spinal cord and nerves in the body) to malfunction in people with ME/CFS? Could this understanding lead to new treatments?
Priority 8	Is there a genetic link to ME/CFS? If yes, how does this affect the risk of ME/CFS in families? Could this lead to new treatments?
Priority 9	What causes ME/CFS to become severe?
Priority 10	How are mitochondria, responsible for the body's energy production, affected in ME/CFS? Could this understanding lead to new treatments?
Priority 10+	Does poor delivery or use of oxygen within the body cause ME/CFS symptoms? If so, how is this best treated?

"Now that we have the Top 10+, researchers, funders and government must work with people with ME/CFS to produce the highest quality research into these areas, and continue to prioritise ME"

- Gemma Hoyes, steering group member

This process was led entirely by people with ME/CFS, carers and health and care professionals, keeping the best interests of our community as our driving principle throughout.

Thank you to the thousands of people in the ME/CFS community who participated - ensuring the success of this project and making it one of the most highly engaged-in Priority Setting Partnerships ever.

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Funding for this project was awarded to Action for M.E. who worked with the James Lind Alliance to facilitate the steering group in leading the process.

With thanks to our funders:

The Rt Hon Sajid Javid MP

Secretary of State for Health and Social Care

I welcome the publication of this Priority Setting Partnership which sets out the Top 10+ research priorities for ME/CFS. The Government recognises that myalgic encephalomyelitis (ME) is an under-researched area and pledges to support research funders and the academic community to respond to this independent report.

I would like to thank Action for M.E. and all the people who took part in this important work, recognising that for many this would have taken considerable effort and mental and physical reserve, which came at a cost. It is so important that the voice of those with lived experience of ME, and those that represent them, is at the heart of all future work to improve the lives of people living with this debilitating illness.

Foreword

This report provides a powerful and unique opportunity for the voices and lived experiences of children and adults with ME to be heard, having been empowered to set priorities for ME research themselves.

For too long, people with ME have struggled to get their condition diagnosed, understood and acknowledged. With so many misconceptions and with a lack of societal understanding, including within educational settings, workplaces and even among health professionals, the case for change is clear.

ME affects an estimated 250,000 people in the UK and up to 30 million people worldwide. It is a long-term fluctuating neurological condition affecting many body systems, most commonly the nervous and immune systems and can be highly disabling. Myalgic encephalomyelitis is estimated to cost the UK over £6 billion a year. Yet, at present, there is no definitive diagnostic test, no universally effective treatment and no known cure.

Action for M.E. was funded to lead the ME/CFS Priority Setting Partnership (PSP) but in reality, our role was facilitative. For two years, we worked with a seed group of ME charity representatives and the Patient Advisory Group to the UK ME Research Collaborative in readiness to launch a PSP placing people with lived experience at the very core. And the result was that people with ME, their carers, and family members have been at the heart of this PSP throughout, leading it at every level and working collaboratively with clinicians. The commitment from our steering group members has been humbling, with many choosing to use very limited energy to help ensure that the process has been as inclusive as possible; their experiences and insight have shaped every part of this PSP.

We now have our Top 10+ priorities, but this is just a start. It is essential that we work together with researchers, institutions, funders and policy/decision-makers to form programmes of research to take the priorities forward. Action for M.E. has committed to working collaboratively to drive this forward as part of our new five-year research strategy, Breakthrough-ME.

If you would like to keep updated on our progress or get involved, please head to our website actionforme.org.uk

Sonya Chowdhury

CEO Action for M.E.

Executive summary

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a common neuro-immune condition causing fluctuating levels of physical and/or mental exhaustion associated with post-exertional malaise. Pain, sleep disorders, cardiovascular and gastrointestinal problems, and sensory impairments are also common. ME/CFS can be highly disabling, which impacts on quality of life and has a high economic burden: ME/CFS is estimated to cost over £6 billion/year in the UK. Despite the impact of ME/CFS on both individuals and society, it is poorly understood. The cause is unknown and there is no definitive diagnostic test, no cure, and no universally effective treatments. Consequently, it is also unclear how best to support people with ME/CFS, their families and carers to manage the condition, and there is little evidence to inform clinical services.

Clearly, there is a need for research to better understand ME/CFS and how to treat it, but historically, research has been under-funded. This James Lind Alliance (JLA) Priority Setting Partnership aims to facilitate much-needed research by making the Top 10 research issues that matter most to people with ME/CFS clear to researchers and funders.

To complete this exercise, the JLA's well-established processes were followed, but adapted for the needs of people with ME/CFS. A steering group was convened from the ME/CFS organisations that initiated the Partnership, plus people with ME/CFS, carers and health care professionals recruited via open advertisement. The steering group's job was to define the scope of the project, ensure equitable access, oversee all stages of the process and write the final report. Action for M.E. was funded to provide administrative support and coordination throughout, but every decision was taken by the steering group as a whole.

The first stage was to gather ideas for research questions from people with ME/CFS, their carers, and health care professionals. A survey was launched in May 2021, with a very strong response: over 5,300 research ideas were submitted. These were categorised into key themes, which were then summarised into a single overarching question for each theme, producing 59 summary questions.

The next stage was to assess whether the summary research questions had already been answered by research. It is a reflection of the lack of high-quality research into ME/CFS that none of the summary questions were ruled out at this stage.

People with ME/CFS, their carers and healthcare professionals were then asked to choose their top 10 questions from those submitted in a second survey. This ran October – December 2021 with 1752 respondents. From the results, the steering group produced a shortlist of 18 questions.

Finally, three online workshops were held to finalise the top ten priority research questions from the shortlist of 18. Applications to attend the workshops were accepted from people who had expressed an interest in doing so in the second survey, as well as the wider public. 36 people were selected, ensuring that all demographics, severity of ME/CFS, and roles were represented. Attendees held iterative small group discussions until the final Top 10+ priorities were identified and agreed.

The James Lind Alliance brings patients, carers and clinicians together in Priority Setting Partnerships (PSPs) to identify and prioritise the Top 10 unanswered research questions that they agree are the most important. The aim is to make sure that health researchers and funders are aware of the issues that matter most to the people who need to use the research in their everyday lives.

What is ME/CFS?

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a long-term (chronic), fluctuating, neurological condition that causes symptoms affecting many body systems, most commonly the nervous and immune systems. ME/CFS affects an estimated 250,000 people in the UK, and up to 30 million people worldwide.[1] Roughly 70% of people with ME/CFS are women.[2]

The World Health Organization has classified ME as a neurological disease since 1969.[3] The exact underlying mechanisms of the condition are unknown. However, people with ME/CFS experience severe, persistent symptoms including physical and mental exhaustion associated with post-exertional malaise (symptoms caused or made worse by expending even small amounts of energy, which can be delayed), pain, cardiovascular and gastrointestinal problems, sensory impairments and sleep disorders. A key feature is that symptoms tend to fluctuate in terms of type and severity over time.

James Lind Alliance
Priority Setting Partnerships

Why does this ME/CFS Priority Setting Partnership matter?

ME/CFS has a highly disabling impact on people's everyday lives. One quarter of people with ME/CFS are severely or very severely affected, leaving them housebound or bedbound.[4] Fewer than 50% of people with ME/CFS are able to work or study fulltime and 20% are unable to work at all.[5] The yearly economic cost of ME/CFS is estimated to be over £6 billion in the UK.[6] Quality of life of people with ME/CFS is lower than many other disabling chronic conditions, including multiple sclerosis, rheumatoid arthritis, congestive heart failure and some forms of cancer.[7] Despite the impact of ME/CFS on both individuals and society, it is poorly understood. There is no definitive diagnostic test, no cure and no universally effective treatment. It is unclear how best to support people with ME/CFS and their carers, families and supporters to manage the condition, and there is little evidence to inform clinical services.

Historically, ME/CFS has faced significant under-investment in biomedical and clinical research, particularly when compared to other severe disabling conditions. For example, funding for research into multiple sclerosis is about 20 times greater than ME/CFS despite being far less common.[8] There is an indisputable need for more research into ME/CFS to address knowledge gaps.

Our process

Creating a steering group

Made up of people with ME/CFS, carers and health care professionals, our first task was to write a protocol.

Initial survey to gather research ideas

Respondents were asked for all their ME/CFS research ideas in this open answer survey.

Grouping and summarising questions

The steering group looked through all 5,300 ideas and summarised them into 59 questions.

Checking summary questions against research

We searched all the research on ME/CFS to check the questions hadn't already been answered - none of them had.

Ranking the long-list of questions

A second survey was shared asking people to choose their top 10 research priorities from the 59 summary questions.

Shortlisting the highest ranked questions

We shortlisted 18 questions to go through to the final workshops, taking into account minority groups' priorities.

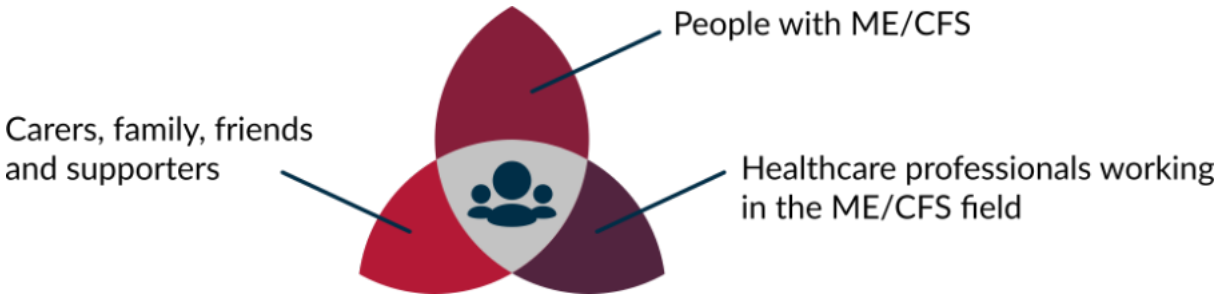
Workshops to finalise the Top 10 priorities

In three workshops the shortlisted questions were discussed and the Top 10 priorities finalised.

Our participants

Thousands of people engaged in this process. All of our participants came from one or more of the groups below, and were:

- over 16 years old
- living or working in the UK.



Our methodology

The James Lind Alliance (JLA) has a defined process for Priority Setting Partnerships (PSPs), which the steering group followed. The decisions we made in this PSP are explained below.

The JLA method of processing survey data is a social analysis rather than a scientific one. This takes into account the influence of the people able to be a part of the steering group and the participants who access the surveys at each stage.

Steering Group Creation

An initial seed steering group consisted of representatives from Action for M.E., the Patient Advisory Group to the ME Research Collaborative, Science for ME, and Forward ME, with JLA support.

Applications to join the steering group from the general public were ranked by the seed members, considering the attributes that each applicant could bring to the task and the need for balanced representation.

Scope of the Project

Establishing the scope of the project was essential to make sure the aims of the PSP were achieved. A key consideration was which diagnostic criteria should be used when assessing whether proposed questions had already been answered by research. Research using either Institute of Medicine (IoM) 2015,[9] or 2003 Canadian Consensus Criteria (CCC)[10] was automatically included. Research that used other criteria was only considered when post-exertional malaise (PEM) was a mandatory requirement.

The scope included:

- causes, prevention, risk factors, diagnosis
- living with and disability associated with ME/CFS
- symptoms, relapses, treatment or management
- issues for carers
- services relevant to the condition and access to services.

The scope excluded:

- people without a diagnosis of ME/CFS (or CFS/ME, chronic fatigue syndrome, or ME)
- the symptom of chronic fatigue caused by other conditions
- studies of ME/CFS using the Oxford Criteria,[11] NICE 2007 criteria[12] or Fukuda Criteria[13] without mandatory PEM.

Throughout the process the steering group was aware that fluctuations of ME/CFS impact on people's ability to participate. Those affected more severely may also struggle to take part due to major limitations on cognitive and physical function. Furthermore, we were only able to produce the surveys in English, thereby limiting access to those who were not fluent in English. People from minority ethnic backgrounds may face additional barriers to accessing diagnosis and support for ME/CFS which could impact representation. We acknowledged the possibility of bias these limitations could introduce by trying to ensure from the start that these groups of people and their representatives had an equitable voice.

Initial Survey

Over 5,300 research ideas were submitted

The initial survey (appendix 3) was designed to gather any and all ideas for research questions. It was open to people with ME/CFS, their carers and families, and health care professionals working with people with ME/CFS. Online and paper surveys made the process more accessible. Additional support for people with severe and very severe ME/CFS, provided by the 25% ME Group, also improved accessibility.

Once released, the survey was publicised widely, through the JLA website, a dedicated psp-me.co.uk website, social media accounts, UK ME/CFS charities and support groups, both online and in print. It was also highlighted at the British Association of Clinicians in ME/CFS (BACME) conference 2021.

Collection and analysis of Initial Survey results

The appointed JLA Information Specialist went through all responses submitted (appendix 4), grouping questions based on their key themes and labelling them accordingly. To minimise unintentional bias this analysis was overseen by a subgroup from the steering group, which included people with ME/CFS, carers, and health care professionals.

Grouping and summarising questions

After completing thematic analysis of initial survey responses, we summarised each group of questions into one overarching question. This was generated in steering group discussion, with individual questions read carefully to ensure all areas of importance were considered. When several specific examples were mentioned in the initial questions, the three most common were listed in the summary question.

A sizeable minority of the questions received fell outside the original scope. While these questions could not be included in the thematic analysis, we agreed this data should not be lost, as many important issues were raised. The hope is to reach out to ME/CFS charities to use this information further in the future.

Evidence checking

The 59 summary questions were checked to see if they had been answered by research already. The JLA process requires reliable or recent systematic reviews for any question. None were found, so all 59 summary questions (appendix 1) were included in the long-list of research priorities.

The second survey

After verifying that summary questions had not yet been answered by research, we prepared the second survey (appendix 3). This asked participants to choose their top 10 questions in order to create a shortlist for the final prioritisation stage, the workshop.

The survey had two stages. Firstly, respondents selected all questions they judged to be important. Then they reduced their selection down to 10 priorities.

We publicised the survey to all who had completed the first survey and asked to be directly contacted with updates. Alongside this, we made sure there was broad coverage on social media, through ME/CFS charities, and in local groups. To extend the reach of the survey to minority groups, posters were produced in languages other than English, including Arabic and Urdu, and shared through local groups, and online.

The second survey was launched in October 2021, with a closing date of December 2021. Those completing the survey were asked to express if they had an interest in attending the final workshop.

The long-list of questions was grouped into the following categories:

- Causes and Prevention
- Diagnosis
- Lifetime Risks and Course of Illness
- Treatment and Management
- Underlying Mechanisms and their Treatments
- Health Services
- Causes of Symptoms and their Treatments
- Social and Psychological Impacts and Support.

1,752 people shortlisted their top 10 priorities

Ensuring survey accessibility included:

- online and paper versions
- online version automatically saving so respondents could take a break
- the 25% ME Group provided specialist phone support to those with severe and very severe ME/CFS
- grouping the long-list of 59 questions into categories to break the questions into more manageable chunks
- producing printouts and a searchable webpage for the long-list.

The shortlist of 18 questions

The steering group reviewed the results of the second survey to finalise the shortlist for the workshop. A decision was made to limit the number of shortlisted questions to 18 to reduce the cognitive challenge for people with ME/CFS. It was important to consider all views, including groups with fewer respondents (such as people with very severe ME/CFS, or health care professionals), so the top seven questions from each of 'people with ME/CFS', 'carers' and 'healthcare professionals' were automatically included. This gave 11 questions. A further 13 questions were ranked highly by different demographic groups and considered for inclusion. We included the question on pain as it was high priority for people with very severe ME/CFS. The remaining 12 were then ranked according to their priority for different subgroups, and the seven highest selected. The resulting 18 questions (appendix 2) were considered in the final workshops.

The final workshops

The task for the workshops was to identify the final Top 10 priority questions. We invited applications from people with ME/CFS, carers, and health care professionals, who expressed an interest in taking part in the second survey or responded to advertisements.

147 people applied of whom 36 were invited to attend the workshops:

- 18 people with ME/CFS
- 9 carers, family members and supporters
- 9 healthcare professionals.

Some participants fell into more than one category. This spread allowed a broad range of viewpoints (demographics, severity of ME/CFS, and role) to be heard while ensuring people with ME/CFS had a strong voice. 35 people joined the first workshop, 34 the second and 33 the final workshop. Drop outs were due to illness and unforeseen circumstances.

Three online workshops were held, formatted to accommodate the needs of people with ME/CFS. They involved iterative small-group discussions to identify and rank attendees' priorities. The rankings from the groups were then combined to produce the final Top 10. Two questions came in equal tenth place, resulting in a Top 10+.

"This PSP has set a record for the numbers of research ideas submitted in the first survey, and for the number of people who wanted to participate in the final workshops. Additionally, the commitment and expertise of the steering group was incredible throughout. All of this demonstrates just how much people with ME/CFS can and should be a part of research."

- Toto Gronlund, JLA facilitator

Exploring the Top 10+ priorities

Priority 1

What is the biological mechanism that causes post-exertional malaise (symptoms caused or made worse by physical, mental or emotional effort, which can be delayed) in people with ME/CFS? How is this best treated and managed?

Why does this priority matter?

This question was unanimously ranked as the top priority by every group at the workshop, and by respondents overall in the second questionnaire. Post-exertional malaise (PEM) is considered the hallmark symptom of ME/CFS, with evidence from two-day cardiopulmonary exercise testing (CPET) demonstrating an indicative drop in functioning 24 hours after exertion.[14, 15] It is a highly restrictive and debilitating aspect of ME/CFS. Understanding the biological mechanism behind post-exertional malaise would likely unlock major clues to the cause of ME/CFS, and how to manage and treat it.

Workshop participants noted that PEM triggers symptoms of ME/CFS. If PEM is understood, then the mechanisms behind other symptoms such as cognitive dysfunction, fatigue, pain and sleep problems may also be understood.

Priority 2

Which existing drugs used to treat other conditions might be useful for treating ME/CFS, such as low dose naltrexone, or drugs used to treat Postural Orthostatic Tachycardia Syndrome (POTS)?

Why does this priority matter?

This question was unanimously ranked second by all small groups at the workshops. People with ME/CFS in the UK are sometimes prescribed off-label drugs, or are prescribed drugs for other conditions they live with, that appear to significantly improve their ME/CFS. However anecdotal reports do not give the evidence needed for these drugs to be used in everyday clinical practice.

Symptoms common to other diseases, such as pain, nausea, orthostatic intolerance, fatigue, migraines, cognitive dysfunction and many more are all potential targets for drug trials in ME/CFS.

Workshop participants were clear that answering this question could be the fastest route to improving the quality of life of people with ME/CFS.

Priority 3

How can an accurate and reliable diagnostic test be developed for ME/CFS?

Why does this priority matter?

Despite its prevalence and the impact ME/CFS has on people's lives, no diagnostic test is available. An accurate and reliable diagnostic test could carry huge benefits, including:

- Speeding up diagnosis to ensure early and accurate advice on managing the disease
- Preventing misdiagnosis and inappropriate treatment
- Ruling out other possible causes for symptoms
- Providing clues about the underlying biology of this disease – a recurring theme through this priority setting process
- Enabling accurate identification of subjects for future research studies.

There was strong consensus throughout the workshops that this was a high priority with practical importance for people with ME/CFS, carers and health care professionals.

Priority 4

Is ME/CFS caused by a faulty immune system? Is ME/CFS an autoimmune condition?

Why does this priority matter?

This question speaks to a strong desire to understand the biological causes of the disease. There are similarities between ME/CFS and some other autoimmune conditions. Indicators, such as high prevalence among women, increased autoantibody levels,[16] and altered cytokine expression,[17] all suggest immune dysfunction. Understanding this would provide direction to the search for treatments and a cure.

During the prioritisation survey another question on the immune system was highly ranked, but not taken through to the workshop due to overlap with this one. Instead, we highlight it here: Does the immune system continue to over-function or under-function in some people with ME/CFS to cause symptoms? What does this mean for treatment and risks from infections and vaccinations, including COVID-19?

Priority 5

Are there different types of ME/CFS linked to different causes and how severe it becomes? Do different types of ME/CFS need different treatments or have different chances of recovery?

Why does this priority matter?

People with ME/CFS present with a wide range of symptoms and there is huge variation in the symptoms that individuals find the most debilitating. We have no way of predicting if someone will become severely ill, or if they will recover. Anecdotally, treatments or strategies that help one person often do not help another.

During workshop discussions, participants in different groups repeatedly mentioned their hope that this question would lead to more research into severe ME/CFS.

Future research and disease management would hugely benefit from the ability to categorise ME/CFS into more specific groups of people with similar symptoms, underlying biology or prognosis.

Across health care, we are discovering that we can, and should, tailor treatments to the individual. Reaching this point in our understanding of ME/CFS would be an important leap forward.

Priority 6

Why do some people develop ME/CFS following an infection? Is there a link with long-COVID?

Why does this priority matter?

Up to 80% of people with ME/CFS first develop symptoms after a viral infection and there are many similarities between ME/CFS and long-COVID.[18, 19] The response to the COVID-19 pandemic, and corresponding research interest into the long-term effects of viral infection, is an important opportunity to understand the role of infectious agents in causing ME/CFS. Workshop participants commented on the need for people with ME/CFS to be included in long-COVID research studies and vice versa.

Priority 7

What causes the central and peripheral nervous systems (brain, spinal cord and nerves in the body) to malfunction in people with ME/CFS? Could this understanding lead to new treatments?

Why does this priority matter?

Many of the symptoms seen in ME/CFS indicate probable involvement or malfunction of the nervous systems, including orthostatic intolerance, dysregulated body temperature, exercise intolerance, some gut symptoms, and sensory sensitivities. Understanding the underlying mechanisms would direct the search for diagnostic tests, treatments, and a cure.

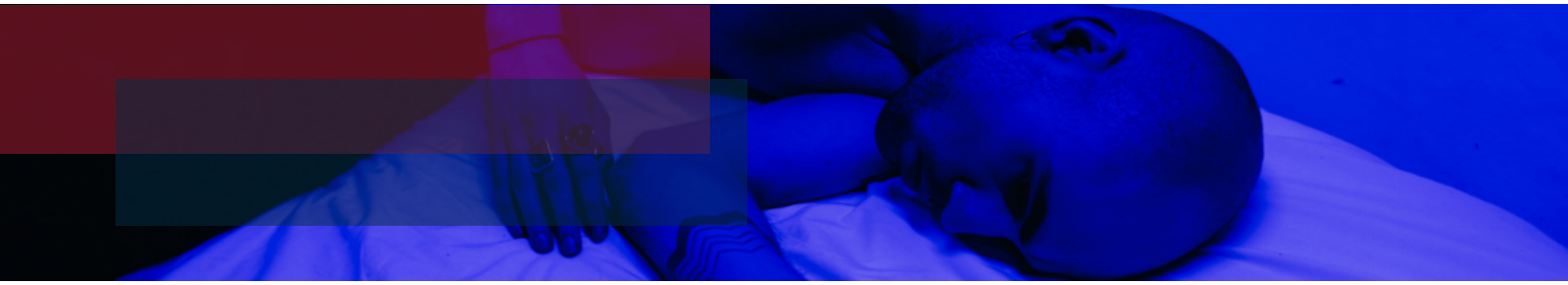
Workshop participants prioritised this over questions about individual symptoms as they felt it would incorporate investigation of the mechanisms underlying cognitive dysfunction, fatigue, pain and sleep problems. Cognitive dysfunction was noted as having a distinct impact on children and young people's education, as well as being a primary reason some people with ME/CFS cannot work.

Priority 8

Is there a genetic link to ME/CFS? If yes, how does this affect the risk of ME/CFS in families? Could this lead to new treatments?

Why does this priority matter?

Many people with ME/CFS report that other members of their immediate or extended families also have the disease. This has led to speculation about genetic causes. At the time of this report, the first large-scale genome-wide association study (GWAS) of 25,000 people with ME/CFS, called the DecodeME study, is underway.[20] Workshop participants ranked this question lower than it otherwise might have been because of DecodeME, but they noted that its results should be considered a starting point for further research. If genetic links to ME/CFS are found, further research will be needed to understand this, and in particular to transfer this knowledge into understanding underlying mechanisms, developing or assessing treatments, and hopefully a cure. This information could also impact on family planning.



Priority 9

What causes ME/CFS to become severe?

Why does this priority matter?

Quality of life for people with ME/CFS is generally lower than other disabling diseases with which it has been compared.[21] People with severe ME/CFS live with extreme disability: housebound or bedbound, they experience constant, severely debilitating symptoms, limiting all activities of daily living. For those with very severe ME/CFS, tube-feeding can become necessary, light and sound are usually intolerable, pain is often unmanageable, and speech may not be possible. Some describe it as a living death. Historically, research has neglected and excluded this population.

Understanding what causes ME/CFS to become severe could prevent others suffering the same fate, and give us clues on how to best to support and treat this under-served population.

Severe ME/CFS was discussed as a high priority by all small groups at the workshops. It was highlighted that normal research methods need adapting to include people with severe ME/CFS, for example by conducting home visits.

Priority 10

How are mitochondria, responsible for the body's energy production, affected in ME/CFS? Could this understanding lead to new treatments?

Why does this priority matter?

Many small-scale studies have shown that people with ME/CFS have dysfunctional mitochondria, or the under- or over-expression of related proteins.[22] Mitochondrial research is a promising area which needs to be taken forward on a larger scale, with studies designed to replicate and progress current findings in well-defined cohorts. New drugs could be developed, or existing drugs repurposed, to target this dysfunction once there is a better understanding of the pathology.

Priority 10+

Does poor delivery or use of oxygen within the body cause ME/CFS symptoms? If so, how is this best treated?

Why does this priority matter?

Initial research suggests peak oxygen uptake is lower in people with ME/CFS than healthy controls.[23] "Air hunger" is sometimes reported as a symptom, and this question was a high priority for those with very severe ME/CFS in the second survey. Investigating delivery and use of oxygen could incorporate research into impaired blood flow, clotting, movement of molecules within cells, and whether cardiac function is impacted in ME/CFS. Workshops participants prioritised this question in order to further explore underlying mechanisms of this disease.

Broader research themes important to those affected by ME/CFS

Throughout this process, the steering group was aware of broader concerns about the state of research into ME/CFS that the PSP was not formulated to address. That said, it would be remiss not to mention some of the key themes that arose during the first survey, and which reflect online public discussions about this project.

Three key themes arose:

- need for biomedical research, with a focus on understanding causes and finding a cure
- necessity of patient and public involvement
- high quality study and trial design.

Biomedical research

In the initial survey, respondents were able to suggest research questions in an open text box. Many also took this opportunity to state a strong desire that research should focus on biomedical aspects of the disease, with many ideas emphasising cure and underlying mechanisms. Historically, there has been minimal funding in the UK and elsewhere for research into abnormal biological mechanisms. Charities and organisations involved with ME/CFS have worked tirelessly to highlight this lack, and have raised funds for pilot studies. However major investment from governments is required to enable the sort of large scale research studies that could create real change in people with ME/CFS's lives.

Furthermore, respondents to the initial survey wanted to see previous small studies replicated, an end to clinical trials focused on behavioural changes, and increased research funding overall.

The necessity of patient and public involvement

Historically, those whose lives are most affected by a disease, namely patients, their carers and families, and clinicians, have been denied input at the critical stage of setting the research agenda. This is just as true of ME/CFS as of other conditions. The JLA set up the first PSP in 2004 to address this, and have been a force for good in driving forward the importance of patient and public involvement (PPI) in setting and ranking research priorities ever since.

Priority setting is only the first stage of patient and public involvement in research and it is essential that patients and supporters are at the heart of developing any research proposals and protocols going forward.

DecodeME has already shown us that good co-production is not only possible, but essential.[24, 25] Many of those who have engaged with this PSP have expressed a deep commitment to continue to support this public and patient involvement.

High quality study and trial design

People with ME/CFS report being harmed by therapies previously recommended as evidence-based. NICE no longer recommends these therapies, rating all research on them as low or very low quality.[26] However their legacy remains, and the importance of high quality trial design is still at the fore of the ME/CFS communities' considerations, with comments often focusing on the need for objective outcome measures in research studies.

We recommend these themes are taken into consideration in the awarding of future research funding.

"I was surprised how many systematic reviews were all reaching the same conclusion - that research into ME/CFS to date is commonly poor quality and inclusion criteria are often unreliable. I kept thinking why waste money doing a systematic review when that issue is well known, invest the money in good quality research instead!"

- Kristina Staley, JLA Information Specialist

What next?

The research interests of patients, carers and healthcare professionals are at the heart of all PSPs but identifying the priorities does not automatically translate into commissioned research. There has been woeful underinvestment for research into ME/CFS. This must change and the appetite for this is there.

These Top 10+ priorities provide a community-chosen focus that charities, government, services, funders, researchers, and institutions should now get behind.

Research is the main focus of any PSP, but highlighting questions is not the only impact these processes can have. Our PSP has engaged at least 2,000 people in thinking about ME/CFS in more depth. It has created discussion and debate, brought together diverse community members, and spotlighted the lack of research funding to date in this disease area. These triumphs should be also celebrated.

Through the commitments made below, we are determined that the Top 10+ ME/CFS research priorities should have a lasting and tangible impact.

What we're doing

We are committed to promoting the Top 10+ research priorities as widely as we can. To do so, we aim to publish our findings in a peer reviewed journal. We will promote the Top 10+ through our own networks, and continue to promote the power and necessity of patient and public involvement.

What you can do

You can commit to promoting the Top 10+ research ideas to your MP, in campaigning or awareness raising efforts, and get involved in research where you are able to.

Visit psp-me.co.uk to find further resources to help you promote the Top 10+.

What Action for M.E. are doing

Action for M.E., who were funded to coordinate this PSP, commit to progressing research into the Top 10+ and ensuring that people with lived experience are at the heart of all research they support or fund. They are also actively engaged with the government calling for a national strategy for ME/CFS that will:

- invest in the necessary expansion of capacity in the ME/CFS genetics research field
- utilise, engage and invigorate existing research excellence from across the UK and global research community
- catalyse and facilitate collaboration and partnership opportunities
- exploit potential for crossover learning from COVID-19 and long-COVID research
- develop funded research programmes on the Top 10+ ME/CFS research priorities determined by this PSP.

Action for M.E. will also maintain the PSP website to ensure people can find information about the process and all the research ideas submitted, not just the final Top 10+ questions.

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This is a new initiative that is not linked to any previous research or agenda.

Steering group

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Organisation Representatives

- Sonya Chowdhury, PSP Lead, Action for M.E.
- Russell Fleming, Forward-ME
- Debbie Smith, Science for ME Forum
- Representatives from the ME Research Collaborative Patient Advisory Group – Adrian Baldwin, Rachel Ephgrave, Simon Everitt, Gemma Hoyes, Susan O'Shea, Opal Webster-Philp

Patient Representatives

- Annette Barclay
- Dr Monica Bolton
- Sian Leary
- Dr Ben Marsh

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- Rachel Elliott
- Mike Emmans Dean
- Ann West

Health and Care Professional Representatives

- Tina Betts
- Joan Crawford
- Professor Vinod Patel and proxy Helen Baxter
- Professor Sarah Tyson

James Lind Alliance Advisors and Specialists

- Toto Gronlund, JLA Facilitator
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- Kristina Staley, Information Specialist
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Coordinators

- Claire Dransfield, Action for M.E.
- Sam Bromiley (previously Action for M.E.)

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Appendices

All appendices can be found at psp-me.co.uk/defining-future-me-cfs-research-appendices

1. Long-list of 59 research questions
2. Shortlist of 18 research questions
3. Surveys
4. Link to all research ideas submitted in first survey

The ME/CFS Priority Setting Partnership

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