



The UK CFS/M.E. Research Collaborative

Rising to the challenge of understanding the mechanisms of chronic fatigue syndrome/myalgic encephalomyelitis (CFS/M.E.)

What is CFS/M.E.? CFS/M.E. is a long-term (chronic), fluctuating, neurological condition that causes symptoms affecting many body systems, more commonly the nervous and immune systems, which affects all age groups (including children and adolescents) and all ethnic and socioeconomic strata. People with M.E. experience severe, persistent fatigue associated with post-exertional malaise, the body's inability to recover after expending even small amounts of energy, leading to a flare-up in symptoms. Few make good progress and may recover, while most others remain ill for a number of years and may never recover. People with CFS/M.E. score lower overall on health-related quality of life tests than most other chronic conditions. An estimated 250,000 people are affected by CFS/M.E. in the UK.

NICE Guidelines: NICE acknowledges that the physical symptoms can be disabling. NICE identifies three levels of severity: **Mild:** Are mobile, can care for themselves and can do light domestic tasks with difficulty; **Moderate:** Have reduced mobility have usually stopped work, school and are restricted in all activities of daily living and **Severe:** Unable to do any activity themselves, are often unable to leave the house, depend on a wheelchair for mobility and experience severe cognitive difficulties.

Myths surrounding CFS/M.E.: There is a great deal of mythology surrounding M.E./CFS due, in part, to the perpetuation of popular stereotypes in the media. Of particular concern is that many of these myths are also promulgated by medical and other health practitioners as well as employers and teachers. Prominent among these is that M.E./CFS is a psychiatric or psychological disorder, whereas numerous studies have documented abnormal immune system, endocrine system, and nervous system function in patients with M.E./CFS. The poor reproducibility of some studies reflect their small sample size and the very likely possibility of multiple disease subtypes and endotypes.

A New Look at CFS/M.E. by the IOM and NIH: The 2015 [US Institute of Medicine Report](#) concludes that CFS/M.E. comprises a serious and debilitating condition yet, despite substantial efforts by researchers, there is no known cause or effective treatment. Diagnosing the disease remains a challenge, and patients often struggle with their illness for years before an identification is made. Many health professionals have been sceptical about the serious physiological - rather than psychological or psychiatric - nature of the illness. Once diagnosed, patients often complain of receiving hostility from their health care provider as well as being subjected to treatment strategies that may exacerbate their symptoms.

Some key facts from the IOM Report: 1) CFS/M.E. is not a psychiatric or psychological illness, but a complex, multisystem, and often devastating disorder affecting 836,000 -2.5 million Americans; an estimated 84-91% of people have not yet been diagnosed, so that the true prevalence of CFS/M.E. is unknown, 2) CFS/M.E. affects women more often than men, 3) most patients currently diagnosed are Caucasian, but some studies suggest CFS/M.E. is more common in minority groups, 4) the average age of onset is 33yrs, although can occur in patients younger than age 10yrs and older than age 70yrs, 5) At least 25% of CFS/M.E. patients are bed- or house-bound at some point in their illness, 6) CFS/M.E. patients experience loss of productivity and high medical costs that contribute to a total economic burden in the US of \$17 to \$24 billion annually, 7) the cause of CFS/M.E. remains unknown, although symptoms may be triggered by certain infections, such as

Epstein-Barr virus, 8) there are therapies available for the management of symptoms of CFS/M.E., but their efficacy is not well understood and some are controversial, and 8) there is no existing cure for CFS/M.E. Acting on this high level Report, Francis Collins, Director of the NIH, recommended that new steps be urgently taken to provide a firm foundation to improve diagnosis and treatment.

The scale and impact of CFS/M.E. on individuals and society are profound. Around 250,000 people in the UK have M.E./CFS. Many more people - carers, children and family members alike - are directly affected by the illness each year. The illness strikes people in the prime of life, contributing to an economic cost for the UK in 2014-15 of £3.4 billion/yr.

CFS/M.E. research is clearly deserving of special funding arrangements. CFS/M.E. research funding is exceptionally low compared to other neurological or multisystem disorders. It is at least as disabling as multiple sclerosis yet, per person, it receives 20-times less funding. People with CFS/M.E. experience a lower quality of life than those with rheumatoid arthritis, cancer or congestive heart failure. Unlike other disorders, CFS/M.E. patients most severely affected currently receive the least care. Frustratingly, therapeutic approaches have failed to deliver tangible benefits for most patients. Patients and patient organisations are now seeking new approaches for discovery of causal biomolecular mechanisms in the face of a medical community that still deny even its very existence.

The UK CFS/M.E. Collaborative: In 2008 MRC set up the CFS/M.E. Expert Group (EG) chaired by Stephen Holgate (then Chair PSMB) to consider how new high-quality research into CFS/M.E. and partnerships between researchers already working on CFS/M.E. and those in associated areas, might be encouraged. This work followed on from a Research Advisory Group in 2003 and a joint workshop held with Action for M.E. in 2006. In 2009, the EG convened a workshop in Oxford, which, importantly, included experts from outside the field, and identified an extensive list of research areas that were in need of investigation. Subsequently, a prioritisation group chaired by Hugh Perry (Chair MRC NMHB) comprising members of the EG and other workshop attendees identified short-, medium- and long-term research topics to study. In the short-term these were: Autonomic dysfunction, Cognitive symptoms, Fatigue, Immune dysregulation, Pain and Sleep disorders as being key. In 2011, MRC identified £1.5 million for new research into the mechanisms of CFS/M.E. focused on the previously identified short-term priority areas. A key aim of this call was to encourage new and innovative partnerships between researchers already working on CFS/M.E. and those in associated areas. Because of the recognised conscious and unconscious bias known to influence peer review in the CFS/M.E. (for reasons described above) guidance on assessing the proposals was provided. As a result, 5 projects all scoring very highly, were supported and have now been successfully completed.

Buoyed by this success, it was clearly appreciated that for the research field to progress in the UK, collaboration between researcher, patients, funders and industry was the only way forward, recognising the low level and fragmented nature of current research. The MRC Workshop had identified serious barriers to those entering the field including understanding the relationship between mind and body, no single discipline “owning” CFS/M.E., insufficient inter-disciplinary collaboration, insufficient funding for pilot work, and a view by some patient advocates that discouraged researchers from entering the field. Thus, in April 2013, the [UK CFS/M.E. Research Collaborative](#) (CMRC) was launched to stimulate a national joined-up collaborative research approach involving patients, NHS, charities and the research councils. Its aims were to promote current research in CFS/M.E., review underlying mechanisms and sub-phenotypes of CFS/ME., identify research opportunities, encourage new research towards understanding the basis of the disease, produce a framework for conducting high quality research in the future and to work to achieve clear lines of communication and synergy among all stakeholders with an interest in this area. Over its 5 years, the CMRC Executive comprised basic and applied researchers in and outside the field, CFS/M.E. Medical Charities (Action for M.E., the M.E. Association, the CFS Research

Foundation, M.E. Research UK, the Association of Young People with M.E. (AYME), the British Association for CFS/ME (BACME), Wellcome Trust and Arthritis Research UK), MRC, NIHR and industry (UCB, GSK). Despite some changes to the Medical Charities over the 5 years, with some merging, others leaving and new ones joining, the CMRC remains strong. We have held on average four Executive meetings each year, hosted by MRC, run four annual 2-day meetings (2 in Bristol and 2 in Newcastle) and have held a number of task-orientated workshops.

On Jan 18th 2018, a CMRC Away-day was convened in Southampton in order to reflect on progress and consider the future. Despite some difficult times, there have been considerable successes. These include facilitation of multiple new research collaborations, a consistent (although still small) increase in grant funding, involvement of researchers from outside the field and the successful creation of a unique national research network, the M.E./CFS Epidemiology and Genomics Alliance ([MEGA](#)). MEGA comprises a group of 15 UK scientists and three patient charities working to establish a “big data” research study of >10,000 adults and 2,000 children and young people that drove a submission to the MRC Human Tissue Banking and Linked Data Initiative. This grant application reached the final round, but was not funded, however, a modified MEGA proposal remains a possibility. Other achievements include a high impact of our four conferences, including participation of overseas speakers from many countries (e.g. those listed [here](#)), the creation of international collaborations and special sessions with researchers and patients (including live streaming), new links with industry, undertaking a [survey of CFS/M.E. national and international funding](#), helping the MRC update its Highlight Notice and reviewing the [NIH sponsored CFS/M.E Common Data Elements](#).

Looking forward: We believe that there is now a limited window of opportunity for building a national CFS/M.E research platform to undertake: (i) hypothesis-free investigation into the genetic determinants of CFS/M.E. susceptibility, (ii) objective identification of biomarkers using standard and multi-omics technologies that permit CFS/M.E. stratification. In addition, the CMRC advocates for a high level interdisciplinary report identifying the research needs for patients with CFS/M.E and, through the [NIHR-funded James Lind Alliance](#), bring patients, carers and clinicians together to agree which, among the many uncertainties, which matter most and deserve priority attention for research. This would build on an earlier 2007 JLA Workshop identifying the need for this.

The time has also arrived to have patients fully involved in helping set the agenda for the CMRC and have thus formed a Patient Advisory Group with representation at all our future meetings. Having involved John Gallagher (Director of [Dementias Platform UK](#) – DPUK) in our summer meeting and Away-day, the CMRC considered that the only way forward was for the CFS/M.E Research Platform to be established using the same principles. This would be timely following the recent launch of the [4 US CFS/M.E. and 1 CIHR National Canadian Centres](#). After our last CMRC Conference, we met with Vicky Whittemore, who leads Frances Collins’ NIH programme, and were encouraged to move forward a modified MEGA consortium grant to join this international effort. Moreover, we have been approached by the CMO, Dame Sally Davies, to explore with the SoS for Health, Jeremy Hunt and the DH Chief Scientist, Chris Whitty, how the DH/NIHR could enhance quality research in this field. A CFS/M.E. Platform in the UK would, through the large number of patients available in the dedicated speciality clinics (but then extending beyond this to include severely affected patients and other subgroups), would be a unique resource for additional studies, including identification of diagnostic markers and delivery of experimental medicine.

As Prof Sir John Bell has pointed out in a recent conversation on CFS/M.E., prejudice and stigma that wrongly remains associated with this condition and which still affects health and social care, will only be dispelled by discovery of its causal biomolecular mechanisms.