European ME Alliance

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European ME Alliance Response to RFI Notice Number: NOT-NS-16-024 Request for Information: Soliciting Input for New Research Strategies for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME)

This is a submission from the European ME Alliance regarding **NOT-NS-16-024**.

The European ME Alliance (EMEA) is an organisation of national patient organisations and charities in thirteen European countries (in Belgium, Iceland, Denmark, Finland, Germany, Holland, Ireland, Italy, Norway, Spain, Sweden, Switzerland and UK) campaigning for better research and more funding for research into Myalgic Encephalomyelitis (ME or ME/CFS), as defined by WHO-ICD-10-G93.3.

We hope you find this useful,

Best wishes,

The Chairman and Board of EMEA

Content

ASSUMPTIONS

The IOM and P2P reports are recent reports and we assume that the good findings from these reports are built upon in these future plans being developed. It is also recognised that the IOM performed a literature search on ME already and we therefore have not provided research references.

Much of the content in this response has already been discussed and documented by the European ME Research Group (EMERG) which set an overall goal to define a sound research strategy to address the research issues and constraints for ME – more details from Professor Simon Carding at UEA/IFR.

Emerging needs and opportunities that should be considered as new ME research strategies are developed.

Biomarker discovery:

Establishing reliable biomarkers would be a major boost for all research, treatment and perception around the disease.

Therefore, consideration and a collaborative action plan should be given to the following –

- The use of comprehensive and validated scales, instrumentation and measurements for agreeing biomarkers
- Identification of the most promising marker(s) (antibodies, soluble, cellular, microbial or genetic markers) should be targeted as lines of research
    - Biomarkers should always be (cor)related with symptom patterns (see database later) Mapping back to patient stratification
    - Cross matched vs. relevant controls to identify specifics to ME
        - Disease controls – other fatigue-related illnesses, sedentary individuals, different ME case definitions?
        - "Healthy" controls – related, same household, unrelated (age/sex/race matched) individuals – defining criteria?
    - Also to be stored and correlated by gender, age and length of illness
- Multinational cohort studies
- Reference labs should be established
- Imaging:
    - Studies on specific brain findings need to be replicated and expanded

Clinical trials:

A need for multi-national clinical trials is present. This allows replication, verification and direct paths to possible treatments.

Currently the following might be viewed as potential, initial trials

- Rituximab, Ampligen, LDN, FMT

What is important, for whatever trials are conducted, are the following -

- Defining meaningful endpoints for trials
- National and international collaboration in multinational trials

It is suggested that a rituximab trial could combine existing projects underway in Norway (Haukeland University Hospital) and UK (EMERG/Invest in ME UK rituximab trial) to form a multi-national, multi-site clinical trial set – or knowledgebase, and could be used as a template for future collaboration.

This itself would give a boost for this collaboration as well as sending out strong signals to the research, academic and clinical communities – as well as to patients and their families. This is also achievable as links are already established between the groups undertaking this work. This sort of research needs to be performed in clinical trials and data made available rather than being performed on an ad-hoc basis by individual doctors.

Longitudinal studies

There needs to be consideration for longitudinal studies to elucidate the natural history of ME. Due to failings of the past by funding organisations we start from a position of a lack of any coordinated strategy for research and we need to build in this component to ensure future research can be augmented by this type of data. Such studies help to evidence how ME changes over time and may also help inform of the risk of relapses for people who are supposedly recovered or in remission?

Distinct plasma immune signatures in ME are present early in the course of illness, but differ in long-term patients and such differences could be investigated further.

Changed content of immune proteins a few years after the onset of ME.

Challenges or barriers to progress in research on ME.

Diagnosis

A central issue to all of the research into ME is correct diagnosis. Currently a vast number of wildly disparate and arbitrarily used case definitions and criteria exist for ME and CFS research and diagnostic purposes. A substantial body of evidence suggests that these definitions do not all represent the same disease and that there are significant differences in patient populations, making some of these definitions highly unreliable and inaccurate. evidence reviews and such like usually don't acknowledge the differences, nor the consequent problems and risks, and therefore often present their findings in such a way that the uninformed reader is led to believe that their conclusions are applicable to all patients meeting any CFS or ME definition regardless of the research criteria used in a particular study.

The lack of standard, up-to-date and accurate criteria being used in all ME research has impacted on the reliability of research in the past, as well as directly increasing the risk of harm to patients due to flawed "results" (e.g. the PACE trial).

Standard diagnostic criteria must be used for diagnosis – with standard sets of research criteria being formed from within these criteria.
These criteria need to be as refined as possible to avoid misdiagnosis and should evolve as research data is gained and confirmed.
A starting point should be the criteria which have been commonly used in recent years – CCC, ICC, IOM. The definition from Ramsay is favoured by many patients but they have not been used in research or properly evaluated. Yet from these sources a standard could be decided.
Comparative studies of different ME definitions may be necessary to achieve this.

Since post-exertional malaise/muscle weakness is a key feature of ME then it is important that future research is based on criteria where PEM is a required symptom. The effects of exercise should be taken into account in research.

Patient Stratification

Patient stratification is required for all research into ME to ensure well-defined patient cohorts – and this should include full disease spectrum/subgroups and inclusion/exclusion criteria.

The diagnosis must be accurate, reliable, universal, useful using standard diagnostic guidelines.

Appropriate (disease) control groups must be established.

The quality and standards of sample collection must be formulated for all to use and take into account the types of samples required, when and how often they are taken, and how many.

Also it has to be decided on what patient stratification is made – is it via onset type, severity, by biomarkers?

Databases of patients need to be set up and maintained. These need to consider

- Individuals
- Demographics
- Clinical Features
- Treatment History
- Systematic studies of patients' health history, including which infections the patient has undergone before the onset of ME, needs to be recorded.

The database may be used to identify/define sub-groups – such as

- Differences in biological pathologies
- Duration of illness
- Symptom clusters
- Level of severity
- Acute vs gradual onset
- Infectious vs non-infectious onset
- Triggers
- Pathogens
- Single vs cluster outbreaks
- Fluctuating pattern vs progressive decline
- Increased susceptibility to infection vs decreased susceptibility to infection since onset of ME

Data collection approaches are an issue with questionnaires not being sufficient, and questionnaires + patient visits may be subject to variation depending on the level of expertise of visiting nurses/research assistants.

Data Protection

This will be a challenge when working across different national or continental boundaries.

Ethics

This will be a challenge when working across different national or continental healthcare systems?

Sample Standardisation

National and international collaboration in setting standard operating procedures would be beneficial such as -

- Standard Operating Procedures (SOPs) –
    - Collection
    - Transport
    - Storing
    - Distribution
    - Sample Life History
    - Samples linked to documentation relevant to ME
    - Sample Types: Blood, Urine, Stool, Tissue, Spinal Fluid
    - Sample Quality and Frequency (of samples)
    - Challenge of selecting and "assuring" cohorts, comparable with epidemiology
    - Universal analysis protocols and quality control procedures

Bio/Tissue/Sample banks

These should include comprehensive samples with protocols which are standardised for ME research.

Many academic institutions have already established this facility so what is necessary is to standardise the registry and collection processes so that all can be assured of the provenance of the samples and they can be joined for research purposes.

The standardisation of registry and collection for biobanks to allow all academic biobanks to be joined as one resource for ME research rather than concentrating on single biobanks is the way forward.

This would allow, and encourage, sharing and collaboration and could reduce costs and avoid unnecessary "ownership" issues from being built up which become another obstacle to collaboration and progress.

It would also guarantee the provenance of sample definition and maintenance.

These sample bio/tissue banks in research organisations should be viewed as a necessary resource and not as an economic function.

Lack of funding

The need for more funding for biomedical research into ME has been recognised by many patient organisations around the world – but also by the recent IOM and P2P reports. The lack of appropriate funding for mainstreaming ME research makes it impossible to resolve this disease.

A substantial uplift in funding for biomedical research into ME would, we suggest, encourage new researchers to enter the field as well as create the necessary environment to allow causality to be established and treatments to be developed.

One of the later points regarding collaboration between NIH consortium and EMERG would provide a huge boost to the chances for increasing in funding for research into ME.
This investment would, in turn, save far more money than is spent by giving patients their lives back and reducing costs on healthcare.

Education

The Involvement of doctors in ME research needs to be encouraged.
A method of distributing knowledge of current and planned research to enable healthcare professionals to be made aware of ME needs to be looked at.
Existing methods seem not to be working.

The curriculum for medical students needs complete overhaul.
In the UK, for example, the education of medical students is based on erroneous information and borders on negligence by academic institutions responsible for setting the curriculum, and by the overriding regulatory body that governs this.

All of the above affect public and political perception and treatment of the disease.
They affect the likely interest of new researchers in participating in research into ME.

Gaps and opportunities across the research continuum from basic through clinical studies

Sample sharing

- This helps with research, establishes academic links between institutes and researchers and facilitates collaboration and standardisation
- If linked to sample standardisation then validation of results from small groups is possible
- "Freshness and validity" of samples and over time can be made possible across multiple centres and storage conditions
- Epidemiology: natural course of the disease progression and cross-checking definitions. Epidemiological studies are long overdue despite data being collected by healthcare services.

Database of Research

The database of research needs also to be built up and available to all researchers and not dependent on Journal publication alone. It needs to consider inclusion of negative results also – which may be useful for future research.
This is obviously affected by the results of research being published.
But it is one area that needs to be analysed.

Paediatric research

Paediatric biomedical research has been poorly served by research funding bodies.

A view is held by some that children often improve and the prognosis for children is much better for children than for adults.

Yet many children are ill for a long time, often very ill for a very long time.

So where is the evidence for this?

Could it be that the prognosis for children actually isn't as good as currently claimed, or do they become long-term sufferers because they aren't receiving adequate help or are often removed from the healthcare system due to apathy or decide to withdraw as a self-protection measure?

The lack of attention to paediatric ME research allows false beliefs about the disease to creep into healthcare systems and prejudice and ignorance is allowed to be built up (an example being the ridiculous use of the term "pervasive refusal syndrome" which is attributed to children with ME).

A subgroup to be studied should eventually include children and look at aspects that may affect the prognosis (acute vs gradual onset, type of trigger, subgroup, symptom clusters, severity, severity during the first 5 years, degree of PEM, frequent over-exertion, genetics etc.)

What proportion of children with ME become severely affected long-term? How is their illness changing over time?

Such studies overlap with epidemiological studies, education of doctors (and researchers) and even social considerations.

As a great deal of abuse from clinicians (and some researchers) towards children and young people with ME is based on this unproven expectation of recovery within 3-5 years then this warrants further research.

But it is also important with regards to health insurance, in dealing with schools and social services and other authorities etc.

It is also necessary to investigate heritability and familial associations - e.g. do symptoms differ between children and adults, and if so in what way?

Replication and validation of existing biomedical studies

Initial small studies are rarely followed up by larger or complementary confirmatory studies, due to lack of any longer term strategy and/or funding. The strategy for research needs to consider this point.

Centres of Excellence

The NIH have intimated that a number of Centres of Excellence for expert clinical care, biomedical research and clinical trials, may be established.

Similar plan exists in UK in Norwich Research Park which would link EMERG work.

These should collaborate and build on a research foundation that could fast-track biomedical research and eventual treatments for ME.

General Comments

The lack of consistency in research criteria, the flawed policy of funding psychiatric theories and the failure to even standardise on methods and terminology are all shown to contribute to the mediocrity and lack of vision that has characterised research into ME for the last decades, until perhaps the last couple of years.

Characterization and evaluation of the hallmark symptom post-exertional malaise (PEM) in carefully designed high-quality studies with large cohorts is absolutely essential.
Fatigue is often misleadingly stated to be the most important and/or characteristic symptom of ME, whereas in fact leading experts agree that the actual cardinal symptom of ME is post-exertional malaise (PEM), also called post-exertional amplification of symptoms or post-exertional crash.
'Fatigue' fails to capture the essence of this complex condition. Reducing a complex multisystem illness such as ME to just one single diffuse symptom that can also be found in a myriad of other illnesses, that can't even be measured objectively, is valueless.
Recognizing PEM as a distinguishing symptom is important in improving both the research field and clinical care for ME patients.

ADDITIONAL POINTS

The overriding themes which pervade all of these considerations are the following -

Collaboration:

It was evident from the Invest in ME International Colloquium and Conference events in London in June 2016 that USA and European researchers (and patient groups) can work together, and are doing so.
We would suggest that the NIH use the European ME Research Group (EMERG) as partners in research. This can begin immediately and will create a very powerful research potential which includes major European research institutions.
We would also suggest that NIH can use the European ME Alliance (EMEA) as partners for patient related considerations. It is extremely important that the NIH can work with a European patient organisation as this will bring major benefits for the research which is undertaken.

There is a great need for international collaboration in order to tackle this disease. This is an easy route for fast tracking research and improving education and awareness.
This will also expand research, force correct education of healthcare professionals and open up new avenues for research funding.

This all leads to improved chances for translating research into effective treatments which will lead to improvements in the lives of patients and their families.

Standardisation:

By now it is clear that standard protocols, diagnostic and research criteria and terminology should be used by the international research community. So this issue must be tackled – and it would certainly be possible if the previous Collaboration theme was to be embraced.

Biomarkers and Subgroups

As indicated earlier the discovery of biomarkers and possible determination of subgroups would be of great help in the daily lives of patients since this would allow impartial validation that a patient had ME following tests, would underline the fact that ME is a serious disease, allow healthcare professionals to work with the patient rather than against them and would be helpful in gaining aid from social services etc. – all serving to dispel mistrust with which many patients are confronted.

The Future

We hope that the NIH will involve the EMERG group and EMEA in future collaboration and cooperation.

There is a real chance being created here to do things right for patients – and EMEA will be willing to play a full role on progressing this opportunity based on solid and progressive biomedical research and international collaboration.