# How to enhance your ME research by involving People with ME as advisors and participants

As a researcher preparing to undertake work in Myalgic Encephalomyelitis (ME; also known as Chronic Fatigue Syndrome (CFS) or ME/CFS), you will know it is a highly disabling, neuro-immune condition that affects >17 million people worldwide regardless of ethnicity, or socio-economic background. Symptoms are heterogeneous and can reflect dysfunction of most body systems. They are however often invisible and tend to fluctuate. This can make it difficult to recognise the difficulties people with ME have in everyday life. The aim of this document is to present information and advice for ME researchers about how to structure and adapt research projects to make them suitable for people with ME (PwME), whether as participants or members of the research/ Patient and Public Involvement (PPI) team. It builds on the experience of successful ME researchers covering a wide range of research methodologies and approaches who have shared their know-how and recommendations for working with PwME (details below).

## Executive Summary

This document is to present information and advice for ME researchers about how to structure and adapt research projects to make them suitable for PwME, whether as participants or members of the research/ PPI team.

The key to successfully completing research into ME is to invest time and resource to talk with, and listen to PwME about what they can and cannot do, and what works best for them. The impact of ME is highly individual, and as many of these effects are invisible, the impact is not obvious without asking the PwME. So to enable people to participate, you need to be flexible and accommodating to their needs.

ME has a controversial history and many PwME feel stigmatised and concerned that others do not understand their difficulties. To successfully undertake ME research, it is important to gain PwME's trust by showing that you understand that ME is a physical condition. Make it clear that you believe them, recognise their difficulties, and accommodate their needs. The 2021 NICE Guidelines for ME is a useful 'primer' to understand the condition. [Overview | Myalgic encephalomyelitis (or encephalopathy)/chronic fatigue syndrome: diagnosis and management | Guidance | NICE]

The bottom line: Invest time and resources to listen to PwME, be flexible, sensitive and accommodating.

> *"They [PwME] ensured we were asking the right questions in the right way; acted as a sounding board so that the investigators are not misunderstood by the community; gave trust and validity to the project".* (Prof Chris Ponting, DecodeME)

## Before starting, some things you should know

- The main feature of ME is physical and/or mental exhaustion/fatigue triggered by trivial levels of activity and unrelieved by rest. The cardinal symptom which differentiates ME from other conditions is post-exertional malaise (PEM or, more accurately post-exertional symptom exacerbation). This is an increase in symptoms following activity. Its onset may be delayed and/or last for hours, days, or in the worst case scenario, become permanent.

- It is not only physical activity that is exhausting and can cause PEM; cognitive and social/emotional activity can be equally as draining.
- PwME also suffer a range of other symptoms which can affect most body systems, including pain, cardio-vascular and gastrointestinal problems, sensory impairments and hypersensitivities, and sleep disorders. The nature and severity of these symptoms are highly variable, although people with very/severe ME tend to have more symptoms, more severely. They also fluctuate within individuals.
- The exhaustion associated with ME includes cognitive as well as physical function. This cognitive impairment means that PwME may have difficulty absorbing, or retaining information. This means that at times they may not understand or retain simple conversations. In demanding conditions (such as a meeting, new surroundings or discussing new topics) cognitive function may deteriorate rapidly. You can help by making any comments and explanations brief, putting important business at the start of meetings and summarising discussions and conclusions frequently.
- PwME have to carefully manage how they spend their limited energy to minimise the severity of their symptoms and disability, and/or prevent deterioration by managing their life and energy expenditure carefully. Thus the demands of being involved in research at any level needs to be balanced with the other demands of an individual's life. PwME do not have the capacity to 'raise the bar' or 'go the extra mile'.
- PwME are desperate for biomedical and clinical research that may improve their lives, and others with ME. Therefore they are keen to support and be involved in research. However for this to be successful, the difficulties mentioned above need to be accommodated so they can be involved/ participate without making their condition worse. As many ME symptoms are invisible and/or delayed, it can be difficult to appreciate what the PwME is dealing with, or the management strategies they are using without discussing it with them. Researchers need to understand and accommodate PwME's needs by taking steps to ensure the demands of participation are acceptable to them and thy can be confident it will not cause them harm (by triggering PEM). This involves open and responsive consultation with PwME i.e. listening to the PwME and being flexible and adaptable. This will probably mean adapting the usual way that you conduct research to suit the PwME. It is not unusual for researchers to make unconscious assumptions about how they conduct research and PwME's abilities which make it difficult or impossible for PwME to participate. Structure your research routines and processes to suit the PwME, rather than vice versa.
- PwME's energy and capacity fluctuate during the day and are highly individual. It is unlikely there will be one day of the week or one time of day to be involved in research that suits everyone. So be flexible with any timetabling.
- The impact of some of those invisible symptoms and disabilities mean that:
    - Cognitive energy limitations (AKA brain fog) and the need to pace activity means it takes PwME longer to read material, take in information and make decisions,

    so the timescales need to be longer than for people: PwME cannot work to tight deadlines or pressurised timescales. Be flexible about any timescales and modes of communication. Agree these in discussion with individuals.
  - Travel can be challenging. It is often uncomfortable and demanding for PwME, so participation will be enhanced if travel demands are minimised and home visits or remote interactions (e.g. by video consultation or phone) are offered.
  - If travel is unavoidable, you will need to accommodate individuals' needs to make it feasible. Transport will need to be offered and arranged as many PwME are unable to drive. This may involve ambulance transport for those with more severe (postural) orthostatic intolerance who are unable to be upright for long. They will need to be able to lie flat and/or sit with their legs raised and/or the back rest lowered to a greater or lesser extent. As many PwME's mobility is limited, wheelchairs need to available (with help to push them if necessary). Any venue should be wheelchair accessible with minimal distances to travel after arriving. Recognise this will exclude people with severe/very severe ME, who are bed- or housebound.
  - If the PwME has to travel, the environment (for the journey and the destination) needs to be low impact. These needs are highly individual and need to discussed and negotiated with each participant, but bear in mind that many will need a quiet environment with low lighting, and no fragrances from cleaning products, perfume etc for people with sensory sensitivities. There needs to be comfortable seating, and also an area for people with orthostatic intolerance to lie down or be semi-lying with legs up. Some will need take regular drinks and snacks to maintain hydration, blood sugar levels etc.
  - As PwME's capacity to engage in activity is much less than healthy people (and many other conditions), any interactions may need to be spread over more than one session.
- Many PwME have a very limited income so make sure to cover all expenses. It can also help those who feel stigmatised to appreciate their input is valued. The NIHR offer guidance on this: [Payment guidance for researchers and professionals | NIHR] Compensation should meet these recommendations, at least. However, recognise that not all participants will want payment as it can interfere with Dept of Work and Pensions and other benefits.
- ME has a controversial history in which ME was dismissed as a psychosomatic condition. Many PwME feel stigmatised and concerned that others do not understand, or acknowledge their difficulties. Many will also be concerned that they, or others will be pushed to undertake a level of activity which would trigger PEM and, potentially worsen their condition. To successfully undertake ME research, it is important to gain PwME's trust by showing that you understand that ME is a physical condition, making clear that you believe them, recognising their difficulties, and accommodating their needs.
- Further details of practical steps to enable PwME's participation as a research participant or PPI representative are found in the appendix at the end of the document.

## Patient and Public Involvement

All the contributors reported that involving PwME and their supporters in their research was invaluable. They were keen to emphasise that PwME's input was important throughout the project, not just at the start or when applying for funding. They emphasised the importance of understanding the challenges for PwME when it came to recruitment, data collection, and dissemination, and how to accommodate their needs (see Appendix for further details). All the contributors had invested time and effort into establishing effective collaborations with PwME, and (where appropriate) their supporters, charities and ME clinicians before, or at the start of their work. All had an advisory or steering group of PwME with whom they consulted at all stages of the project(s). Different methods had been used to convene the advisory groups. The bigger studies started by involving established groups (e.g. the ME Research Collaborative' s (MERC) Patient Advisory Group) and ME charities (e.g. Action for ME and the ME Association) and other ME Support groups, before recruiting further volunteers from their members to be involved in the research. Others started with PwME with whom they had personal contacts and then reached out to participants in previous studies and/or more widely via social media (particularly Twitter) to recruit other members.

## Participant Selection and Recruitment

If steps are taken to ensure the demands of participating are acceptable to PwME, recruitment can be very successful. For example, Dr Clague-Baker (Physios For ME, University of Liverpool) took many of the steps recommended here and in the appendix, and recruited to target numbers within 24 hours of opening in one of their (albeit small) studies! She had expected it to take months based on her experience of working in other conditions. However, it is important for recruitment (and everyone's well-being) that you address the stigma and distrust some PwME feel towards researchers and clinical services by demonstrating that you believe in, and understand PwME. One way to do this is to clearly and transparently state your understanding of the underlying cause of, and difficulties caused by ME and which diagnostic criteria you are planning to use for recruitment. This can be a challenge as full consensus on which are most effective has yet to be reached. However the NICE Guidelines for ME (2021) recommend the Institute of Medicine's 2015 criteria as the 'best of the bunch' and the most useful for clinical use. The 'Canadian Consensus Criteria' (Carruthers et al 2003) are also widely used.

When devising selection criteria, researchers need to balance a desire to recruit as representative a sample as possible against the demands made on the PwME. It is recommended to keep the selection criteria as broad as possible to maximise recruitment, particularly those with very/severe ME who are often under-represented. Researchers need to specifically consider how to involve, engage, recruit (and retain) people with severe ME/CFS in studies. All the contributors highlighted this issue and made additional adaptations to involve people with very/severe as far as possible e.g. allowing questionnaires to be completed by a proxy, and being flexible with time scales or the ways of presenting information. Your PwME advisory group will be able to give you an insight into the issues and how to address them, and/or support groups for people with very/severe ME (such as the 25% ME Group) may be able to provide specific advice and support. Helen

Baxter of the 25% Group has published a paper with specific advice about involving people with very severe ME. Ensuring the Voice of the Very Severely Affected Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Patient Is Heard in Research

All contributors recommend recruiting through the ME community (ME Charities and support groups, FB groups, Twitter etc) rather than clinical services. This is because access to specialist ME services is limited and the majority of PwME will not be in contact with them either because they have completed treatment or have never had access to them. Furthermore people with very/ severe ME are generally under-represented in clinic populations as they are too unwell to travel to attend, and not all services offer home visits. They also may not have access to the internet, recruiting by placing invites in charities paper magazines is also a beneficial. Screening through primary care is not recommended as clinical coding of ME is inconsistent.

People from minoritised backgrounds are under-represented in both participant cohorts, and patient advisory groups and other PPI activities. Therefore researchers will need to make additional efforts to make contact with, and recruit PwME for a minoritised background.

## Choice of Outcomes and Outcome Measures

The choice of outcomes and how to measure them can be more complex than might initially appear in ME. Fatigue is often a primary outcome, but this is only one of many symptoms PwME experience. Thus studying and measuring it in isolation of other symptoms may miss important insights and impacts. For example, a treatment that reduces PwME's disability and/or symptoms other than fatigue would improve people's quality of life and be very welcome, even if fatigue levels are unaffected. Alternatively, PwME may pace their activities to reduce symptoms including fatigue. Recording a reduction in fatigue may not indicate the PwME is 'better', rather that they are effectively managing their condition this way. An increase in function/activity without an increase in PEM and symptoms may be a more accurate measure. Outcome measures need to reflect the full range of activity/disability and symptomology.

Some research studies have used a 'cure' or resolution of ME as their primary outcome. Anyone with ME would welcome a cure, but many recognise that this is unlikely to happen soon and focus on minimising the symptom severity and disability. Researchers should avoid arbitrary definitions of 'cure' as an outcome, especially the primary outcome.

Open and responsive consultation with PwME about the choice of outcomes and how to measure them is needed to ensure they are meaningful and relevant to PwME, and feasible and acceptable to collect.

## Data Collection

When arranging data collection, talk with the participant about their needs and preferences. Try to find out what they can/cannot do and how they do things - and be flexible and sensitive to accommodating them. Also reassure the PwME that they are free to express discomfort, stop data collection, or withdraw participation at any point. It is important to consider the risk, even when mitigations are made, that data collection may make the PwME 'overdo it' and trigger PEM (or crash, as it is often called). In this case, especially if it involves activity in which it is difficult for the PwME to just stop and rest (preferably in their own environment), it is worth devising an individualised contingency plan with the PwME to support them. This should be reflected in risk assessments and protocols regarding data collection.

Bear in mind:

- The cognitive and social/emotional, as well as the physical demands of participating in the research.
- PwME's energy levels fluctuate during the day and most have a time(s) of days when they are 'better' than others; be flexible about scheduling visits/data collection.
- Minimise travel demands by offering home visits or remote data collection (e.g. by remote video consultation or phone) whenever possible. If travel is unavoidable, offer and arrange transport to meet their needs.
- Learn to recognise when a PwME is starting to become more fatigued. For example speaking more quietly, or slowly, or a change in facial expression or pallor might indicate this. When this happens suggest taking a break or stopping to lessen the severity of the PEM.
- If sending material through the post, make sure there are no labels/logos etc which would identify the recipient as having ME to respect their privacy.

## Feedback

People with ME are often keen to better understand their condition and how to manage it and say they would value feedback about their individual results, including why screening was unsuccessful if rejected at the recruitment stage. Offering such feedback is likely to enhance both recruitment and retention. If feedback is not offered, it should be a conscious choice and justified/explained in any patient information.

## The Contributors

**Professor Chris Ponting (University of Edinburgh), chief investigator of the DecodeME;** the largest ME Study in the world to date which aims to find genetic causes for why people develop ME. It was funded by the Medical Research Council and National Institute for Health and Care Research. It involves recruiting up to 25,000 PwME to provide saliva samples for DNA analysis and complete online or paper–based questionnaires.

**Dr Nicola Clague-Baker (University of Liverpool), principal investigator for Physios for ME.** Physios For ME are a group of physiotherapists in the UK with a special interest in ME. Their aim is to research, educate and advocate to improve physiotherapy management for PwME. At present, work focusses on preparatory and feasibility studies to pave the way for larger, more definitive studies with the potential to impact on PwME's life's and recovery. Current and previous studies include assessing the feasibility of using physiological monitoring techniques during everyday activity in

PwME's homes as a possible way to measure post-exertional malaise and diagnose ME; heart rate monitoring to pace activity and to monitor post-exertional malaise, and vagal nerve stimulation (a possible treatment). They used mixed (qualitative and quantitative) methods including physiological monitoring. Some work has been funded by the ME Association, but most is self-funded with applications to ME Charities and the NIHR being prepared.

**Caroline Kingdon (London School of Hygiene and Tropical Medicine), UK Biobank for ME.** The UK Biobank for ME was established by a consortium of ME charities and a private donor in 2011. It is now funded by the National Institute for Research (United States) and the ME Association (UK). It has created an open biobank resource to enable translational research into the clinical and biomedical understanding of ME. The bank involves blood samples from PwME plus questionnaire data on participants' epidemiology/demography, personal and family history, potential risk factors, and symptomology and disability which are shared with ME researchers across the globe.

**Sonya Chowdury and Claire Dransfield and (Action for ME and Decode ME).** Action for ME led the James Lind Alliance Priority Setting Partnership for ME which involved working with PwME, their supporters and health care professionals to identify the top research priorities for PwME. A steering group of PwME, their supporters and health care professionals oversaw two rounds of online surveys and workshops for all stakeholders. Thus it truly was a project conceived and led by PwME. They are also co-leaders of DecodeME with Prof Ponting.

## *Appendix. Practical Steps to take to facilitate PwME's participation in research*

### Meetings

### General

- Wherever possible reuse resources (information, material, approaches, questionnaires, policies, protocols etc) which have been previously coproduced with PwME in order to maximise reproducibility and minimise the demands on PwME's energy.
- Long meetings will be infeasible for many. So be prepared to hold several shorter meetings instead. Maximum meeting time should be around one hour with at least one break built in. Any longer should be negotiated with participants, further negotiation may be needed for people with very/severe ME
- Allow (negotiated) time for recovery between meetings. For example, giving at least a week between meetings.
- Ensure chairs/ facilitators are sensitive to participants' needs to take breaks during meetings
- Cognitive impairment can make it difficult for PwME to follow conversations (especially if there is more than one at once), and take in and retain information. The chair can facilitate engagement by making any comments and explanations brief; putting important business at the start of meetings; and summarising discussion and conclusions frequently
- Material to prepare for, or participate in meetings need to be provided in a range of formats. Short video or audio recordings to explain/ talk through meeting papers or processes can be useful for PwME have limited energy for reading. Some research groups have set up a private YouTube channel to make the videos available in advance of meetings. However, other PwME are hypersensitive to sensory stimuli and are unable to tolerate visual or auditory stimuli for prolonged periods, so they would prefer written material. They may wish also material to be provided in a range of formats - electronically, paper/post, email etc.
- Although most will work online, some will prefer/need paper versions. So make sure these are available and any returns can be made electronically or in hard copy/post. Recognise that it will take longer for returns to arrive by post, so adjust deadlines accordingly.
- However material is provided, make sure they are provided in advance. PwME's need time to prepare for meetings. Commit to share all meeting papers in written or video/ audio form at least two weeks in advance. And stick to it.
- Recognise that it can also take time to respond to questions, requests for information, ideas, or to review material. Take advice from the PwME about what is a reasonable timescale to expect a response – and stick to it.
- Be aware that much of the business of a series of meetings will need to take place offline so PwME can work at their own pace. Make sure these are easily available eg via email, Teams or an online repository such as GoogleDocs.
- Send a reminder and the agenda a day or two in advance of the meeting or any other deadlines.

- Vary meeting times (early/late am/pm and days of the week) to facilitate attendance/ contribution from many people as possible. However, first thing in the morning is the least popular option.
- Maximum one hour meetings with a short break included and one meeting per week.
- ME is a fluctuating disease and so it cannot be assumed that all PwME will be able to contribute long-term. Assume that some members will need to take a break (either temporarily, or sometime permanently) from attending meetings due to health or personal circumstances. This should be reflected in the initial numbers recruited, or be prepared to have further rounds of recruitment during the project.
- If members were too unwell to attend a meeting, the option to contribute by other means (e.g. email, individual phone calls or remote meetings) should be offered either before or soon after the meeting.
- Respond to feedback about how meeting could be made more accessible/ acceptable.

### For written and online material

- Minimise the number of words - include nothing that isn't essential.
- Pay careful attention to colours, font style and size and any graphics to ensure they are easy for PwME to read and understand. Pilot the text to ensure the wording and instructions are clear. For example use a clean Sans Serif font and allow plenty of spaces between text and paragraphs. A mid-grey background can reduce the glare of white or extreme contrasts which some find jarring.  Building an accessibility widget into websites enable the user to customise screen to their individual needs. Include the ability to download and obtain a paper copy of any information.
- Provide any extra information (e.g. Q&A's or supporting information) in a separate document or link to keep main documents (e.g. consent, surveys/questionnaires) concise
- When structuring online material (e.g. consent/ surveys/questionnaires) arrange any work (e.g. reading text, answering questions etc) into manageable chunks or stages, so respondents can take a break, completing the work over several days if necessary.
    - Any entries need to be automatically saved, and structured so the participant can stop and restart after having a break, or exit the material and then return to the place they left.
    - Let people know what they are being asked to do and how long it might take to complete (recognising that it will vary between individuals) before starting, they are able to manage the energy demands.
    - If the written material is extensive, provide a search function so respondents can find the section which is more important/relevant to them.
- Divide emails into 'essential information' and 'more information if time or energy allow' sections

### Remote meetings

- During meetings, respect PwME's needs to restrict visual or audio stimulation. This may include turning the camera off, ensuring no-one has bright or moving backgrounds, and keeping background noise to a minimum.

- Some people have difficulty following multiple conversations and may find it easier to use the chat function during meetings rather than speaking, so encourage this.
- Some people may not be able to attend 'in person' whether remotely or in real life, however joining by phone (no visual stimulus to cope with) may be a possibility.
- Make sure all participants are familiar with, and confident to use any technology (e.g. Zoom) before the meeting. This may involve written, or video guides, or 'practice sessions'. Include advice on on-screen display options, backgrounds and filters, noise reduction, etc. to ensure the meetings were as accessible as possible.
- Send a reminder of any login details a day or two in advance of the meeting.

### Face-to-face meetings

- If a face-to-face meeting is planned, consider the layout of the room. Try to avoid seating PwME facing windows or other light sources as this may be uncomfortable for those with light sensitivity. If possible have a separate room that can be used as a quiet rest/pacing area.

### Data collection

- Pilot data collection methods with PwME before the 'full launch'. Do not assume that processes that were successful for other conditions will be suitable for PwME. Make sure to include people with the full range of severity of illness, and types of symptoms that will be recruited in the full study.
- Allow more time than you expect for any response, negotiate realistic timescales with each individual.
- Send reminders before any deadlines.
- Some people with very/severe symptoms may be unable to respond electronically, or in writing but may be able to do so by phone or video conferencing call. Alternatively, they may be able to respond verbally, or with a proxy to complete any forms.