Guidelines for the Design of Clinical Studies in ME/CFS

The Community Advisory Committee (CAC) for the NIH ME/CFS Research Network was established to bridge the gap between researchers and the ME/CFS community with the goal of accelerating the pace of ME/CFS research. The CAC is a group of 15 individuals from various professional backgrounds, all of whom have lived experience of the disease.

The CAC - Study Feasibility working group developed this quick reference guide to aid researchers in the design of clinical studies and the development of IRB protocols for studies involving the ME/CFS population. These recommendations provide the patient perspective on accommodating the unique sensitivities and limitations of the population to produce more robust studies by improving study retention and completion.

The Study Feasibility working group will be holding **informational sessions** to discuss items related to the submission of the NIH CRC grant applications on the following **Wednesdays at 3PM ET: May 4, May 11 and May 18, 2022.**

Researchers, study coordinators and/or administrators are encouraged to contact us at any time at: CAC.MECFS@gmail.com

The authors of this guide and the hosts of the upcoming informational sessions are: Kathi Kuehnel, Cherylle McFarlane, Jaime Seltzer (chair) and Susan Taylor-Brown (co-chair) and CAC Director, Allison Kanas.

Eligibility Criteria

ME/CFS case selection criteria have historically been inconsistent. To ensure compatibility of study data and results, the use of following case selection criteria is highly recommended. More than one set of criteria may be used to determine subject eligibility. These definitions include the cardinal symptom of post-exertional malaise (PEM).

- Canadian Consensus Criteria (2003)
- International Consensus Criteria (2011)
- Institute of Medicine (2015)

Instrumentation & Measurement Tools

- Use NINDS Common Data Elements
- Consider incorporating the use of wearable devices to measure activity levels
- Consider incorporating the use of symptom tracking apps, such as You+M.E.

Recruitment

Recruiting ME/CFS participants can be difficult due to barriers to diagnosis. The disease causes fatigue and may feature sensory sensitivities, cognitive impairment, and a limited ability to work, contributing to physical and economic barriers to participation.

General Strategies

- Partner with this Community Advisory Committee for specific guidance on reaching target populations
- Contact advocacy organizations, e.g. #MEAction, Solve ME for study promotion
- Post open studies on ME/CFSnet website
- Utilize Clinical and Translational Science Awards (CTSAs) hubs
- Post on Clinical Trials.gov (note: non-interventional studies are allowed)
- Use paid recruitment services such as researchmatch.org
- Use site-specific recruitment services (eg Columbia University Recruit Me)
- Partner with ME/CFS clinical sites in the region, such as:
    - Bateman Horne Center (Utah)
    - Susan Levine, MD (New York)
    - Simmaron Research (Nevada)
    - Institute for Neuro-Immune Medicine (New York, Upstate)
    - Hunter-Hopkins Center (North Carolina)
    - Pain and Fatigue Center at Icahn School of Medicine at Mt. Sinai (New York)
    - The Harvard ME/CFS Collaboration (Massachusetts)
    - Stanford ME/CFS Initiative (California, Bay Area)

Target Populations

Many research studies have included primarily white women with access to ME/CFS medical specialists, increasing the risk for sampling bias. BIPOC patients, the severely ill, and men often go undiagnosed, and thus are often under-represented in studies. Sedentary controls are recommended to rule out deconditioning as a potential confound.

Severely ill subjects

Since 25% of people with ME/CFS are housebound or bedbound, their enrollment in research studies poses a significant challenge. Without inclusion of the severely ill, the study findings may not be generalizable. Potential approaches for the recruitment of severely ill subjects include:

- Partnering with multiple ME clinics and/or clinicians to reach recruitment goals for severe patients
- Contacting social media groups for severely ill patients and caregivers

BIPOC populations

Recruiting participants who are Black, Indigenous and People of Color (BIPOC) may pose a challenge due to documented health care disparities in these populations. Under-representation in studies is not just a health equity concern but affects the quality and generalizability of findings. The use of the DePaul Symptom Questionnaire (DSQ) may allow for an increased diagnosis rate, thus expanding the potential subject pool. Oversampling in underserved and/or underrepresented populations is recommended. Suggestions for recruiting BIPOC subjects include:

- **Contact:**
    - Federally Qualified Health Centers and other medical providers or public health care clincs that serve BIPOC communities
    - Local ESL learning centers and translate recruitment flyers into multiple languages
    - Organizations such as WEGO Health to identify patient leaders
    - BIPOC fraternities and sororities and/or National Pan-Hellenic Council (The “Divine Nine”)
    - Religious, spiritual and community centers
    - Veterans Administration Clinics

- **Advertise** in outlets focused on the target population, including:
    - Articles in magazines/journals
    - Podcasts
    - Social media

Men

- Place online flyers within groups designated for men with ME/CFS, such as the #MEAction Men's Facebook Group

Sedentary controls

Matching healthy controls based on activity level, along with demographic data is recommended. Suggested sources for reaching sedentary controls include:

- College campuses for young, sedentary controls from university health centers
- Physical therapy practices with access to subjects who are healthy yet sedentary
- Clinical entities, such as the Bateman-Horne Center, with a connection to a university hospital system, or large-scale care providers such as Kaiser or One Medical

Accommodations & Study Retention

Providing appropriate accommodations helps to ensure subject retention and study completion.

General Strategies

- Ensure that all study materials are available in advance, online, and are printable
- Use disability-accessible fonts and formatting for all study materials. Using boldface on key concepts may be helpful
- Whenever feasible, hold study visits remotely
- Provide flexible appointment options for in-person visits
- Avoid early morning start time and limit the duration of visits
- For the severely ill, consider home visits with a mobile phlebotomist or research nurse
- Consider enlisting a patient advocate, sensitive to the needs of the population, to help subjects complete the study materials and navigate the visits
- Provide transportation assistance by arranging transportation services (car, taxi, medical van, ambulance) or provide travel vouchers (taxi, subway cards, bus tickets, medical vans) or provide transportation reimbursement
- Provide compensation for study participation preferably in the form of cash or a credit card. Single vendor gift cards are discouraged
- Provide a listing of social worker support services
- Create a study resources package and/or accompanying video to include:
    - Directions and maps to the room location, including transit, road, campus and building maps
    - List of available transportation options
    - A study summary explaining the study goals and an explanation of the activities to be performed at each study visit
    - Link to online/printable study materials
    - Directions for downloading and using a screen reader for devices
    - List of available childcare options with contact information
    - Contact information for study coordinator and on-site clinic office

Study Visit Recommendations

Before the visit

Contact the participant or caregiver via phone or email to:

- Ensure they and/or their caregivers received the study resources package
- Answer any questions
- Remind them of the transportation options and offer additional assistance
- Ensure they have all necessary maps, including a campus and building map
- Inquire if an escort or a wheelchair is needed
- Offer priority parking, if available

During the visit

Offer participants:

- A quiet, dark area where they can rest in a reclined position
- Accommodations for accompanying caregivers
- A screen reader for viewing electronic study materials
- Printed copies of study materials, in case they have difficulty reading a screen

Blood sample collection:

- Advise participants to maximize fluid intake before, during and after blood draws.
- Provide water, free-of-common-allergen snacks, and/or electrolyte powder
- Provide a skilled phlebotomist. People with ME/CFS are often “hard sticks”
- Remember that POTS is often comorbid with ME/CFS and increases the risk of syncope
- People with ME/CFS may have low blood volume, so it is especially important to set a fixed upper limit for the total volume drawn. While no more than 120mL are recommended for ill adults in a 24 hour period, we recommend <80mL for people with ME/CFS.
- Coordinate draws for subjects participating in more than one study to avoid exceeding recommended blood draw volume limit

After the visit

Contact the subject or caregiver via phone or email to:

- Thank them for their participation
- Ask how they tolerated the experience and monitor for PEM symptoms
- Ensure they received compensation for their participation
- Remind them of upcoming study visits or activities
- Ensure they have the coordinators’ contact information
- Remind them they may be contacted regarding future research, if applicable

Special Considerations

It is important to remain aware that people with ME/CFS are often more ill than they may appear. Many have been ill for decades. They may have sensory sensitivities, moderate cognitive dysfunction and may experience PEM following either physical or mental exertion. Many report symptom fluctuations based on seasonality.

They also may be less trusting of the medical community because they have often been incorrectly diagnosed, marginalized, and stigmatized. For these reasons:

- Use clear and accessible language about how study data will be used and stored
- Consider the potential for seasonality differences in the study design
- Consider incorporating long-term follow-up in the study design to ensure that subjects' symptoms have not worsened following study participation
- Clearly define the differences between researchers and clinicians
- Explain whether the subject will have access to study data or results or obtain medical care as a part of their participation
- Design studies that do not require the subjects to cease medical interventions as this may induce negative long-term health consequences

This work was supported by US Public Health Service Grant 5U54AI138370. The content does not represent the official views of the National Institute of Neurological Disorders and Stroke or the National Institutes of Health.