

Research Case Definition Consensus Statement

Internationally, clinical definitions for Myalgic Encephalomyelitis (ME), sometimes called ME/CFS, have been adopted in many countries, but there is still no consensus around research criteria. In 2015, the Institute of Medicine in the US developed a clinical case definition for ME/CFS, but this was never meant to be used for research. For decades, research into ME has been hampered by heterogeneous diagnostic criteria and the inclusion of participants who may not actually have ME.

This has impacted the validity of many studies and created a risk of harm for patients. There is still not an international consensus on a research case definition or case definitions.

The core problem is that many case definitions do not require key symptoms such as post-exertional malaise and do not take the severity of the symptoms into account. Further, methods for evaluating cases have been inconsistent. The time has come to improve cross-study comparability and ensure study participants have ME. We the undersigned believe the time has come to sponsor an international effort to create a consensus on the criteria and methods for selecting cases in research. Such a consensus will need to address multiple issues, including those below.

- A consistent set of required inclusion criteria. One example is the requirement for **substantial impairment in functioning** and **post-exertional malaise**¹ lasting six months or more in all research criteria for people with ME, with **cognitive impairment** and **unrefreshing sleep** considered key features.^{2,3,4*}
- A consistent approach to **exclusionary conditions**. This includes any previously diagnosed medical condition whose resolution has not been documented beyond reasonable clinical doubt and whose continued activity may explain the symptoms of ME.^{5**}
- A consistent **approach for evaluation of key criteria**. This is done with structured questionnaires that evaluate both symptom severity and frequency as well as level of functional impairment. An example of a widely used method is the DePaul Symptom Questionnaire.^{6,7,8} Research publications should outline how criteria have been operationalized.
- A consistent approach to characterizing and labeling overall disease severity of cases^{9,10,11,12,13***}

* There are many secondary symptoms that may be experienced by people with ME including orthostatic intolerance, pain, immune, and gastro-intestinal complaints.

** While clinically a patient can have both ME and other diagnoses, in research, it's important to have a consistent approach to exclusions to improve cross-study comparability.

The Canadian Consensus Criteria, ME-International Consensus Criteria, and NICE 2021 criteria meet many of these standards. The IOM criteria meet these standards when using the proposed exclusionary criteria and when cognitive impairment is required. The Fukuda criteria do not meet these standards.

The following individuals and organizations support the statements above and call for the convening of an international effort to create a consensus on the criteria and methods for selecting cases in ME research.

Scientists/Clinicians

Daniel M Altmann, PhD, Professor, Department of Immunology and Inflammation, Imperial College, UK

Christopher W Armstrong, PhD, Research Fellow, Department of Biochemistry & Pharmacology, The University of Melbourne, Australia

Duncan Baird, PhD, Professor of Cancer and Genetics, Cardiff University, UK

Sara Ballouz, Ph.D., Garvan-Weizmann Centre for Cellular Genomics at the Garvan Institute of Medical Research, Australia.

Jonas Bergquist, MD PhD, Director of the ME/CSF CRC at Biomedical Centre, Uppsala University Sweden, Chief Medical Officer Open Medicine Foundation, Sweden

Saul Berkovitz, MD, Consultant Physician, University College London Hospitals NHS Foundation Trust, UK

Hector Bonilla, MD, Associate Professor of Medicine and Infectious Diseases, Director, ME/CFS Clinic, Co-Director, Stanford Post-Acute COVID-19 Syndrome Clinic, CA, USA

Jos A. Bosch, PhD, University of Amsterdam, Faculty of Social and Behavioural Sciences, Programme group Clinical Psychology, Netherlands

Geraldine Cambridge PhD UK, Cambridge Department Medicine, University College London, UK

Kenny L. De Meirleir, MD, PhD, Professor Emeritus Physiology and Medicine (Vrije Universiteit Brussels). Medical Director, Whittemore-Peterson Institute, University of Nevada, NV, USA

Paul R Fisher, PhD, Emeritus Professor of Microbiology, Head of Microbial Cell Biology Group, La Trobe University, Melbourne, Victoria, Australia.

Øystein Fluge, MD, Senior Consultant, Department of Oncology and Medical Physics, University of Bergen, Haukeland University Hospital, Bergen, Norway

Fred Friedberg, PhD, Research Professor, School of Medicine, Stony Brook University, NY, USA

Kenneth J. Friedman, Adjunct Associate Professor of Medicine, Rowan School of Osteopathic Medicine Stratford, NJ, USA

Jacob Furst, PhD, Professor of College of Computing and Digital Media, DePaul University, IL, USA

Elisa Josefa Oltra Garcia, PhD, Professor of Cell and Molecular Biology at the Universidad Católica de Valencia "San Vicente Mártir", Valencia, Spain.

Minghao Gong, PhD, The Jackson Laboratory for Genomic Medicine, CT, USA

Carl-Gerhard Gottfries, MD, PhD, Professor, University of Gothenburg, Sweden

Monica Verduzco Gutierrez, MD, Dept of Rehab Medicine, UT Health San Antonio, TX, USA

Tonya Hall, PhD, Chicago State University, IL, USA

Kathryn Hoffmann, MD, PhD, MPH, Professor, Department of Primary Care Medicine, Medical University of Vienna, Austria

H. Timothy Hsiao, PhD, CSO, Solve M.E., CA, USA

Brian Hughes, PhD, Professor of Psychology at the University of Galway, Ireland

Leonard A Jason PhD, Director Center for Community Research, DePaul University, IL, USA

Ben Katz, MD, Ann & Robert H. Lurie Children's Hospital, IL, USA

Caroline Kingdon RN, MSc, NICE Committee Member, UK

Charles Lapp, MD, Director Hunter-Hopkins Center, NC, USA

Eliana Lacerda MD, PhD, MSc, Clinical Assistant Professor, London School of Hygiene and Tropical Medicine, London, UK

Karl Morten, PhD. Nuffield Department of Obstetrics and Gynaecology, John Radcliffe Hospital, Oxford University, UK

Nina Muirhead, MD, Doctors with ME, UK

Modra Murovska, MD, PhD, Institute of Microbiology and Virology, Riga Stradins University, Latvia

Luis Nacul, MD, Medical Director of the Complex Chronic Diseases Program at British Columbia Women's Hospital in Vancouver, Canada

Raymond Perrin, DO PhD., Honorary Senior lecturer at the Allied Health Professions Research Unit, University of Central Lancashire, in Preston, UK.

Chris Ponting, PhD, Section Head at Biomedical Genomics, Chair of Medical Bioinformatics, and a Principal Investigator at the MRC Human Genetics Unit, Institute of Genetics and Molecular Medicine at the University of Edinburgh, UK

Judith A. Richman, PhD, Professor Emerita of Psychiatry, University of Illinois at Chicago, IL, USA

Doreen Salina, Ph.D., Northwestern University, IL, USA

Carmen Scheibenbogen, ME, Director of the Institute for Medical Immunology of the Charité University Hospital in Berlin, Germany

Eran Segal. PhD. Professor. Weizmann Institute of Science. Israel

Charles Shepherd, MB, BS, Honorary Medical Adviser to the ME Association, UK

Zaki Sherif, MD Professor, Department of Biochemistry & Molecular Biology. Howard University College of Medicine, DC, USA

Matthew R. Sorenson, PhD, Associate Dean for Graduate Nursing Education, Texas A&M University, TX, USA

David Systrom, MD, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

Taylor-Brown, Susan, PhD, clinical professor (Ret.), Pediatrics, Golisano Children's Hospital, NY, USA

David Tuller, DrPH, Senior Fellow in Public Health and Journalism, Center for Global Public Health, University of California, Berkeley

Derya Unutmaz MD, The Jackson Laboratory for Genomic Medicine, USA

Dmitry Veprintsev, Professor of Molecular and Cellular Pharmacology at the University of Nottingham. UK

Thomas Vogl, PhD. Medical University of Vienna, Austria

Francisco Westermeier, PhD. FH Joanneum, University of Applied Sciences, Graz, Austria

Organizations

12ME, Michiel Tack, Belgium

25% ME Group, Helen Baxter, UK

Emerge Australia. Anne Wilson, Melbourne, Australia.

Groep ME-Den Haag, Mirande de Rijke, Netherlands

Health Rising. Cort Johnson Founder and President

Hope 4 ME & Fibro Northern Ireland. Joan McParland MBE, UK

#MEAAction, Laurie Jones, USA

#MEAAction Scotland, Janet Sylvester,

#MEAAction UK, Denise Spreag

Massachusetts ME/CFS & FM Assoc. Susan Buckley, President. Massachusetts, USA

ME/cvs Vereniging, Jordy de Haan - Voorzitter, Netherlands

ME Research UK, Jonathan Davies, Chair of Trustees, UK

Minnesota MECFS Alliance, Suzanne Wheeler, President. Minnesota, USA

Millions Missing Canada. Barbara Fifield, Cofounder. Kitchener, Canada

Open Medicine Foundation. Linda Tannenbaum, Founder & CEO/President. CA, USA

Pandora Org. Lori Kroger, RN CEO. Michigan, USA

Richmond and Kingston ME Group, Fernando Campo, Treasurer, UK

Solve M.E. Emily Taylor, President. CA, USA

The Associated New Zealand ME Society (ANZMES). Fiona Charlton, President. New Zealand
Welsh Association of ME& CFS Support (WAMES). Jan Russell. UK

Patients, Advocates, and Supporters

Lindsay Baran, MS, USA

Mary Dimmock, Patient Advocate, USA

Billy Hanlon, Director of Advocacy & Outreach, Minnesota ME/CFS Alliance

Adam Lowe, Poet, Patient Advocate, NICE Lay Committee Member, UK

Suvetha Ravichandran, BA DePaul University, USA

Rivka Solomon, ME/CFS & Long COVID Patient Advocate, USA

Janet Stone, Patient Advocate, Innova Consulting and Advocacy, USA

Footnotes

¹ Recently, the World ME Alliance, with 24 member organizations across 17 countries, supported the inclusion of PEM as a core symptom. Standing Strong: Global ME Community unified in support of NICE 2021 ME/CFS Guideline. 2023. Available at:
<https://worldmealliance.org/2023/08/standing-strong-global-me-community-unified-in-support-of-nice-2021-me-cfs-guideline/>

² Kingdon, C, Abken, E, Lacerda, E & Nacul, L. A proposal for consensus diagnostic criteria for ME/CFS research. Poster presented at the meeting of the International Association of ME/CFS, Stonybrook University, N.Y. 2023

³ Jason, L. A. & Ravichandran, S. An effort to develop a consensus on critical ME/CFS definitional issues. Poster presented at the meeting of the International Association of ME/CFS, Stonybrook University, N.Y. 2023

⁴ Nacul L, Authier FJ, Scheibenbogen C, Lorusso L, Helland IB, Martin JA, Sirbu CA, Mengshoel AM, Polo O, Behrends U, Nielsen H, Grabowski P, Sekulic S, Sepulveda N, Estévez-López F, Zalewski P, Pheby DFH, Castro-Marrero J, Sakkas GK, Capelli E, Brundsdlund I, Cullinan J, Krumina A, Bergquist J, Murovska M, Vermuelen RCW, Lacerda EM. European Network on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (EUROMENE): Expert Consensus on the Diagnosis, Service Provision, and Care of People with ME/CFS in Europe. *Medicina* (Kaunas). 2021 May 19;57(5):510. doi: 10.3390/medicina57050510.

⁵ See Table 2 in Jason, L.A., Ravichandran, S., Katz, B.Z., Natelson, B.H., & Bonilla, H.F. Establishing a consensus on ME/CFS exclusionary illnesses. *Fatigue: Biomedicine, Health & Behavior*, 2023; 11(1), 1-13. <https://doi.org/10.1080/21641846.2022.2150487>

⁶ Nacul L, Kingdon CC, Bowman EW, Curran H, Lacerda EM. Differing case definitions point to the need for an accurate diagnosis of myalgic encephalomyelitis/chronic fatigue syndrome. *Fatigue: Biomedicine, Health & Behavior*, 2017;5(1):1-4. doi: 10.1080/21641846.2017.1273863. PMID: 29250461; PMCID: PMC5730342.

⁷ Sunnquist, M., Lazarus, S., & Jason, L.A. The development of a short form of the DePaul Symptom Questionnaire. *Rehabilitation Psychology*, 2019, 64(4), 453–462. [PMCID: PMC6697554
https://doi.org/10.1037/rep0000285](https://doi.org/10.1037/rep0000285)

⁸ Cotler, J., Holtzman, C., Dudun, C., & Jason, L.A. A brief questionnaire to assess post-exertional malaise. *Diagnostics*, 2018, 8, 66. doi:10.3390/diagnostics8030066

⁹ Carruthers BM, van de Sande MI, De Meirleir KL, et al. Myalgic encephalomyelitis: International Consensus Criteria. *J Intern Med*. 2011; 270: 327-338.

¹⁰ Bateman L, Bested AC, Bonilla HF, et al. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: essentials of diagnosis and management. *Mayo Clinic Proc*. 2021;96(11):2861–2878. Available from: <https://www.mayoclinicproceedings.org/action/showPdf?pii=S0025-6196%2821%2900513-9#page=10>

¹¹ Cox, D. L., & Findley, L.J. The Management of Chronic Fatigue Syndrome in an Inpatient Setting: Presentation of an Approach and Perceived Outcome. *British Journal of Occupational Therapy*, 1998, 61(9), 405–09. <https://journals.sagepub.com/doi/10.1177/030802269806100907>

¹² Conroy, K., Bhatia, S., Islam, M., & Jason, L.A. Homebound versus bedridden status among patients with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. *Healthcare*, 2021, 9(2), 106. <https://doi.org/10.3390/healthcare9020106>

¹³ Wiedbusch, E., & Jason, L.A. Comparing operationalized approaches for substantial reduction of functioning in Chronic Fatigue Syndrome and Myalgic Encephalomyelitis. *Archives of Community Medicine*, 2022, 4(1), 59-63. PMCID: PMC9168545 <https://doi.org/10.36959/547/653>