FEBRUARY 2025

Designing Studies for Patients with PEM/PESE

For Researchers Active in Sweden

Svenska Covidföreningen

Purpose of the Guide

A thorough understanding of PEM/PESE is crucial for ensuring high-quality research on populations experiencing exertion-induced symptom exacerbation. Proper knowledge helps generate useful results and reduces risks for study participants. Therefore, we have compiled best practices and recommendations for study design in this guide, specifically aimed at researchers. It also includes a brief introduction to PEM/PESE.

This guide has been fact-checked by Marianne Hartford, MD and PhD.

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The Short Checklist

- Have patient representatives been involved at an early stage?
- Are risks associated with PEM described in the ethics application and in the information provided to research participants?
- Are criteria used that can identify and distinguish patients with PEM?
- Are outcome measures used that can capture worsened or improved PEM during the study period?
- Is PEM measured at the appropriate times?
- Is the study designed to allow patients who withdraw due to worsened PEM to report their reasons for doing so?
- Has a risk/benefit assessment been conducted for the various components of the study? How can the study be adapted to reduce the risk of PEM?
- Does the study capture changes in the patient's overall activity level? (To compensate for the burden of study participation, the patient may reduce other activities in an effort to avoid PEM).

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2. PEM/PESE in Brief

2.1 Present in Approximately 50 Percent of Patients

Exertion-induced symptom exacerbation is common in post-COVID and occurs in about 50 percent of patients.[1] It is also a mandatory diagnostic criterion for ME – a disease that can also arise after a viral infection.[2] In English, the condition is referred to as **post-exertional malaise (PEM)** or **post-exertional symptom exacerbation (PESE)**. The abbreviations, PEM/PESE, are also used in Swedish.

2.2 A Medical Disability

PEM/PESE is a medical disability that falls under the category of *energy impairment*—i.e., disabilities related to the body's energy production.[3] Unlike other conditions, exercise or other energy-demanding activities can be detrimental to the body and reduce long-term functionality for individuals with PEM/PESE. Research has shown that PEM/PESE is physiologically distinct from deconditioning, meaning it is not simply poor physical fitness.[4]

The degree of disability from PEM/PESE can vary from person to person, but it can also fluctuate for the same individual over time. This is referred to as episodic disability. A person may experience both **permanent and episodic disabilities at the same time**, but there are still clear differences between them. Episodic disability is characterized by better and worse periods (macro-cycling) and better and worse days (micro-cycling) – in other words, well-being and disability levels can fluctuate over time.

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[1] See e.g. 2024 NASEM definition, Wesley, E., Brown, M., Fineberg, H., Long Covid Defined, New England Journal of Medicine, 2024/08/01, DOI: 10.1056/NEJMsb2408466; Pagen DME, Van Herck M, van Bilsen CJA, Brinkhues S, Konings K, den Heijer CDJ, et al. High proportions of post-exertional malaise and orthostatic intolerance in people living with post-COVID-19 condition: the PRIME post-COVID study. Frontiers in Medicine Available from: https://doi.org/10.3389/fmed.2023.1292446, cited in SBU's report, Insatser vid postcovid och andra närliggande tillstånd och syndrom, 2024, p. 12 footnote 28, https://www.sbu.se/sv/publikationer/sbu-bereder/insatser-vid-postcovid-och-andra-narliggande-tillstand-och-syndrom--en-kartlaggning/ and Davis, H.E., McCorkell, L., Vogel, J.M. et al. Long COVID: major findings, mechanisms and recommendations. Nat Rev Microbiol 21, 133–146 (2023). https://doi.org/10.1038/s41579-022-00846-2 with referrals (footnote 10, 11, 29 100).
[2] See Canadian Consensus Criteria and ICC.
[3] Chronic Illness Inclusion, What are energy impairment and ELCI?, 2021, https://chronicillnessinclusion.org.uk/2021/04/28/what-are-energy-impairment-and-elci/ and Energy Limiting Conditions and Disability, https://chronicillnessinclusion.org.uk/our-work/elci-energy-impairment-disability/. See also Ed Yong, Fatigue can Shatter a Person, The Atlantic, 27 juli 2023, https://www.theatlantic.com/health/archive/2023/07/chronic-fatigue-long-covid-symptoms/674834/
[4] Joseph P, Singh I, Oliveira R, et al. Exercise Pathophysiology in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome and Postacute Sequelae of SARS-CoV-2: More in Common Than Not?. Chest. 2023;164(3):717-726. doi:10.1016/j.chest.2023.03.049

2.3 WHO's Description of PEM/PESE

The World Health Organization (WHO) describes PEM/PESE as "worsening of symptoms that can follow minimal cognitive, physical, emotional, or social activity, or activity that could previously be tolerated. Symptoms typically worsen 12 to 72 hours after activity and can last for days or even weeks, sometimes leading to a relapse. PESE can contribute to the episodic nature of disability in post COVID-19 condition, often presenting as unpredictable fluctuations in symptoms and function."[5]

2.4 Symptom Deterioration in Focus

The clinical picture of PEM/PESE differs from what individuals with fatigue might experience if they exceed their energy limit. This is partly because the symptom deterioration is *more pronounced* and also because it *encompasses multiple types of symptoms*.

For example, the following symptoms may arise or worsen: fever, pain, headache, sleep difficulties, flu-like symptoms, cognitive impairment, fatigue, blurred vision, swollen lymph nodes, breathing difficulties/dysfunctional breathing patterns, orthostatic intolerance, and high heart rate (symptoms from the autonomic nervous system, such as abnormally high heart rate in an upright position and orthostatic intolerance, are common in POTS).

PEM/PESE also differs from fatigue, exhaustion, and deconditioning (poor fitness) on a pathophysiological level (see section 2.5, What causes PEM/PESE according to research? as well as footnote 4).

Symptom deterioration may occur directly during an activity or with some delay. Sometimes, the deterioration happens only after the individual has exceeded their energy limit repeatedly over a longer period. This can be referred to as accumulated PEM/PESE. A certain activity may be manageable for three consecutive days without causing deterioration, but when repeated on days four and five, it triggers PEM/PESE.For patients with a higher functional level, it may be possible to work part-time for two months before the crash occurs. How long the deterioration lasts depends on how much and how long the energy account has been "overdrawn."

This delayed feedback loop can make it especially difficult to see the connection between the level of exertion and the symptom level—particularly for newly diagnosed patients who have not yet identified the pattern. Perhaps the patient does not make the connection at all, instead thinking they are suffering from infections intermittently (since common symptoms of PEM/PESE include fever, sore throat, cold symptoms, and swollen lymph nodes).

[5] WHO, Clinical Management of COVID-19, Living Guideline, august 2023, p. 115, https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2023.2

2.5 What Causes PEM/PESE According to Research?

In September 2024, a review article was published in the scientific journal *Infection*, which can deepen the understanding of PEM/PESE in post-COVID and ME. The authors describe that during physical activity, affected patients show reduced systemic oxygen extraction and disturbed oxygen metabolism. An increasing number of studies suggest that this is mediated by dysfunction in the mitochondria (the energy-producing organelles of the cells) and disturbed microcirculation on multiple levels, disturbances that are sustained by latent immune activation. The accumulation of molecules such as lactate and reactive oxygen species (ROS), which have been observed in studies, can further trigger local and systemic immunological effects. This disturbed peripheral energy metabolism can, according to the accumulated evidence, theoretically explain the long-term deterioration of symptoms and reduced recovery capacity exhibited by patients with PEM/PESE.[6]

3. Considering PEM/PESE Brings Benefits for Researchers

Taking PEM/PESE into account is not just a methodological and ethical issue—it also provides several benefits for researchers:

- A well-adapted study design makes it significantly easier to recruit patients. Many patients are willing to participate in studies but must decline because study protocols are too burdensome, which can delay or even prevent study recruitment.
- Only an adapted study design allows research on the most severely affected patients, who exhibit pronounced functional impairments—an area of interest for many researchers.
- An adapted study design reduces the risk that any positive effects of an intervention are overshadowed by the increased exertion that study participation itself imposes on patients.

[6] Haunhorst S, Dudziak D, Scheibenbogen C, et al. Towards an understanding of physical activity-induced post-exertional malaise: Insights into microvascular alterations and immunometabolic interactions in post-COVID condition and myalgic encephalomyelitis/chronic fatigue syndrome. Infection. Published online September 6, 2024.https://doi.org/10.1007/s15010-024-02386-8

4. Selection of Study Population & Inclusion Criteria

4.1 Post-COVID

It should always be possible to stratify the study population based on the presence of exertion-induced symptom exacerbation. To enable this, tools capable of identifying PEM/PESE should be included, such as:

- **DSQ-PEM**[7]
- **SEID criteria**[8]

4.2 ME

Since PEM/PESE is the hallmark symptom of ME, inclusion criteria requiring the presence of PEM/PESE should be chosen, such as:

- **Canadian Consensus Criteria (CCC)**[9]
- **International Consensus Criteria for ME (ICC)**[10]
- **SEID criteria**[11]

The **Fukuda Criteria and Oxford Criteria should be avoided**, as they do not list PEM/PESE as a mandatory symptom.[12]

[7] Cotler J, Holtzman C, Dudun C, Jason LA. A Brief Questionnaire to Assess Post-Exertional Malaise. Diagnostics (Basel). 2018 Sep 11;8(3):66. doi: 10.3390/diagnostics8030066. PMID: 30208578; PMCID: PMC6165517. Official translation to Swedish is available at Svenska Covidföreningen's web site, https://covidforeningen.se/wp-content/uploads/dsq-pem-officiell-oversattning-svenska.pdf

[8] Institute of Medicine of the National Academies, Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, Report Guide for Clinicians, https://nap.nationalacademies.org/resource/19012/MECFScliniciansguide.pdf

[9] Now also available in Swedish via viss.nu, Kunsskapsstöd, Vårdprogram ME/CFS, under headline Utredning, Diagnoskriterier, https://viss.nu/kunskapsstod/vardprogram/me-cfs#Kriterier

[10] ME Resarch UK, International Consensus Criteria, https://www.meresearch.org.uk/research/international-criteria/

[11] Institute of Medicine of the National Academies, Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, Report Guide for Clinicians, https://nap.nationalacademies.org/resource/19012/MECFScliniciansguide.pdf

[12] MEPEDIA, Fukuda criteria, https://me-pedia.org/wiki/Fukuda_criteria and Oxford criteria, https://me-pedia.org/wiki/Oxford_criteria

5. Choice of Outcome Measures

Outcome measures that can **assess the severity of PEM/PESE** and capture exacerbations typical of PEM/PESE should be selected, such as:

- **DSQ-PEM**[13]
- **FUNCAP (Assessing Functional Capacity in Patients with PEM)** – This is a relatively new questionnaire developed in collaboration with patients.[14] Instead of asking whether a patient "can" perform an activity, it asks about the consequences of performing the activity. This way, FUNCAP highlights **exertion-induced symptom exacerbation**, which is central to post-COVID and ME. FUNCAP comes in two versions: a longer one with **55 questions** and a shorter version with **27 questions**. It can be used alongside more established PEM/PESE instruments.
- Questionnaires where patients estimate the presence and severity of various symptoms common in PEM/PESE.
- **MAPS: Malmö POTS-Score**[15]
- **Mental Fatigue Scale**[16]
- **Questionnaires measuring dysfunctional breathing patterns**, such as the Nijmegen questionnaire.[17]

Different symptom rating scales complement each other. If only general fatigue or tiredness questionnaires are used, **patients with PEM/PESE risk scoring near the maximum from the start**, which means they may not be able to indicate worsening of their fatigue (ceiling effect). Moreover, symptom exacerbation in **PEM/PESE encompasses more than just fatigue**.

Regarding **measurement timing**, it should be considered that PEM/PESE can occur with a delay after exertion (typically 24-72 hours). Researchers should also account for **accumulated PEM/PESE**, where exertion over the energy threshold may be sustainable for a period before a crash occurs. Therefore, the **measurement period should not be too short, and there should be multiple measurement points over time**. Patients may also compensate for the

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[13] Cotler J, Holtzman C, Dudun C, Jason LA. A Brief Questionnaire to Assess Post-Exertional Malaise. Diagnostics (Basel). 2018 Sep 11;8(3):66. doi: 10.3390/diagnostics8030066. PMID: 30208578; PMCID: PMC6165517. Official translation to Swedish is available at Svenska Covidföreningen's web site, https://covidforeningen.se/wp-content/uploads/dsq-pem-officiell-oversattning-svenska.pdf

[14] FUNCAP, https://www.funcap.no/. Questionnaire is available in both Swedish and English

[15] Jasmina Medic Spahic, Viktor Hamrefors, Madeleine Johansson, Fabrizio Ricci, Olle Melander, Richard Sutton, Artur Fedorowski, 1055 MALMÖ POTS SYMPTOM SCORE: ASSESSING SYMPTOM BURDEN IN POSTURAL ORTHOSTATIC TACHYCARDIA SYNDROME, European Heart Journal Supplements, Volume 24, Issue Supplement_K, December 2022, suac121.072, https://doi.org/10.1093/eurheartjsupp/suac121.072, Also available in Swedish https://www.standinguptopots.org/sites/default/files/MAPS22-11%20Svenska.pdf

[16] Available in English: https://brainfatigue.se/wp-content/uploads/2020/06/MFS-English.pdf and Swedish https://brainfatigue.se/wp-content/uploads/2020/06/MFS-Svenska.pdf

[17] https://hgs.uhb.nhs.uk/wp-content/uploads/Nijmegen_Questionnaire.pdf Available in Swedish via region Dalarna's guidelines for postcovid, see bilaga 3, https://www.regiondalarna.se/contentassets/b5d0627b13b9432d95d24ca7980c340e/fysioterapeutiska-riktlinjer-for-patienter-med-dysfunktionell-andning.pdf

exertion caused by study participation by reducing other activities to avoid PEM/PESE. Hence, tools should be in place to measure the **patient's overall activity level over time**. This can be done through:

- **Activity tracking**
- **Symptom questionnaires**
- **Health data from wearable devices** (e.g., sleep patterns, heart rate, heart rate variability (HRV), step count)

Tips: PEM/PESE Can Be Considered as an Adverse Effect

PEM/PESE can be viewed as an **adverse effect** where some patients experience severe side effects from treatments or rehabilitation. Just as some patients can tolerate dosage increases of medication while others cannot, some patients with PEM/PESE can handle a certain level of exertion - while others cannot.

In **clinical trials**, adverse effects are documented as **adverse events (AEs)**. If PEM/PESE is tracked in an intervention study through careful monitoring of AEs at appropriate time points, this would provide valuable insights. This could, for instance, involve monitoring symptoms that typically worsen or arise during PEM/PESE and following up on these with the patient. Tools like FUNCAP can also be used for this purpose.

When measuring adverse effects, it is important to remember that PEM/PESE **generally occurs 24–72 hours after exertion** and that **accumulated PEM/PESE** can also occur. Therefore, patients need to be followed up multiple times and over an extended period.

6. Results Presentation

If the study cohort is mixed, it should always be possible to report the results based on the presence of PEM/PESE.

Results from interventions studied on patients with, for example, fatigue or exhaustion cannot automatically be transferred to patients with PEM/PESE.[18] Such an approach risks leading to patient safety issues.

7. Ethical Management of Risks Associated with PEM/PESE (Adjustments)

Before finalizing the study protocol, the study design should be reviewed, ideally with the help of patient representatives, with an awareness that any form of energy-demanding activity can lead

[18] See section 10 and in particular footnote 24.

to PEM/PESE in the research participants. The design should therefore be adjusted to minimize the risk of both short-term and long-term deterioration. This means that participants should be screened for the severity of their condition, and adjustments should be offered accordingly.[19] Such adjustments may be necessary to enable individuals with moderate to severe post-COVID and ME to participate in the studies – either at all or in an ethical manner.
Adjustments may include, for example:

- Limiting the necessary data collection to the most essential data points. Physical tests should be kept to a minimum.
- Offering participation from home may be necessary to include patients with moderate to severe post-COVID or ME. Home study designs could involve symptom tracking via apps, study staff visiting participants at home for sample collection or other testing, as well as biological sampling kits such as oral swabs or home blood collection equipment that participants can send in themselves.
- Offering information in a format suited to the individual patient, for example, on paper, via screen, or orally.
- Allowing a family member to assist participants in answering questionnaires and permitting the filling out of questionnaires in stages.
- Study staff can also proactively ask participants if they have any needs for adjustments that the study has not addressed (such information may be valuable even if the study protocol does not allow for changes during the ongoing study).

Inspiration can be drawn from the research project *Hjärtbussen*, where, among other things, imaging and functional diagnostic methods can be applied in the patient's local area.[20]

Tips: Would you like to learn more about adjusting study design

For more advice on how the study design can be adjusted, see *Designing and optimizing clinical trials for long COVID*[21].

[19] Adjustments must of course not affect the results of the study
[20] Västra Götalandsregionen, Forskningsstudien Hjärtbussen, https://www.sahlgrenska.se/forskning-utbildning-innovation/forskning/delta-i-forskning/hjartbussen/?fbclid=IwZXh0bgNhZW0CMTEAAR3lARtVv6V-y4LxICWkT-utTY0oEjo7y2RHyuytZLjrY25Jzx8ax1YkYpM_aem_c9iRvrioeIImONNgQvAztw
[21] Julia Moore Vogel, Beth Pollack, Ezra Spier, Lisa McCorkell, Toni Wall Jaudon, Megan Fitzgerald, Hannah Davis, Alison K. Cohen, Designing and optimizing clinical trials for long COVID, Life Sciences, Volume 355, 2024, https://doi.org/10.1016/j.lfs.2024.122970.

8. The Risk of PEM/PESE Must Be Addressed in the Ethics Application

The risk of PEM/PESE must also be highlighted in the application to the Ethics Review Board. It constitutes a risk that should be stated in the participant information sheet to enable informed consent. This is especially important if the study aims to explore the pathophysiological mechanisms underlying PEM/PESE, or if study participation involves any form of physical training or testing.

9. Patient Participation

Patient collaboration is a cornerstone of modern research and something that is recommended by, among others, the Swedish Research Council's committee for clinical treatment research (Vetenskapsrådets kommitté för klinisk behandlingsforskning).[22] Patient knowledge can, for example, be valuable in identifying knowledge gaps, prioritizing research questions, and developing relevant health outcomes. Patients can also contribute in adapting study designs to suit the disabilities of the patient group (such as PEM/PESE), which in turn can facilitate recruitment of research participants.

- Take time to plan and budget for participation.
- Include patient representatives with relevant knowledge and experience for the project early in the process.
- Offer patient representatives financial compensation for their work
- Are accessibility adjustments needed for patient representatives to participate (e.g., easy-to-access information, meeting places, meeting times, etc.)?
- Be open, honest, and transparent about your working methods. Be clear about resource limitations and other constraints.
- Value patient experiences. Identify, document, and encourage people's contributions.
- Provide feedback on the results of their involvement and show them how appreciated they are.
- Avoid symbolic measures.

[22] Vetenskapsrådet, Forskningsöversikt 2019 - Klinisk behandlingsforskning, https://www.vr.se/download/18.5511f9a7168876f741cb0/1552382761773/Forskningsoversikt-klinisk-behandlingsforskning_VR_2019.pdf

TIP - NIHR's Briefing Notes for Researchers
The UK has made significant progress in involving patients in healthcare and research. The National Institute for Health and Care Research (NIHR) has developed a series of *Briefing Notes for Researchers*, which detail what researchers should consider when involving patients in research.

10. Do Not Repeat Bad Examples – How Methodologically Flawed Research May Appear

10.1 The Assumption that PEM/PESE Is Caused by Incorrect Thought Patterns

Despite ongoing progress in research on PEM/PESE and its underlying mechanisms, there are still researchers who assume that PEM/PESE is related to incorrect thought patterns and an unfounded fear of activity.

In order to maintain that this hypothesis applies to all individuals showing signs of PEM/PESE, it is often necessary to disregard the existing research on pathophysiological mechanisms that could theoretically explain PEM/PESE, distinguishing it from other forms of fatigue or exhaustion, as well as from simple deconditioning (see section 2, "PEM/PESE in Brief," particularly footnote 4).

10.2 The Assumption Influences the Choice of Inclusion Criteria

When some research groups assume that PEM/PESE is not a distinct pathophysiological phenomenon, but rather a result of incorrect thought patterns, this influences the approach to participant selection in the study. The stance becomes that PEM/PESE does not need to be distinguished from other types of energy limitations. This tends to affect the choice of inclusion and exclusion criteria.

There are examples of ongoing studies, even in Sweden, where patient groups with various forms of energy limitations are mixed in the same study, often under the umbrella criterion "individuals with fatigue/exhaustion/tiredness." It is often stated that the cardinal symptom of ME is fatigue, when it is actually PEM/PESE that distinguishes this patient group (a pathognomonic symptom).[23]

[23] See e.g.ethics application with dnr 2024-05857-01, approved by Etikprövningsmyndigheten on the 9th of october 2024.

When a study population consists of patients with different causes of fatigue, some with PEM/PESE and others without, the study's results may become skewed. Some patients with fatigue but without PEM/PESE may report improvements after treatments such as CBT and GET. If such patients are included in a study alongside those with PEM/PESE - who do not improve or even worsen with the intervention - this could lead to misinterpretation of the results. The conclusion could be that CBT or GET may be recommended on a group level, even though the effect of the intervention cannot be generalized to the entire population from which the study cohort was selected.

10.3 The Assumption Influences the Choice of Outcome Measures

The assumption that PEM/PESE does not need to be distinguished from other forms of fatigue and is related to "incorrect thought patterns" can also affect the study design through the selection of measurement tools and outcome measures. In an ongoing study in Sweden, the primary outcome measure is the change in the self-assessment form Checklist Individual Strength, CIS-F, which is one of several forms used to assess symptom burden in ME.[24] However, it has been described as problematic to use CIS-F alone to assess changes in functional ability in ME. Since the form contains very general questions about fatigue, such as "I feel tired"/"I feel weak," many ME patients often score close to the maximum on the scale for the measurement tool right from the start. As a result, a large proportion of ME patients, using CIS-F, can't report further deterioration in their fatigue, and a statistical phenomenon known as the "ceiling effect" occurs.[25] With this instrument, the study is unable to detect differences above the upper limit of the test's numeric range, and any potential deterioration is therefore not captured in the results.

In some studies, there is also a lack of outcome measures that can capture other types of symptom worsening that are typical of PEM/PESE, such as the onset or exacerbation of the following symptoms: fever, pain, breathing difficulties, flu-like symptoms, and swollen lymph nodes, as well as symptoms from the autonomic nervous system (e.g. increased heart rate in an upright position). When these PEM/PESE-related symptoms are not considered relevant by researchers, or are assumed to be due to incorrect thought patterns or somatization of psychological causes, part of the treatment may involve teaching the patient to ignore them or to endure despite increasing disabling symptoms. Deterioration due to PEM/PESE may then be incorrectly interpreted as the patient not wanting to get better or not trying hard enough to change their thought patterns.

In an ongoing study in Sweden, for example, the Negative Effects Questionnaire (NEQ) is used to measure any potential negative effects of the treatment.[26] However, as this form only contains

[24] See ethics application in footnote 23 and MEPEDIA, Questionnaires and tools to assess ME/CFS symptoms or severity, https://me-pedia.org/wiki/Questionnaires_and_tools_to_assess_ME/CFS_symptoms_or_severity
[25] MEPEDIA, Checklist individual strength, https://me-pedia.org/wiki/Checklist_Individual_Strength
[26] Study protocol, Characterization, treatment, and long-term follow-up of patients in primary care, Etikprövningsmyndighetens dnr 2024-05857-01-632156 (see footnote 23)

questions related to mental well-being, it cannot capture relevant symptom increases related to PEM/PESE.

Patients with PEM/PESE who do not improve (or even worsen) from an intervention, such as gradually increased exercise or GET, may need to discontinue study participation or treatment, without the underlying reason being documented. If the study leadership assumes that avoidance of discomfort is the reason for discontinuation, without understanding the long-term risks of symptom exacerbation in PEM/PESE, serious side effects of the treatment may go unnoticed. Discontinued study participation may therefore not be included in the study results as an adverse event but may be incorrectly recorded as a discontinuation "at the patient's request," which in clinical research can happen without further explanation or recording of the cause.

As a result, the worsening of symptoms due to the intervention is not considered a reason to question or reject the hypothesis that the treatment is effective for individuals with PEM/PESE. Instead, it may be interpreted in the analysis as evidence to the contrary, reinforcing the assumption that PEM is rooted in thought patterns that perpetuate a fear of discomfort.

This leads to a type of result distortion due to attrition bias, which occurs when there is a systematic difference between patients who drop out of the study early and those who remain. This reasoning further results in the study's hypothesis (that the treatment is effective) becoming non-falsifiable—undermining the strict scientific approach on which the analysis and conclusion are supposed to rest. Thus, the choice of measurement methods and outcome measures can also lead to skewed results in the study if PEM/PESE is not measured.

10.4 Perceptions of Study Results and Applicability

The presentation of results in studies based on the aforementioned assumptions is rarely stratified by the presence or absence of PEM/PESE. Despite this, and despite the absence of relevant outcome measures to assess or detect the effects of PEM/PESE, the results are often perceived as applicable to patients with PEM/PESE—even though there is no real evidence to support this.

10.5 Summary of Study Validity

The underlying assumption about the causes of PEM/PESE thus affects the selection of the study population and outcome measures, which in turn systematically influences study results and perceptions of the generalizability of those results—in other words, the validity of the study.

In this way, through methodologically flawed research, the dismissive and minimizing attitudes toward the diagnoses of ME, post-COVID, and exertion-induced symptom exacerbation (PEM/PESE) are sustained and reinforced.