Rehabilitation from Persistent Fatigue (REHAB-FATIGUE): A Multi-Centre Transdiagnostic Randomized Clinical Trial

1. Summary

Persistent fatigue (PF) is a common, disabling symptom in many conditions, and requires tailored rehabilitation. Recently, we demonstrated that a brief psychological-behavioural program called Mind-Body Reprogramming Therapy (MBRT) and consisting of four outpatient sessions reduced PF and improved physical functioning in Long COVID patients. REHAB-FATIGUE takes a transdiagnostic approach and will determine the efficacy, safety and costs of MBRT across different triggering causes of PF (Fig. 1), comparing MBRT with care as usual (CAU) in a nation-wide, multi-centre, parallel-group, randomized clinical trial with 12 months' follow-up. Primary endpoint is the Physical Function subscale of the 36-item Short-Form Health Survey (SF-36-PFS). Positive trial results can immediately be implemented in primary and secondary health care and will provide a much sought-after rehabilitation tool. The project is managed by a world-leading group of PF researchers and an established collaborative network of regional clinical rehabilitation units.

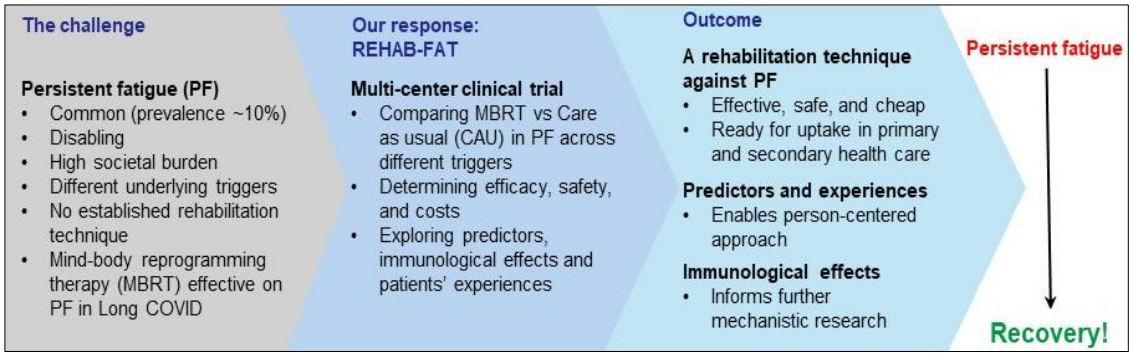

Figure 1. Gross outline of REHAB-FATIGUE background, content and outcome

2. Introduction

Persistent fatigue (PF) is common. A recent review concluded that about 10 % of the general adult population is afflicted to some extent,[39] corresponding with previous Norwegian data.[28] PF is a major cause of disability and sick leave, with strong negative consequences for the individual, families and social networks, health care utilization, and society in general.[11] Effective and safe rehabilitation measures for disabled PF sufferers are strongly warranted but are currently lacking, as PF has been an under-researched field.[34] PF is a feature of several disorders, such as cancers,[14] infections,[32] autoimmune disorders (e.g., inflammatory bowel disease),[24] myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS),[31] and chronic pain syndromes (e.g., fibromyalgia).[9] Hence, PF should be considered a transdiagnostic phenomenon, corroborating recent adjustment of clinical management in many countries (e.g., Denmark). PF may occur even after successful treatment of the triggering condition, such as in post-cancer and post-infective fatigue syndromes. Common accompanying symptoms include post-exertional malaise (PEM), brain fog, and pain.

The cause of PF is incompletely understood. Recent neuroscience evidence shows that PF is underpinned by functional brain alterations whereby symptom-associated brain networks become erroneously activated, creating a discrepancy between symptom experience and the actual state of the body.[4,26,33] This phenomenon is explained by the brain's dependency on automatic expectations (predictive brain theory); i.e., symptom experience results from a central inferential process depending on sensory information (bottom-up signals) as well as the brain's predictions (top-down signals, commonly labelled "priors").[17] If the predictions are too strong (i.e., "fixed priors"), they may "overrule" the sensory input and erroneously activate symptom-associated brain networks, creating an experience that no longer corresponds to reality.[26,33] In turn, the flawed brain network activation triggers a bodily stress response characterized by sympathetic over parasympathetic predominance as well as hormonal and immunological disturbances,[36] potentially explaining recent experimental findings from our own research group (Fig. 2).

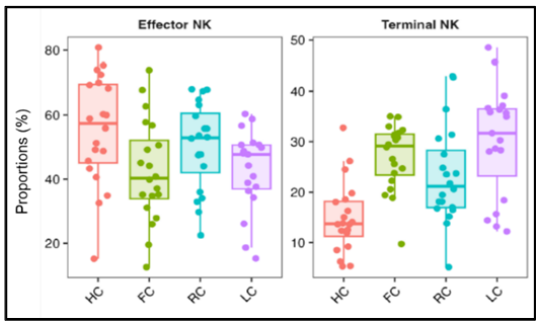

Figure 2. Frequency of NK-cell phenotypes among healthy controls (HC), fatigued controls (FC), recovered COVID-19 patients (RC), and Long COVID patients (LC) (unpublished). The results suggest immunological disturbances caused by fatigue (rather than COVID-19), which may be due to a bodily stress response.

Treatment of PF – preliminary results. Current management of PF is highly variable, reflecting the poor understanding of underlying pathophysiology and relative lack of clinical trials. However, the brain's "fixed priors" are amendable through unconscious learning processes, providing an explanation for studies showing that cognitive-behavioural treatment approaches significantly attenuate symptoms and disability in post-infective fatigue conditions (such as Long COVID),[25,40] post-cancer fatigue,[13] fatigue in inflammatory bowel disease,[18] and ME/CFS.[19] Data from our own research group support these findings (Fig. 3). A recently completed randomised clinical trial (MINIRICO) of a brief cognitive-behavioural intervention (mind-body reprogramming therapy, MBRT) vs. care as usual in Long COVID showed a favourable effect on physical function as well as other measures of symptoms and capabilities.[37] Likewise, another trial (SIPCOV) of a similar brief cognitive-behavioural intervention in Long COVID showed remarkable similar beneficial effects with persistence over time.[30] Also, the intervention was associated with lower costs and higher quality adjusted life years as compared to the control group. Both trials had reassuring safety results, with lower incidence of negative effects in the intervention group than the control group.

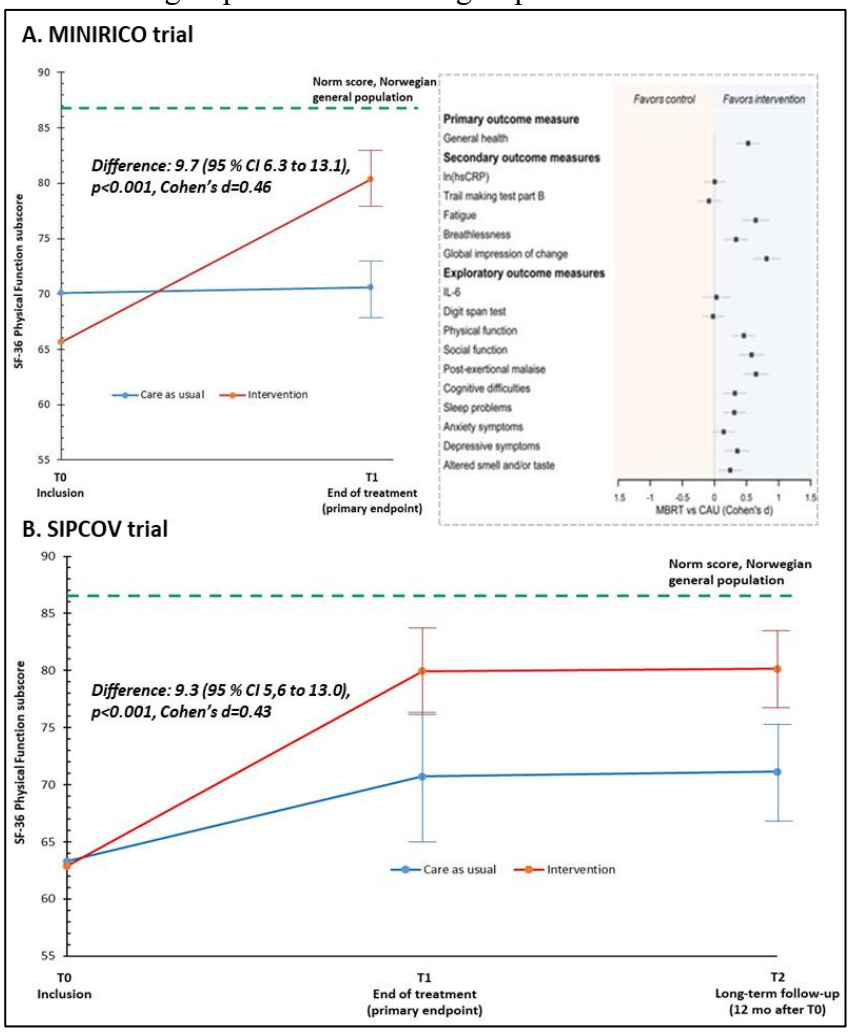

Figure 3. Preliminary result from two randomized clinical trials of MBRT (MINIRICO trial, panel A)[37] and a closely related treatment approach (SIPCOV trial, panel B).[30]

MBRT – a promising treatment for PF. The MINIRICO trial was the first clinical efficacy assessment of MBRT, which is a novel psychological-behavioral treatment program that is specifically tailored to target functional brain alterations, associated stress responses and negatively reinforcing behavioural patterns. MBRT integrates evidence-based therapeutic approaches such as the Pain Reprocessing Therapy (PRT),[2] Unlearn Your Pain,[21] the Bergen 4-day Treatment (B4DT),[16] clinical hypnosis,[27] Acceptance and Commitment Therapy (ACT),[15] and stress interventions,[22] with recent insights from stress and pain neuroscience.[2,33] Central to MBRT is the dual focus on validating the patient's experience[6] and providing clear neuroscience-informed explanations of persistent symptoms. These are combined with targeted exercises and techniques aimed at regulating

stress responses and the brain's processing of symptom alarms. If MBRT is effective against fatigue in general, as assessed in the present project, a much sought-after rehabilitation tool will be available for implementation in primary and secondary health care. Hence, REHAB-FATIGUE is likely to provide new knowledge and could have large effects on clinical practice.

2.1. Needs description

REHAB-FATIGUE addresses an urgent need in rehabilitation medicine and complies with the prioritized areas in KlinBeForsk's call for proposals as well as national priorities and policies (cf. White paper #9 2023/24, §3.3).

Patients' needs: Reduce symptoms and improve function and quality of life. PF commonly affects young adults, affecting academic development, family dynamics, working ability and social networks.[3] The fact that PF is in a sense "invisible" may lead to accusation of not being "real ill" and evoke feelings of shame and guilt, increasing the burden even more. Hence, measures that relieve symptoms and improve functions will have a huge impact on the individual patients.

Healthcare needs: Get access to an evidence-based rehabilitation tool. At present, rehabilitation approaches to PF patients vary, are scarcely supported by evidence, and may appear "fragmented" with unclear responsibilities and insufficient collaboration between the primary and secondary health care level. An evidence-based rehabilitation method will provide a much-needed tool for primary and secondary health care workers alike.

Societal needs: Reduce burden and promote gender equality. PF is a huge public health problem and a major cause of sick leave and permanent disability, reducing the total workforce and burdening social security and healthcare systems.[11] Caregivers suffer from emotional distress, loss of income and increase in expenditures.[29] Hence, PF is immensely *costly*, in both the human and financial sense of the word. Across all triggering conditions, PF is more common among females than males (3:1 ratio);[39] hence, PF is a major threat to women's health and gender equality.

Academic needs: Close substantial knowledge gaps. Rehabilitation of PF by a brief cognitive-behavioral approach may be effective, safe and cheap. While there is some evidence for this conclusion in post-infective fatigue,[25,30,37,40] few studies have been conducted in PF triggered by other causes. Also, little is known on the specific method of MBRT; knowledge gaps include effects at a group level and individual patient experiences, as well as predictors of treatment effects and impact on immunological disturbances. Closing these gaps are important at an international level.

3. Hypotheses, aims and objectives

The overarching aim of REHAB-FATIGUE is to test a rehabilitation intervention for PF independent of triggering cause within a multi-centre randomized clinical trial. The following objectives (O) and hypotheses (H) will be addressed:

O1. To determine the efficacy and safety of MBRT for PF. **H1**. MBRT improves physical functions, symptoms and quality of life as compared to care as usual (CAU), with low risk of adverse effects. | **O2**. To determine the cost-effectiveness of MBRT for PF. **H2**. MBRT comes with lower costs and higher quality adjusted life years (QALY) than CAU. | **O3**. To investigate predictors of MBRT treatment effects. **H3**. No one (explorative objective). | **O4**. To explore individual patient's experience of MBRT. **H4**. No one (explorative objective). | **O5**. To describe the effect of MBRT on immunological disturbances. **H5**. MBRT reduces inflammation and NK-cell alterations.

4. Project methodology

4.1. Project arrangements, method selection and analyses

Design overview. The present project is a parallel-group randomized clinical trial comparing MBRT with CAU at the rehabilitation units at five study sites (Fig. 4): Stavanger University Hospital (SUS); St. Olav University Hospital, Trondheim (StOlav); The University Hospital of Northern Norway, Tromsø (UNN); Kysthospitalet i Stavern, Vestfold Hospital Trust (Kysta) og Akershus University Hospital (Ahus, coordinating site). Hence, nation-wide participant recruitment is ensured. The project encompasses three Work Packages (WP):

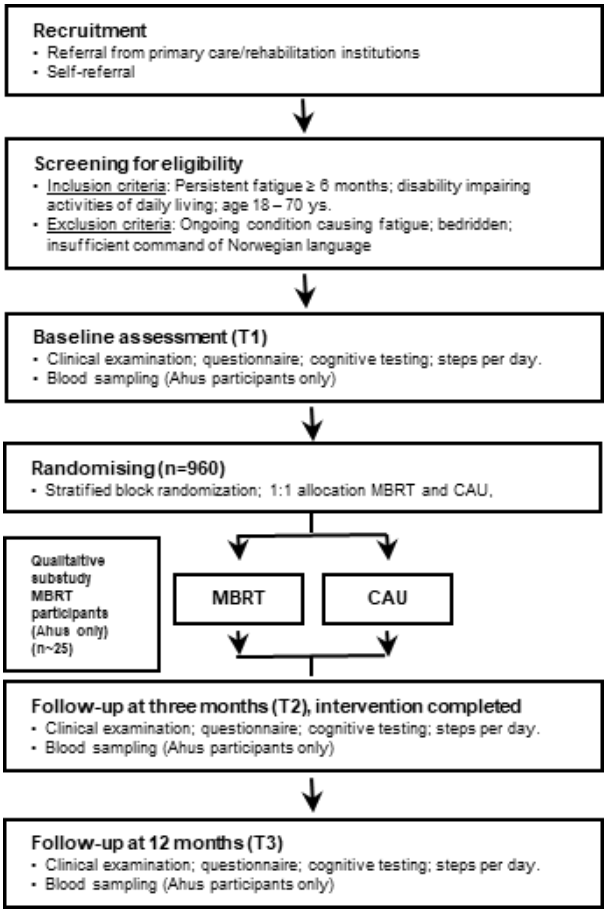

Figure 4. Patent flow in REHAB-FATIGUE.

WP1: Efficacy, safety, costs and predictors addresses the main outcomes of the trial across all study sites, cf. O1-3 above. Assessments of study participants will be performed at baseline prior to randomization (T1); at the completion of the three-month intervention period (T2); and at 12 months follow-up (T3). Data from T2 are pre-defined as the subject of primary analyses. WP2: Patient experiences addresses O4 above and will be conducted at one site (Ahus) applying qualitative methodology on n=25 study participants receiving MBRT. WP3: Immunological disturbances addresses O5 above and will be conducted at one site (Ahus) by functional testing of peripheral blood mononuclear cells (PBMC).

Recruitment, inclusion and exclusion criteria. Patients will mainly be recruited through the ordinary clinical activity at the five participating rehabilitation units. In addition, information will be provided to primary health care workers with a request to inform PF patients. Individuals interested in participating will be contacted by the Ahus study centre for a telephone eligibility screening interview; individuals adhering to the inclusion and exclusion criteria (Tab. 1) will be asked to complete a digital consent form. The plausible trigger of PF (infection, cancer, etc.) will be noted and used for subsequent subgroup analyses (cf. below). Enrolled patients will be referred to one of the participating study sites for T1 (baseline) assessment and randomisation. Based upon previous experience and detailed analyses of existing clinical activity, it is realistic to complete the enrolment phase within two years with an estimated number of included patients n~260 at Ahus, n~200 at Kysta, n~200 at SUS, n~150 at StOlav and n~150 at UNN.

Table 1. Inclusion and exclusion criteria

Inclusion criteria	*Exclusion criteria*
Fatigue (score ≥4 on the bimodal Chalder Fatigue Questionnaire (ref.)), lasting ≥6 months without symptom-free interval	Co-occurrences explaining PF (e.g., organ failure, severe depression, sever brain injury, stressful life event, substance abuse, pregnancy)
Functional disability affecting at least two activities of daily living (work/school, domestic work, leisure/social activities, etc.)	Insufficient command of Norwegian
Age 18 – 70 years	Being bedridden

Randomisation and masking. The prognosis of PF recovery may depend on the length of the illness period, and time since the PF triggering episode (less vs. more than 12 months) is defined as a stratification variable. A computer-based algorithm will be applied to create block randomized series for each stratum ensuring allocation to each of the two treatment arms with a 1:1 probability (block size to vary randomly between four and six), and corresponding sealed, opaque envelopes which will be distributed upfront to the study sites. Immediately after T1 assessment, participants will be designated to a specific stratum by study personnel and provided with an envelope containing allocation information. Allocation will be masked for personnel performing the efficacy analyses; otherwise, masking is impossible due to the nature of the interventions.

Interventions. MBRT will by initiated as soon as possible following T1 assessment. MBRT consists of four outpatient therapy sessions delivered by trained therapists as an intensive program over a maximum of 21 days (Table 2), and a designated website providing digital resources to support self-directed activities.[23,37] Access to the website is pertained throughout the three months intervention period. The first in-person session includes explanation of persistent symptoms as a functional brain alteration. This session should also acknowledge the patient's condition with a detailed discussion of

medical history and recent health-related events. The next three sessions have a stringent structure that is adaptable to patient feedback. In session two, the therapist explores core life values through functional analysis, validation, and targeted exercises. In session three, specific exercises are introduced to help the brain deactivate inappropriate stress responses through visualization. In session four, the participant practices visualization and reprogramming, using repetition to make trigger situations move from feeling unsafe to feeling safe. Also, the participants learn how to apply these techniques in daily life through exposure hierarchies. If more repetitions or explanations are needed, two additional sessions are optional.

Table 2. Therapy sessions in the MBRT intervention – central topics

Session	*Topic*
#1.	Explanatory model – functional brain alterations Self-affirmation exercise Value-based home assignment
#2.	Mindfulness meditation exercise Detailed analysis of a situation where symptoms determined behaviour Exercise in choosing alternative behaviour
#3.	Visualisation of symptom-provoking situation; supervision on how to manage it Defusion exercise – thoughts may not dictate behaviour
#4.	Repetition of exercises Plan for graded activity Plan for relapse management Introduction to designated website

The MBRT designated website consists of eight modules pertaining to prevalent symptoms in PF conditions (fatigue/PEM, "brain fog", sleep problems, pain) as well as other important determinants of a rehabilitation process (exercise, next-of-kins, emotional awareness, return to work). Each module provides information (e.g., online mini-lectures) combined with suggested self-directed activities (e.g., exposure exercises, meditation, graded exercise). The participants will be encouraged to exploit the designated website throughout the period from T1-T2 attending to modules that fit their specific constellation of symptoms and impairments.

Care as usual. The default clinical management of PF varies across study sites and co-occurring diagnoses. Standardization is not possible for practical reasons; however, detailed information on received CAU will be obtained at an individual basis from questionnaires as well as linkage with national registries (Norwegian Patient Registry, NPR; Individual-based Nursing and Care Statistics, IPLOS) and included in sensitivity analyses of intervention effects (cf. below). No specific therapy nor designated website access will be offered to the CAU group.

Assessments. An identical assessment program will be conducted at all study visits (T1–T3) and sites, encompassing clinical examination, neurocognitive testing and questionnaire. The examination will chart current complaints and functional incapabilities, as well as country of origin, previous medical history, co-morbidities and use of pharmaceuticals. The recording unit from the *activPAL* accelerometer device (PAL Technologies Ltd, Glasgow, Scotland) will be attached to the thigh and worn permanently for a recording period of seven days, after which it will be returned by mail in a pre-stamped envelope; this provides valid and reliable activity data.[20]

The neurocognitive tests encompass the Trail Making Test (TMT) part B and will be performed in line with accompanying test manuals by trained personnel. The test requires the participant to draw lines and connect circled numbers and letters in alternating numerical and alphabetical order (i.e., 1-A-2-B etc.). The main read-out is time to task completion measured in seconds. TMT-B is a measure of cognitive flexibility and hence captures an important facet of executive functions.[1]

A composite questionnaire consisting of validated inventories will be used to chart background and efficacy outcome variables, including clinical symptoms, functional disabilities, personality traits, prior illness/therapy beliefs, and social factors as well as basic demographics (Tab. 3). A separate questionnaire developed in the MINIRICO trial will address the occurrence of health problems, health care contacts (e.g., appointments with the general practitioner, hospital admissions), and initiation of therapies (e.g., pharmaceuticals, rehabilitation) during the intervention period (from T1 to T2).[37] A third questionnaire will chart to what extent the participants allocated to MBRT have engaged in self-directed activities.[37] All questionnaires will be administered digitally using the "Nettskjema"-tool administered by the Services for Sensitive Data at the University of Oslo.

In addition, Ahus study site will: a) Conduct semi-structured interviews of n=25 participants allocated to MBRT exploring patients' experiences with the MBRT method and their reflections upon mechanism for changes in PF (if any), cf. WP2; and b) Obtain venous blood samples from about

n=200 participant to get aliquots of plasma, serum, and PBMC; the aliquots will be consecutively biobanked awaiting further analyses, cf. WP3.

Table 3. Composite questionnaire – content

Construct(s)	*Name of inventory*
A. Background and Demographics	
1. Household, socioeconomic level	Not applicable
2. Smoking, alcohol, illicit substances	Not applicable
3. Physical activity	Not applicable
4. Diseases	Not applicable
B. Symptoms and Disability	
1. Fatigue	Chalder Fatigue Questionnaire.
2. Post-exertional malaise (PEM)	PEM items from the DePaul Symptom Questionnaire.
3. Sleep disturbances	Karolinska Sleep Questionnaire
4. Pain	Brief Pain Inventory
5. Depression and anxiety symptoms	Hospital Anxiety and Depression Symptoms
6. Other associated symptoms	CDC symptom inventory for Chronic Fatigue Syndrome
7. Disability and QoL	Short Form Health Survey 36 (SF-36) and EQ-5D-5L
C. Psychological traits and Social factors	
1. Neuroticism	NEO Five-Factor Inventory-30
2. Worrying tendency	Penn State Worry Questionnaire
3. Loneliness	UCLA Loneliness Scale

WP1 – Outcomes and analyses. The SF-36 Physical Function Subscore (SF-36-PFS) at T2 is the primary efficacy outcome measure.[35] SF-36-PFS is a well validated and resonates with PF being defined from the subjective experience of symptoms and functional impairments. The six secondary efficacy outcome measures are symptoms scores for fatigue and PEM; TMT-B performance; EQ-5D index value of QoL; number of steps per day; and work attendance (linkage with registry data from The Norwegian Labor and Welfare Service). Exploratory efficacy outcome measures include other symptom and functional impairment scores, cf. Tab. 3.

For intention-to-treat analyses of efficacy, missing data will be replaced by multiple imputation, and analysis of covariance (ANCOVA) will be applied for modelling of the MBRT vs. CAU comparison across all efficacy variables at T2 and T3 separately. The baseline (T1) values as well as the stratification variable will be included in each model as covariates. The net intervention effect is defined as the mean difference between the intervention group and the control group from the fitted ANCOVA model. Differential intervention effects will be investigated by similar ANCOVA modelling across subgroups defined from presumed triggering event (e.g., infection, cancer), and formally assessed by generalized linear modelling of interaction. Intervention effects in other subgroups (e.g., those fulfilling a diagnosis of ME/CFS) will also be explored. The impact of heterogeneity in the CAU group will be assessed in sensitivity analyses. Compliance with MBRT will be assessed by the questionnaire on self-directed practices, whereas therapist fidelity will be assessed by analysing audio recordings of a random selection of 20% of the therapy sessions.

Safety outcome measures obtained at T2 include SF-36 subscale scores, symptom scores, and clinical findings, as well as questionnaire responses and registry linkages charting new health problems, health care contacts, and initiation of therapies. Safety outcome measures will be reported as numbers/proportions across the two treatment arms without any statistical testing. Adverse events (AEs) will be categorized; serious adverse events (SAE) will be reported one-by-one.

The EQ-5D-5L responses will be transformed into utilities and valued using the Norwegian tariff to obtain alterations in QALYs among the trial participants over the total follow-up period (12 months).[30] Health resource use will be obtained from the questionnaire response on health care utilization as well as data from the Hospital Trust's Head of Analysis and linkage with the NPR and IPLOS registries; valuation will be estimated from national Norwegian databases.

Predictive factors of treatment response will be explored by generalized linear methods using change in the primary endpoint (SF-36-PFS) as dependent variable. A wide array of independent variables (e.g.. sex, age, socioeconomic level, co-occurring conditions, initial symptom burden, activity level, illness/therapy beliefs) will be assessed in bivariate analyses followed by multivariable modelling.

WP2 – Outcomes and analyses. A semi-structured video interview focusing on experiences with the MBRT method and mechanism of eventual change in health status will be conducted with n=25 individuals allocated to the MBRT group. Interviews will take place immediately before T2; they will be audio-recorded, transcribed verbatim and subjected to thematic analysis.[7]

WP3 – Outcomes and analyses. PBMCs from all Ahus participants at all time points (T1, T2 and T3) will be stimulated with phorbol 12-myristate 13-acetate (PMA) and stained using a cocktail of antibodies targeted against surface receptors to provide coverage for major cell types and against

intracellular antigens to assess stimulation-induced cytokine responses. Assaying implies acquisition of multiplexed/barcoded samples followed by high-dimensional single cell profiling. A bioinformatic pipeline will be applied to characterize cellular phenotypes and cytokine response. The read-outs will be compared across intervention groups to explore immunological effects of MBRT and association to PF reduction; in addition, immunological characteristics at baseline (T1) will be explored as predictors of treatment responses.

Sample size consideration is based upon SF-36-PFS, and a difference of 10 points or more is considered clinically significant.[38] The standard deviation of SF-36-PFS was ~21 among the participants in both MINIRICO and SIPCOV, implying a target enrolment of n=266 (α=0.01, 1-β=0.9). However, as treatment responses may vary across triggering event, the sample size should allow analyses across at least three subgroups, yielding a target enrolment of n=3x266=798. Given a drop-out rate of 20% (similar to the SIPCOV trial), final target enrolment is set at n=960.

Gender dimension. PF is more common among females than males (3:1 ratio), and an example of a 'women's disease' with strong health impact but disproportionately low attention scientifically and clinically. The underlying reasons for sex differences are largely unknown and will receive strong attention in the analyses; for instance, sex will be investigated as a predictor of treatment responses.

Risks and mitigation efforts. Generally, the research team is uniquely positioned to contribute to the field, with low risk of failure. Identified risks include:

Recruitment failure. If the assumption on recruitment rate fails (cf. above), the study may intensify information on the study (e.g., using social media) and exploit the network provided by the user representatives; eventually, other rehabilitation units may be recruited as study sites. Also, accepting a somewhat lower statistical power (1-β) of 80%, the required total enrolment is reduced to n=749.

Low therapist fidelity. Therapist fidelity towards the MBRT interventions will be secured by continuous supervision combined with monitoring of therapy sessions based on audio-recording. If low fidelity is noted, supervision and training efforts will be intensified.

High number of dropouts. In REHAB-FATIGUE, the sample size consideration account for 20% drop-out (cf. above). Should there be more losses to follow-up than expected the number of included patients may be increased. However, the MINIRICO trial had a very low drop-out rate of approximately 3% explained by well-working procedures for participant follow-up which will be transferred to the present project.

4.2. Participants, organization and collaborations

Overall governance. REHAB-FATIGUE is managed by the PAEDIA research group at Ahus in collaboration with the four other study sites. A Steering Committee (SC) with representatives from all sites will meet quarterly by digital means (more frequent during the initiation stage) to oversee progress in the specific aims, milestones and performance indicators, and facilitate collaboration and uniform project implementation across all sites. Also, the SC will approve standard operating procedures (SOPs) and manage risk, failures and mitigation efforts. A Consumer Advisory Board (CAB) is scheduled to meet with the SC bi-annually; a CAB representative will act as a non-voting member at the SC meetings. An independent Data Monitoring Committee (IDMC) will be appointed and receive aggregated data on safety on a regular basis as well as immediate notification of any SAE; the IDMC is to meet annually with the SC. Ahus is trial sponsor.

REHAB-FATIGUE will be registered with ClinicalTrials.gov. A detailed study protocol, statistical analysis plan and data management plan will be approved by the SC and made public at ClinicalTrials prior to participant inclusion. All statistical analyses will be performed by statisticians blinded to treatment allocation and not otherwise affiliated with the study.

Steering Committee. The PI of REHAB-FATIGUE is Prof. Vegard Wyller, Ahus, who has been a leading PF researcher for two decades conducting mechanistic research as well as clinical trials (including being PI of SIPCOV and MINIRICO), and who chairs the international COFFI (Collaborative on Fatigue Following Infection) consortium (www.coffi-collaborative.com). Wyller leads the PAEDIA research group - a cutting-edge research environment with a total of eight researchers at different career stages involved in PF studies. The co-PI, Prof. Tobjørn Omland, Ahus,

is a world-leading trialist and translational researcher, and heads a prestigious K.G.Jebsen centre. In REHAB-FATIGUE, Profs. Wyller and Omland will co-supervise the affiliated mid-career researcher and PhD fellow (cf. below), and oversee data acquisition, statistical analyses, publication drafting, and dissemination/exploitation Prof. Silje E. Reme, University of Oslo, led the development of the MBRT intervention and has ample experience on behavioural intervention trials. She will be responsible for therapist supervision and fidelity assessment. The four local PIs (Dr. Christine Falck Moore, Stavanger University Hospital; Dr. Christine Einarsen, St. Olav University Hospital; Dr. Maja Wilhelmsen, The University Hospital of Northern Norway; Dr. Tom Farmen Nerli, Kysthospitalet i Stavern) are all experienced clinicians of rehabilitation medicine as well as active researchers.

Therapists and supportive personnel. At Ahus, we will leverage existing supportive infrastructure and personnel (administrative coordinators, research nurses, laboratory engineer) from the SIPCOV and MINIRICO trials to manage the local as well as multi-site aspects of the REHAB-FATIGUE. Also, experienced therapists from MINIRICO will be allocated to deliver MBRT at Ahus. The local PIs will establish study teams to ensure data acquisition and intervention delivery as well as manage administrative issues at the local sites. All therapists will receive extensive training and supervision in the MBRT method.

Early-/Mid-career researchers. One mid-career researcher and one PhD fellow will be appointed to REHAB-FATIGUE and affiliated with PAEDIA. They will collaborate closely on recruitment and data acquisition; the latter includes performing the assessments at Ahus as well as collating data from the other study sites. Both will attend the educational program for junior researchers within PAEDIA. The mid-career researcher should hold a PhD and have previous experience with managing randomized controlled trials and related statistical analyses. He/she will be responsible for analyses pertaining to the main trial outcomes (WP1), draft SOPs and scholarly papers, contribute to dissemination, and co-supervise the PhD fellow. The PhD fellow should hold an MD or MSc and have previous experience with laboratory methods/translational research. He/she will focus on immunological aberrations (WP3), including performing laboratory analyses at the core facility for high-dimensional single cell analysis at the Norwegian Institute of Public Health (NIPH), drafting scholarly papers and contributing to dissemination.

Collaborators include Prof. Are Hugo Pripp, Oslo University Hospital for statistical analyses (WP1); Prof. Torbjørn Wisløff, Akershus Clinical Research Centre for health economy analyses (WP1); and Prof. Siri Mjaaland, NIPH, for immunological analyses (WP3). Ass. Prof. Line B. Aasen, PAEDIA, Ahus, will perform the qualitative sub-study (WP2). We will leverage the established collaboration with the EpiGen Research Laboratory at Ahus for biobanking and initial laboratory assays. The COFFI consortium provides an extensive international research network.

4.3. Budget

Total budget is NOK 30,338', total sum applied for is NOK 24,999'. Details are given in eSøknad.

4.4. Plan for activities, visibility and dissemination

Total project period is five years; patient enrolment will be completed within two years, and all primary data acquisition within three years. A Gannt diagram showing the main research activities is provided in eSøknad. As for visibility and dissemination, target audiences include the international medical and public health communities, individuals with PF/their relatives, as well as politicians, health care administrators, and the general audience. As the research addresses a disabling and poorly understood condition, wide interest is to be expected. Dissemination to researchers/clinicians includes publications in international, peer-reviewed medical journals with an open access policy (Tab. 4). The main results will be submitted to journals of high impact. In addition, we will present results at national and international meetings (including webinars). As for dissemination to politicians, administrators, and the general public, we will develop a strategy in collaboration with the Communication Office at Ahus. Important elements will be: a) Actively publicizing research results in traditional media; b) Dedicated exploitation of social media, such as Facebook and Twitter/X; c) Distribution of results through patients' organizations.

REHAB-FATIGUE will adhere to the EU's Open Science policy, i.e.: a) Follow an open methodology approach to research by not only sharing the research results but also methods and data; b) Ensure open research data, applying the Findable, Accessible, Interoperable, Reusable (FAIR) principles; c) Promote open access and review, guaranteeing free access to all peer-reviewed publications.

Table 4. Plan for dissemination and communication

Activity	*Description*	*Target group*	*Impact*	*Key performance indicators*
Publications and conferences	• Publish open access in peer-reviewed journals. • Present results at international conferences.	Scientific community, students	Peer validation, knowledge transfer, networking,	Min. 8 papers. Min. 6 conference presentations
Website, social media	• Constantly updated information on results. • Links to social media for sharing relevant information.	All target groups	Awareness raising, spreading knowledge	300 users per month
Patient engagement	• Patient talks (videos) in collaboration with the CAB involving those with lived experience of PF. • Patient-centred website section with an updated list of FAQs and a contact form to the SC	Patients and associations, healthcare providers, gen. audience	Informing on project procedures and objectives	1 workshop, min. 20 participants at event
Digital and Print materials	• Audience-specific materials for healthcare providers • Press releases and regular newsletters for key stakeholders.	Gen. audience, healthcare providers, patients	Information transfer, raising awareness, presenting benefits	30 downloads of individual materials

4.5. Plan for implementation

REHAB-FATIGUE will generate: a) A scientific impact by creating high-quality new knowledge in the areas of rehabilitation, and enabling its diffusion through open science practice; b) A societal impact and contribute to global policy goals by reducing disease-related burden for patients, families, and healthcare providers; c) An economic impact by helping PF sufferers to continue work/education, reducing the burden on insurance systems, and lowering the consumption of health care resources.

A key element in the Roadmap for Exploitation (RfE) (Tab. 5) will be the therapists at trial sites who have been supervised and gained ample experience with MBRT during the project period. These therapists will be used as "change agents" at their respective institutions and enabled to supervise new "generation" of therapists. Furthermore, the RfE will include networking between the trial sites and general practitioners in catchment areas to facilitate uptake of REHAB-FATIGUE results in primary care. Local consumers will be involved in these stages, cf. below.

Table 5. Plan for exploitation

Activity	*Description*	*Target group*	*Impact*
Strategic grant plan	• Strategic grant planning in the last year of the project to identify future funding opportunities	Project partners, other collab.	Pre-selecting relevant calls, follow-up projects
Policy guidelines	• Guidelines, reports and recommendations for policymakers integrating project results into standards of care. • Materials developed will be made freely available through a dedicated website.	Policymakers, authorities, healthcare providers	Inform healthcare providers about new guidelines; brief policymakers; contribute to healthcare standards
Roadmap for Exploitation	• A Roadmap for Exploitation (RfE) outlines a plan for uptake of REHAB-FATIGUE result. • Develop strategies to overcome barriers (PESTLE, SWOT)	Potential collaborators, hospitals, planners	Clear definition of strategies, measures, and time plan for exploitation

5. User involvement

A Consumer Advisory Board (CAB) will be established consisting of five individuals with lived experience of PF from different triggers, hence mirroring the heterogeneity of underlying diagnoses among the trial participants. Representatives to the CAB have already been recruited from The Norwegian Cancer Society (post-cancer PF); The Norwegian Association for Chronic Pain (PF associated with chronic pain); Recovery Norway (post-infective PF); and the Consumer Advisory Group of COFFI (post-infective PF). An additional representative will be recruited from The Norwegian Association for Gut Disorders (PF associated with inflammatory bowel disease). These representatives also reflect a scatter of sex, age, geographical residency and degree of impairment, and one of them has experience as a caregiver.

The CAB is scheduled to meet bi-annually with the SC. The first meeting will be in-person, emphasising the inclusion of consumers as active contributors and counteract feelings of alienation;

subsequent meetings will mainly be digital. Topics for discussion include recruitment strategies, feedback on analytical plans, interpretation of findings and how they can be used in practice, and ethical issues that may emerge. The CAB is regarded a vital contributor to the dissemination/exploitation strategy, suggesting how the results can be expressed in plain language, and by preparing brief videos to be posted on the web/social media to explain the MBRT principles, the study findings and how they fit into current public narratives across the conditions. This approach may importantly inform the public debate in a contentious field and has been highly successful in the COFFI collaborative; one example is displayed here: https://www.youtube.com/watch?v=q0JYwiOiZ8k.

Local consumer groups (2-3 members) at the trial sites will be established during the course of REHAB-FATIGUE; recruitment will be from involved patients' organization as well as already established hospital consumer boards. These groups will primarily contribute to dissemination/exploitation by advising on local networking with general practitioners and help explain how MBRT may help primary care patients (cf. above). The local groups are to meet regularly with the CAB.

All consumer work is paid according to established procedures. Detailed Terms of References will be developed for both CAB and the local groups.

6. Ethical considerations

Participation in the project will be based upon informed consent, and thorough information will be provided orally as well as in writing. Data acquisition will comply with requirements outlined in ethics and data protection regulations such as General Data Protection Regulation 2016/679 (GDPR) and the ePrivacy Directive (2002/58/EC). Approval will be obtained from the Regional Committees for Medical and Health Research Ethics as well as the Data Protection Officer at all trial sites. The project will be pre-registered with ClinicalTrials.gov, the study protocol and statistical analysis plan will be made publicly available prior to inclusion of any participant, and results will be reported following the Consolidation Standards of Reporting Trials (CONSORT) guideline. Strong attention will be directed towards reducing the burden on individual patients, such as scheduling study visits in conjunction with routine clinical appointments. Previous evidence suggests low risk of adverse events related to MBRT.[30,37] Still, safety outcome measures will be thoroughly monitored during the course of the trial and overseen by the IDMC (cf. above), and detailed procedures for the management of AEs and SAEs will be implemented in accordance with the principles of Good Clinical Practice.

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