Title Page

Protocol Title:
The efficacy and safety of a mental intervention program vs. usual care and nicotinamide riboside (NR) vs. placebo for improving health-related quality of life in long covid: A 2 x 2 factorial randomized controlled trial

Amendment Number: #2

Brief Title: Mental Intervention and NIcotinamide RIboside supplementation in long COvid

Acronym: MINIRICO

Study Phase: 2B

Sponsor Name: Akershus University Hospital**,** Sykehusveien 25, P.O.Box 1000, N-1478 Lørenskog, Norway

REK approval Date: 18.11.2022, ref. nr. 533539

Independent Monitor Committee, Contact Information: Ass. Prof. Melanie Rae Simpson, NTNU, Melanie.simpson@ntnu.no.

Amendment #2, 2025/01/23: Summary of amendments

In January 2025, prior to analyses of main results from the trial, the following protocol amendments have been implemented:

- Insertion of correct ClinicalTrials ID.
- Slight adjustment of the study rationale due to recent empirical and theoretical development in neurobiological models of symptom persistence in general (Chapter 1 and 2).
- Adjustments of secondary and exploratory endpoints (paragraph 3,1, Table 2) bringing them up-to-date with recent scientific literature on the post-COVID-19 condition. In particular, executive functioning is seen as a more relevant neurocognitive marker than working memory in the population under study; the Trail Making Test, part B, is therefore included as a secondary outcome measure, substituting Digit Span Total Score which is now included as an exploratory outcome measure. Furthermore, the number of exploratory endpoints is moderately expanded to encompass more facets of potential intervention effects (on inflammation, symptoms, and physical/social functioning). The explorative endpoint related to attention bias has been removed as we were unable to establish the necessary experimental set-up; the description on functional testing procedures (paragraph 8.1.2) is revised accordingly.
- Addition of other objectives related to important RCT design issues, such as compliance, therapist fidelity, dose-response associations, and the effect of prior confidence in the interventions under study (paragraph 3.2, Table 3).

- Rephrasing of the primary estimand paragraph to avoid ambiguities and harmonize with similar statements in the Statistical Analysis Plan (paragraph 3.3).
- Slight adjustments of safety monitoring routines, specifying that questionnaires on side effects were administered twice during the intervention period (paragraph 4.1).
- Minor adjustment of compliance assessment, specifying that the number of self-directed activities in the MBRT intervention where charted at two time points, and that therapist fidelity is assessed from audio recordings of therapy sessions only (paragraph 6.5).
- Addition of a qualitative sub-study with the aim of exploring participants' experiences with the MBRT intervention (paragraph 8.13). Details of this substudy is outlined in a separate protocol.
- Adding some information to the eligibility screening procedure (paragraph 8.2).
- Specifying more details pertaining to the definition of the per-protocol analysis set (paragraph 9.2).
- Providing a detailed description of the committee structure of MINIRICO (paragraph 10.1.6).
- Updating the specific procedures for SAE reports (paragraph 10.2.4).

All amendments were performed prior to database lock and any statistical analyses. They are visualized with "tracked changes" throughout the document. The final version of the protocol is endorsed by the steering committee of MINIRICO and published on the designated ClinicalTrials website.

Table of Contents

1. Protocol Summary

1.1. Synopsis

Protocol Title: The efficacy and safety of a mental intervention program vs. usual care and nicotinamide riboside (NR) vs. placebo for improving health-related quality of life in long covid: A 2 x 2 factorial randomized controlled trial

Brief Title: Mental Intervention and NIcotinamide RIboside supplementation in long COvid (MINIRICO)

ClinicalTrials ID: NCT05703074

Summary:
Long COVID, also referred to as post-acute sequela of COVID-19 (PASC), is present in a substantial number of individuals, and treatment for this is warranted. Two different hypothetical models of Long COVID suggest attenuated mitochondrial energy production and functional brain alterations partly caused by psychosocial load, respectively, to be key mechanisms in the underlying pathophysiology. Given the potential importance of metabolic disturbances, dietary supplement by Nicotinamide Riboside (NR, sales name Niagen®) may be beneficial. Given the potential importance of functional brain alterations, a tailored and personalized Mind-Body Reprocessing Therapy (MBRT) may be beneficial. The MBRT consists of 4 to 6 face-to-face therapist encounters in combination with digital resources available through the DIGNIO® interface.

The primary objective is to determine whether NR 1000 mg twice daily and/or MBRT increase health-related quality of life in individuals with Long COVID compared with care as usual and/or placebo. The Medical Outcome Study 36-item short form (SF-36), general health subscore is the primary endpoint. Secondary objectives are to determine intervention effects on six secondary endpoints: markers of inflammation (hsCRP) and cognitive function (trail making test), cost-effectiveness, and the patient-reported symptoms fatigue, dyspnoea, and global impression of change in symptoms, function and quality of life. Explorative objectives encompass intervention effects on additional cognitive function markers, biological markers (indices of autonomic nervous activity and inflammation), disability markers (work attendance, quality of life) and patient symptoms, as well as the exploration of long-term effects, differential subgroup effects, intervention effect mediators and intervention effect predictors.

The study is a randomized controlled trial featuring a 2 x 2 factorial design where MBRT is compared with usual care and NR is compared with placebo (Figure 1). The latter comparison is double blinded. Eligible participants are individuals (18-70 years) with confirmed Long COVID interfering negatively with daily activities (such as work, socially, normal leisure activities, etc.). Participants will be recruited directly through self-referrals and referrals from general practitioners and hospital services, as well as from previous COVID-19 studies at our institution. A total of 310 participants will be enrolled. After baseline assessment (T1), the participants will be randomized 1:1 for both treatment comparisons, resulting in four treatment groups: a) MBRT and NR; b) usual care and NR; c) MBRT and placebo; d) usual care and placebo. The intervention period last for three months, followed by primary endpoint assessment (T2). Total follow-up time is 12 months (T3). A comprehensive investigational program at

all time points includes clinical examination, functional testing (spirometry, autonomic cardiovascular control, neurocognitive functions), sampling of biological specimens (blood) and questionnaire charting (background/demographics, clinical symptoms, psychosocial factors, study events).

1.2. Schema

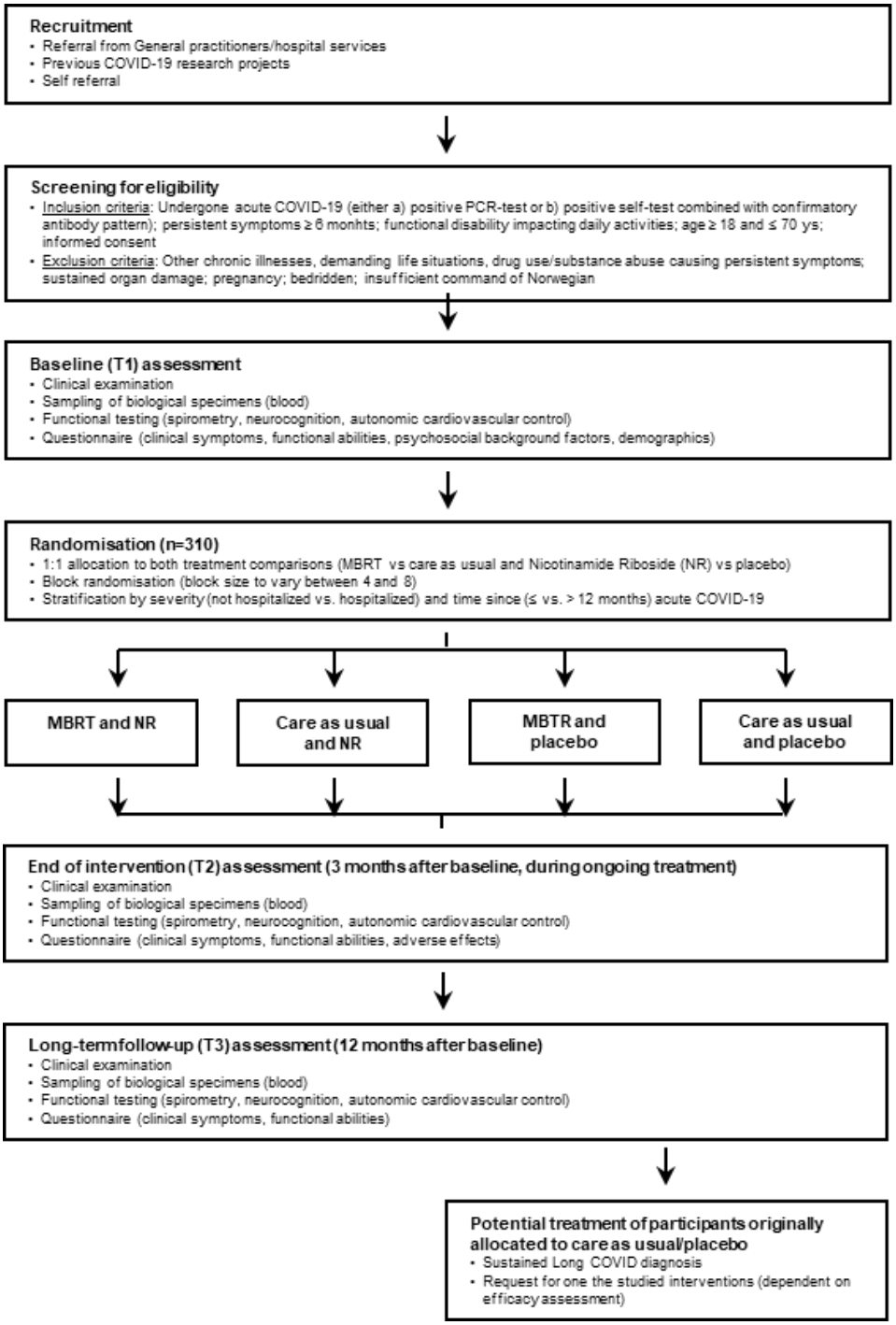

Figure 1.
Study design

1.3. Schedule of Activities (SoA)

Table 1. Schedule of Activities

Procedure	Screening (up to 30 days before Day 1)	Intervention Period (weeks)										Early discon-tinuation	Follow-up (40 weeks after last end of interven tion)
		1	2	3	4	5	6	7	8	9-11	12		
Basic demographics	X												
Informed consent	X	X											
Medical history	X	X											
Inclusion and exclusion criteria assessment	X	X									X		X
Randomization		X											
Physical examination including urine analysis (dipstick analyses and pregnancy tests for woman 18-50 ys.)		X									X		X
Sampling of biological specimens (blood)		X									X		X
Questionnaire		X									X		X
Functional assessments (spirometry, autonomic cardiovascular control, neurocognitive functions)		X									X		X
Study intervention #1 – MBRT vs. care as usual.		←==========→											

Table 1. Schedule of Activities

Procedure	Screening (up to 30 days before Day 1)	Intervention Period (weeks)									Early discon-tinuation	Follow-up (40 weeks after last end of interven tion)
		1	2	3	4	5	6	7	8	9-11	12	
Study intervention #2 – NR capsules 1000 mg x 2 daily vs placebo capsules x 2 daily		←==========→										
AE review		←==========→										X	X
Unsolicited AEs		←==========→										X	X
SAE review		←==========→										X	X
Concomitant medication review		←==========→										X	X

2. Introduction

2.1. Study Rationale

Recent studies show that long-term symptoms following COVID-19, commonly referred to as Long COVID, is present in a substantial number of individuals (Crook 2021; Soriano 2022) and treatment for this is warranted.

The underlying pathophysiology of Long COVID remains to be resolved. As metabolic abnormalities characterized by attenuated mitochondrial function and increased anaerobic energy production appears to be features of other post-infective fatigue states (Sweetman 2020; Navieaux 2016; Lien 2019), it has been suggested that similar mechanisms may underlie Long COVID. However, psychosocial risk factors appear to be better predictors of Long COVID than biological and disease-specific factors, as recently documented in observational cohort studies across different countries (Selvakumar 2022; Berg 2022; Stephenson 2022). Psychosocial load may be main contributors to functional brain alterations which in turn may explain symptom persistence (Van den Bergh 2017).

Given the potential importance of metabolic disturbances, dietary supplement by Nicotinamide riboside (commonly referred to as NR) - a vitamin precursor converted to nicotinamide adenine dinucleotide (NAD^+) in vivo that boosts mitochondrial energy production - may hold promise for improving symptoms and increasing functioning, and thereby increase health-related quality of life (Trammell 2016).

Given the potential importance of functional brain alterations related to psychosocial load, cognitive interventions have shown promise as treatment for persistent symptoms following infection, as well as for other illnesses with similar symptomatology as Long COVID (Keijmel 2017). A tailored and personalized cognitive approach that combines therapist contact with digital content and follow-up, may therefore have potential for improving symptoms and increasing functioning, and thereby increase health-related quality of life.

2.2. Background

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The clinical presentation of acute infection varies from asymptomatic infection over mild upper respiratory tract illness to severe viral pneumonia causing Acute Respiratory Distress Syndrome (ARDS) and respiratory failure. Old age and chronic cardiovascular morbidity are important risk factors for severe outcome (Zhou 2020). Recent studies show that long term symptoms following COVID-19, commonly referred to as Long COVID, is present in a substantial number of individuals (Crook 2021; Soriano 2022), and treatment for this is warranted.

Evidence suggests that most Long COVID cases fit within the label of Persistent Post-Infectious Symptoms (PPIS), encompassing chronic fatigue, pain and other symptoms, but with scarce findings on clinical examination (Sandler 2021). PPIS is a common sequel after several acute infections with a diverse array of pathogens, such as infectious mononucleosis (IM) caused by Epstein-Barr virus, Q-fever caused by the bacterium *Coxiella burnetii*, and gastroenteritis caused by the parasite *Giardia*

lamblia. (Hickie 2006, Hanevik 2014). Across multiple prospective cohort studies, almost one half of subjects report PPIS six months after the infectious event, and 10-15 % satisfy diagnostic criteria for the chronic fatigue syndrome (Hanevik 2014; Buchwald 2000; Hickie 2006; Pedersen 2019). Although

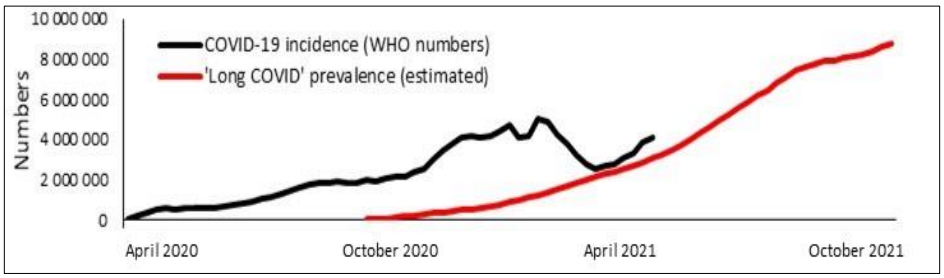

Figure 2.
COVID-19 weekly incidence and an estimate of Long COVID prevalence (based on 10 % and 5 % case rate, respectively, 6 and 12 months after the acute infection).

late recovery may occur chronic disability is common. Given the total number of COVID-19 cases globally, Long COVID may be considered as an epidemic in its own right (Figure 2).

Long COVID is primarily defined from patients' subjective experience of symptoms (Soriano 2022). These symptoms may vary considerably between individuals; while fatigue, dysnoea and "brain fog" are seen as hallmark of the conditions, complaints such as post-exertional malaise (PEM), sleep difficulties, pain, altered smell/taste and depression/anxiety may be features of Long COVID, either alone or in combination (Soriano 2022). As is the case with other PPIS, no biomarkers nor other factors that can be objectively measured are consistently associated with Long COVID. Hence, patient reported outcome measures (PROMs) are seen as the most valid measures to assess treatment effects. Also, a thorough diagnostic assessment at inclusion is required to rule out alternative conditions that may be associated with persistent symptoms, as Long COVID is considered a diagnosis of exclusion (Selvakumar 2022).

The pathophysiology of Long COVID as well as PPIS in general remains to be resolved. Largely speaking, two alternative hypothetical models have been proposed: One model assumes *autoimmunity* to be the underlying mechanisms (Blomberg 2018), supported by reports of low-grade systemic inflammation (Montoya 2017; Nguyen 2017) possibly linked to mitochondrial dysfunction and increased anaerobic energy production (Ajaz 2021; Magnani 2020; Sweetman 2020; Navieaux 2016; Lien 2019). In support of this model, a modest increase of plasma inflammatory markers has been reported across several Long COVID studies (Sommen 2022; Mehandru 2022; Peluso 2021; Vono 2021).

Another model considers *functional brain alterations* to be the central pathophysiological element (Henningsen 2018; Wyller 2009; Van den Bergh 2017), supported by functional brain imaging studies (Almutari 2020; Wortinger 2016 & 2017) and clinical trial outcomes (Kejmel 2017). The latter alternative is assumed to be driven by neurocognitive aberrations such as cognitive fusion and attention bias, which in turn may be linked to personality traits, worrying tendencies and loneliness (Wyller 2009). A recent observational cohort study conducted by our research group provides some support for this model, finding that risk of Long COVID was related to baseline personality traits and loneliness, but not to biological markers (Selvakumar 2022). In addition, this model hypothesizes that the functional brain alterations result in a sympathetic predominance of autonomic nervous system activity which in turn may impact on immunological functions, as has indeed been reported in several previous PPIS studies (Jason 2021; Katz 2019; Kristensen 2019).

Nicotinamide riboside (NR,sales name Niagen®), a vitamin precursor converted to nicotinamide adenine dinucleotide (NAD^+) in vivo (Airhart 2017), acts as a co-factor in several vital metabolic pathways, including aerobic energy production in the mitochondria. NR seems to reduce neurological inflammation and is currently being tested in disorders such as Amyotrophic Lateral Sclerosis (ALS), Parkinson's disease and neurological complications of diabetes mellitus. (Obrador 2021; Lee 2019; Maynard 2020; Chandrasekaran 2019; Chandrasekaran 2020; Mehmel 2020). Recent data suggest that NR supplementation increased brain NAD^+ levels that was associated with altered brain metabolism (Brakedal et al 2022). There is also preliminary evidence for a beneficial effect in acute COVID-19, possibly due to a dampening effect on the hyperinflammatory state associated with severe acute infection (Mehmel 2020). Assuming that Long COVID and other chronic fatigue conditions are caused by mitochondrial dysfunction and subsequent inflammation, NR dietary supplement may hold promise for a beneficial effect.

A recent meta-analysis concluded that the mental intervention method Acceptance and Commitment Therapy (ACT) is among the most promising interventions when it comes to persisting symptoms, somatic and/or psychological, with superior results compared to active control conditions (Gloster et al 2020). In terms of fatigue, Norwegian studies conducted by members of the research team show effects of ACT on persistent fatigue (Jacobsen et al 2017 and 2020). Related mental interventions, such as Cognitive Behavioural Therapy (CBT), has previously been demonstrated to be effective in PPIS (Kejmel 2017) as well as in Long COVID (Kuut et al 2021, 2023). Also, CBT delivered via the internet has been shown to be effective against chronic fatigue states (Janse 2018). Assuming that Long COVID is mainly caused by functional brain aberrations, a tailored and personalized cognitive approach (Mind-Body Reprocessing Therapy, MBRT) using elements from ACT as well as related techniques, and combining therapist contact with digital content and follow-up, may have potential.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of MBRT and NR may be found in the participant information leaflet. A Data Monitoring Committee will be established and given an independent responsibility for overseeing adverse effects related to the intervention, cf. paragraphs 9 and 10.

2.3.1. Risk Assessment

Investigational Intervention

- Psychological interventions have been shown safe to use as treatment in other PPIS as well as in persistent symptom conditions in general, with no serious adverse events (Kejmel 2017; White 2011; Nijhof 2012; Janse 2018; Kuut et al 2023). The internet-based format of part of the MBRT reduces burden on the participants and secures therapy delivery.
- NR is a dietary supplement, where dosage of 1000 mg x 2 daily has been shown safe with no adverse events reported (Mehmel 2020; Airhart 2017). Furthermore, NR was awarded status as "generally recognized as safe" by the Federal Drug Administration (FDA) in the USA in 2016 (GRAS No. 635). In a recent study of toxicity, daily doses up to 1200 mg/kg were well tolerated in rats (Marinescu 2020). Regarding embryo-fetal developmental toxicity, a rat study found a no observed adverse effect level (NOAEL) of 325 mg/kg, corresponding to a daily intake of more than 22,000 mg in an adult of 70 kg (EFSA Panel on Nutrition, 2019).

Study Procedures

- Blood samples collected through venous puncture is the most intrusive procedure in this study. The risk of this procedure is low and well accepted in general.
- As there is no known medical treatment for persistent symptoms following COVID-19, there is no known risk for giving placebo hence not giving medical treatment to half of the participants.

2.3.2. Benefit Assessment

The participants in the study may benefit from a thorough medical examination that may identify other health issues. Also, the subgroups of participants allocated to the active treatment arms may benefit from potential effective therapies against Long COVID. In general, for patients with Long COVID and for the society, there are huge benefits in identifying potential therapeutic options against this condition, givens its high prevalence and disabling consequences.

2.3.3. Overall Benefit Risk Conclusion

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with the MBRT and NR interventions are justified by the anticipated benefits for participants, Long COVID patients in general, and the society at large.

3. Objectives, Endpoints, and Estimands

3.1. Main intervention effects

A total of 20 endpoints are directly related to intervention effects, as outlined in Table 2. The study has one primary endpoint (A1), six secondary endpoints (B1-6), and 13 exploratory endpoints (C1-13), all evaluated at T2.

Table 2. Assessment of intervention effects

	Objectives	***Endpoints***
A	Primary	
A1	To determine whether MBRT/NR increases **health-related quality of life** in individuals with Long COVID compared with care as usual/placebo.	The Medical Outcome Study 36-item short form (SF-36), general health subscore (Jacobsen 2018)
B	Secondary	
B1	To determine whether MBRT/NR reduces **markers of inflammation** in individuals with Long COVID compared with care as usual/placebo	Plasma levels of C-reactive protein, high-sensitive assay (hsCRP) (Pedersen 2019)
B2	To determine whether MBRT/NR increases **executive functioning** in individuals with Long COVID compared with care as usual/placebo.	The Trail Making Test, part B, of neurocognitive functioning (Reitan 1958)
B3	To determine whether MBRT/NR reduces **fatigue** in individuals with Long COVID compared with care as usual/placebo	Chalder Fatigue Questionnaire (CFQ), total sum score (Chalder 1993)
B4	To determine whether MBRT/NR reduces **dyspnoea** in individuals with Long COVID compared with care as usual/placebo	Medical Research Council dyspnoea scale (Bestall 1999)
B5	To determine whether MBRT/NR impact on patients' **global impression of change in symptoms, functions and quality of life** in individuals with Long COVID compared with care as usual/placebo	Patient Global Impression of Change (PGIC) inventory (Hurst 2004)
B6	To determine whether MBRT/NR increases **cost-effectiveness** in individuals with Long COVID compared with care as usual/placebo	Incremental cost-effectiveness ratio, using the 36-item short form (SF-36) general health subscore to determine quality-adjusted life years.
C	Exploratory	
C1	To determine whether MBRT/NR reduces **markers of inflammation (other than hsCRP)** in individuals with Long COVID compared with care as usual/placebo	Plasma levels of interleukin (IL)-6.
C2	To determine whether MBRT/NR increases **working memory** in individuals with Long COVID compared with care as usual/placebo	The Digit Span Test, total score (Grizzle 2011)
C3	To determine whether MBRT/NR reduces **worrying tendencies** in individuals with Long COVID compared with care as usual/placebo	Penn State Worry Questionnaire (PSWQ), total sum score (Pallesen 2006)

C4	To determine whether MBRT/NR reduces **sympathetic predominance of autonomic cardiovascular control** in individuals with Long COVID compared with care as usual/placebo	Heart rate variability (HRV) indices in the time and frequency domain using a 5-minute ECG recording obtained during supine rest (Task Force 1996)
C5	To determine whether MBRT/NR reduces **post-exertional malaise (PEM)** in individuals with Long COVID compared with care as usual/placebo.	PEM items from the DePaul Symptom Questionnaire, total average score across five items (Bedree 2019)
C6	To determine whether MBRT/NR reduces **pain** in individuals with Long COVID compared with care as usual/placebo	Brief Pain Inventory (BPI), average score (Klepstad 2002)
C7	To determine whether MBRT/NR reduces **sleep difficulties** in individuals with Long COVID compared with care as usual/placebo	Karolinska sleep questionnaire (KSQ), total sum score (Akerstedt 20089)
C8	To determine whether MBRT/NR reduces **subjective cognitive difficulties** in individuals with Long COVID compared with care as usual/placebo	Cognitive items from Chronic Fatigue Symptom inventory, average score across four items (Selvakumar 2022)
C9	To determine whether MBRT/NR reduces **depression** in individuals with Long COVID compared with care as usual/placebo	Hospital Anxiety and Depression Symptoms (HADS), Depression subscore (Zigmond 1983)
C10	To determine whether MBRT/NR reduces **anxiety** in individuals with Long COVID compared with care as usual/placebo	Hospital Anxiety and Depression Symptoms (HADS), Anxiety subscore (Zigmond 1983)
C11	To determine whether MBRT/NR reduces **altered smell and taste** in individuals with Long COVID compared with care as usual/placebo	Upper airways symptoms, two single items (Wagner 2005)
C12	To determine whether MBRT/NR increases **physical functioning** in individuals with Long COVID compared with care as usual/placebo.	The Medical Outcome Study 36-item short form (SF-36), physical function subscore (Jacobsen 2018)
C13	To determine whether MBRT/NR increases **social functioning** in individuals with Long COVID compared with care as usual/placebo.	The Medical Outcome Study 36-item short form (SF-36), social function subscore (Jacobsen 2018)

3.2. Additional objectives

In addition to the main intervention effects, this study encompasses several other objectives that fall in three main categories (Table 3):

- Details of the intervention (such as compliance (D1), therapist fidelity (D2), recovery (D3), dose-response associations (D4), effects of a specific element within the MBRT program (D5), interaction effects (D6), subgroup effects (D8 & 9), effect of prior confidence in interventions (D10) and success of double-blinding (D11)), all evaluated at T2.
- Predictors of treatment effects (E1), exploring the associations of a wide array of background and T1-variables with outcome variables at T2, cf. paragraph 9.
- Long-term effects of the intervention, exploiting variables at T3 (F1) as well as linkage with the Norwegian Labour and Welfare Administration registry on sick leave (F2).

Table 3. Additional objectives		
	Objectives	***Outcome measures***
D	Intervention details	
D1	To determine **compliance** with the MBRT/NR interventions.	Whole blood levels of NAD^+; (Trammel 2016); pills taken vs. pills described ratio; patient report of self-directed activities by day 25 and at T2.
D2	To determine **therapist fidelity** to the MBRT intervention	Audio recording and subsequent content analyses of a random selection of therapist-patient-encounters
D3	To determine number of participants meeting **recovery threshold** (population norm) in the four different treatment groups.	The Medical Outcome Study 36-item short form (SF-36), general health subscore compared with population norm (Jacobsen 2018)
D4	To determine **dose-response associations** within the MBRT/NR interventions.	Previously described primary, secondary and exploratory endpoints; whole blood levels of NAD^+; patient report of self-directed activities at T2.
D5	To determine whether **the first medical consultation** ("brief intervention") within the MBRT package improves health-related quality of life in individuals with Long COVID compared with care as usual	Patient Global Impression of Change (PGIC) inventory (Hurst 2004), administered to participants in the MBRT arm immediately after the first medical appointment
D6	To determine **interaction effects** between MBRT and NR	Previously described primary, secondary and exploratory endpoints, analyses of interaction effects
D7	To determine the **safety** of MBRT/NR	Previously described primary, secondary and exploratory endpoints, analyses of deterioration; clinical investigations, analyses of abnormal findings; analyses of adverse events; analyses of health care contacts and treatment initiations
D8	To determine whether MBRT/NR has **differential effects in subgroups** of patients with Long COVID adhering to the Fukuda-definition (Hickie 2006) of PIFS or not	Previously described primary, secondary and exploratory endpoints, analyses of subgroup-effects
D9	To determine whether MBRT/NR has **differential effects in subgroups** of patients with high vs. low levels of post-exertional malaise (PEM)	Previously described primary, secondary and exploratory endpoints, analyses of subgroup-effects
D10	To determine whether **prior confidence** in MBRT and/or NR impacts on intervention effects of MBRT	Previously described primary endpoints; customary questions on treatment confidence at T1
D11	To determine the **success of double-blinding** of the NR/placebo allocation.	Study physicians' and participants' guess on NR/placebo allocation at T2
E	Predictor analyses	

E1	To determine **predictors of MBRT/NR treatment effects** in patients with Long COVID	Previously described primary and secondary endpoint, analyses of baseline predictors
F	Long-term effects	
F1	To determine whether MBRT/NR has any impact on symptoms, function and biological markers at **one year follow-up** of individual with Long COVID compared with care as usual/placebo	Previously described primary and secondary endpoint at 12 months follow-up (T3).
F2	To determine whether MBRT/NR increases **work attendance** in individuals with Long COVID compared with care as usual/placebo	Linkage with the Norwegian Labour and Welfare Administration registry on sick leave

3.3. Primary estimand

The primary clinical question of interest is: What is the difference in health-related quality of life measured by SF-36 (general health subscore) in patients with Long COVID treated with MBRT vs. care as usual and NR vs. placebo regardless of discontinuation of investigational intervention for any reason?

The primary estimand is described by the following attributes:

- *Population*: Patients with a diagnosis of Long COVID, according to the WHO definition (Soriano 2021).
- *Endpoint*: Health-related quality of life measured by general health subscore on SF-36 at 3 months follow-up (T2).
- *Treatment condition:* The investigational interventions regardless of discontinuation for any reason.
- *Remaining intercurrent events*: The intercurrent events "intervention discontinuation for any reason" are addressed by the treatment condition of interest attribute. There are no remaining intercurrent events anticipated at this time.
- *Population-level summary*: Mean difference between treatment conditions

4. Study Design

4.1. Overall Design

This study is a randomized controlled trial featuring a 2 x 2 factorial design where MBRT is compared with usual care and NR is compared with placebo (Figure 1). The latter comparison is double blinded.

Eligible participants are individuals (18-70 years) with confirmed Long COVID interfering negatively with daily activities (such as work, socially, normal leisure activities, etc.). Participants will be recruited from previous COVID-19 studies at our institution, as well as directly through self-referrals and referrals from general practitioners and hospital services. A total of 310 participants will be enrolled. "Enrolled" means participants' agreement to participate in a clinical study following completion of the informed consent process and screening for eligibility. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening.

After baseline assessment (T1), the participants will be randomized in 1:1:1:1 probability for four treatment groups of approximately equal size: a) MBRT and NR; b) usual care and NR; c) MBRT and placebo; d) usual care and placebo. The randomization procedure will utilize a computer-based routine for block randomization; block size will vary randomly between 4 and 8. Allocation will be stratified by: a) Severity of illness during the acute stage of COVID-19, operationalized as (1) no admission to hospital, (2) admission to hospital; and b) Time since acute COVID-19, operationalized as (1) less than one year, (2) one year or more.

The intervention period last for three months, followed by primary endpoint assessment (T2). Total follow-up time is 12 months (T3). Hence, all participants will be scheduled for three study visits. In addition, participants allocated to MBRT will be summoned for an additional 4-6 visits between T1 (baseline) and T2 (three months follow-up).

For the NR vs. placebo comparison, NR capsules of 250 mg will be given at a fixed dose of 1000 mg (ie. four capsules) twice daily in the intervention group, while the control group will receive and identical number of identical looking placebo capsules. Treatment duration is 12 weeks (84 days) in both groups.

For the MBRT vs. usual care comparison, the MBRT will be delivered as one encounter with a medical doctor ("brief intervention") followed by three face-to-face encounters (alternatively video consultations) with a psychiatrist/psychologist trained in the MBRT method. If requested by the participants, additional two encounters with a psychiatrist/psychologist may be offered. The entire MBRT program will be delivered over a time period of approximately 3 weeks. Also, the participants will be provided access to specially developed digital MBRT training resources through Dignio®, an internet-based platform for eHealth services. The usual care group will be offered a short self-help leaflet and their general practitioners will be provided with results from the standard clinical and laboratory examination at baseline (T1); otherwise, no treatment will be given to the usual care-group as part of the present study.

Throughout the study, all participants will be able to report adverse events (AE)/serious adverse events (SAE) through the Dignio® interface, reducing time delay. The study doctors will report to the Data Monitoring Committee weekly about AEs and within 24 hours during weekdays about SAE. Also, adverse events (AE) and serious adverse events (SAE) will be charted by questionnaires at two time points during the intervention period (two and five weeks after baseline (T1)).

A Data Monitoring Committee for the study will be established.

4.2. Scientific Rationale for Study Design

- Randomized controlled trials is the gold standard for assessment of treatment effects. With this design, the untreated participants serve as a control group to the treated participants, and the impact of mediating/confounding factors are minimized with randomization.
- In the present study, testing of NR vs. placebo is double blinded, minimizing the potential bias related to placebo effects. The MBRT vs. usual care comparison is impossible to blind due to the nature of the treatment. However, during endpoint-evaluation, the responsible researchers will be blinded for group allocation
- SF-36 is a well-validated, generic instrument for assessment of health-related quality of life. As Long COVID may encompass a variety of different symptoms, a comprehensive inventory of ill health is considered more appropriate than symptom-specific inventories as primary endpoint. Also, as Long COVID is defined primarily by patients' subjective symptom experiences (no biomarker has been found as yet), a patient reported outcome measure (PROM) is considered the most appropriate primary endpoint.
- The underlying causes of Long COVID remain elusive, and controversies exists regarding the weight given to pure biomedical explanations vs. the potential impact of psychosocial factors (Newman 2021). The 2 x 2 factorial design is a convenient way to test two different treatment strategies grounded in two different hypothetical models of pathophysiology on the same patient population. Hence, treatment effects will be directly comparable and not limited by potential selection bias.

4.2.1. Patient Input into Design

The investigational program in this study is based on the observational cohort study entitled Long-Term Effects of COVID-19 in Adolescents (LoTECA) at Akershus University Hospital (ClinicalTrials ID: NCT04686734). Feedback from LoTECA participants has been taken into account when planning the design of the present study. In addition, the design has been discussed with representatives of the Recovery Norway organization, consisting of individuals having recovered from Long COVID and similar post-infective chronic fatigue states. Finally, the design has been discussed with representative from the Consumer Advisory Committee of the Collaborative of Fatigue Following Infection (COFFI); and international consortium consisting of world-leading researchers on Long COVID and related conditions, and headed by the principal investigator of the present study (cf. www.coffi-collaborative.com).

4.3. Justification for Dose

Studies conducted in both healthy human volunteers and mice suggest that a NR dose of 1000 mg twice daily (2000 mg in total), in line with the present study, can significantly increase steady-state, whole-blood levels of NAD^+ and effectively stimulate NAD^+ metabolism without causing adverse effects (Trammel 2016; Martens 2018). Moreover, NR supplementation (500 mg bid) increases brain NAD^+ levels (Brakedal et al 2022). Furthermore, a study of elimination kinetics indicates that twice-daily dosing of NR should be sufficient to achieve a desired clinical outcome (Airhart 2016).

This protocol allows some alteration from the currently outlined dosing schedule (cf. below), but the maximum daily dose of NR will not exceed 2000 mg.

4.4. End-of-Study Definition

The end of the study is defined as the date of the last visit (T3) of the last participant in the study.
A participant is considered to have completed the study if the participant has completed all periods of the study including the last visit (T3).

5. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Participant must be between 18 and 70 years of age at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participants who have undergone acute COVID-19, confirmed by adhering one of the criteria a. and b. below:
    a. *Either* a positive PCR-test.
    b. *Or* a positive self-test for SARS-CoV-2 combined with an antibody-pattern from serum samples assayed at T1 consistent with previous SARS-CoV-2 infection.
3. Persistent symptoms at least 6 months following acute COVID-19 without symptom-free interval.
4. Functional disability to an extent that impacts negatively on normal activities (such as work attendance, physical exercise, social activities, etc.)

Informed Consent

5. Capable of giving signed informed consent as described in Appendix 1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Other chronic illnesses, demanding life situations or concomitant drug use/substance abuse that is considered a plausible cause of persistent symptoms and associated disability
2. Sustained organ damage (lung, heart, brain) following acute, serious Covid-19
3. Pregnancy.
4. Bedridden.

Prior/Concomitant Therapy

N/A

Other Exclusion Criteria

5. Insufficient command of Norwegian language (orally and in writing).

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

No restrictions

5.3.2. Caffeine, Alcohol, and Tobacco

No restrictions.

5.3.3. Activity

No restrictions.

5.3.4. Other Restrictions

Due to scarce data on embryo-fetal developmental toxicity of Nicotine Riboside, participating women of fertile age will be recommended to use contraceptives during the intervention phase.

5.4. Screen Failures

A screen failure occurs when a participant who has consented to participate in the clinical study is not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE. Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

5.5. Criteria for Temporarily Delaying Administration of Study Intervention

Both acute illness and acute life events may cause a delay in administration study intervention. This is accepted but needs to be recorded.

6. Study Intervention(s) and Concomitant Therapy

Study interventions are all pre-specified, both the dietary supplement NR and the MBRT.

6.1. Study Intervention(s) Administered

Intervention Label	Nicotinamide Riboside	Placebo	Mind-body reprocessing therapy	Usual care
Intervention Name	NR	Placebo	MBRT	Usual care
Intervention Description	4 capsules 2 times daily	4 capsules 2 times daily	4-6 face-to-face meetings, unlimited access to designated online resource through web-based interface	Brief self-help leaflet, otherwise care as usual by the general practitioner
Type	Dietary Supplement	Placebo	Psychological therapy	Usual care
Dose Formulation	Capsule	Capsule	-	-
Unit Dose Strength(s)	250 mg	-	-	-
Dosage Level(s)	1000 mg x 2 daily	4 capsules x 2 daily	-	-
Route of Administration	oral	oral	-	-
Use	experimental	placebo	experimental	sham comparator/no intervention
IMP and NIMP/AxMP.	IMP	IMP	-	-
Sourcing	Provided locally by the study site.	Provided locally by the study site.	Provided locally by the study site.	Provided locally by the study site.
Packaging and Labeling	Study intervention will be provided in a pillbox. Each pillbox will be labeled as required per Norwegian precepts, including dosage instructions	Study intervention will be provided in a pillbox. Each pillbox will be labeled as required per Norwegian precepts, including dosage instructions	Study intervention will be provided face-to-face, as well as over the internet.	-

Arm Title	MBTR and NR	MBTR and placebo	Usual care and NR	Usual care and placebo
Arm Type	Experimental and experimental	Experimental and placebo	No intervention and experimental	No intervention and placebo
Arm Description	MBRT: Face-to-face encounters with medical doctor (1 encounter) and psychiatrist/psychologist (3-5 encounters) as well as access to designated digital resources over a 3 months period. NR 1000 mg x 2 daily for 3 months.	MBRT: Face-to-face encounters with medical doctor (1 encounter) and psychiatrist/psychologist (3-5 encounters) as well as access to designated digital resources over a 3 months period. Placebo capsules x 2 daily for 3 months.	No intervention: Participants will receive a small self-help brochure, and check-ups as usual at the general practitioner. NR 1000 mg x 2 daily for 3 months.	No intervention: Participants will receive a small self-help brochure, and check-ups as usual at the general practitioner.

				Placebo capsules x 2 daily for 3 months.

6.1.1. Medical Devices
N/A

6.2. Preparation, Handling, Storage, and Accountability
- ChromaDex, Inc., USA will supply both nicotinamide riboside (NR) and placebo capsules and ship them to the Akershus University Hospital (Ahus). Placebo pills contain microcrystalline cellulose within a vegetarian capsule..
- NR and placebo capsules will be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the authorized site staff.
- The investigator is responsible for randomization of the participants and for participant information about NR/placebo.

6.3. Assignment to Study Intervention
The study consists of four treatment arms. In addition, two stratification variables are defined: initial severity (not hospitalized vs. hospitalized) of acute COVID-19, and time since (< vs. ≥ 12 months) acute COVID-19, resulting in four strata. For each strata, block randomised series will be created by a computer-based algorithm (1:1:1:1 allocation to the four treatment arms, block size to vary between 4 and 8). After baseline assessment at T1, all included participants will be designated to a specific strata and provided with an envelope containing the allocation to study arm.

6.4. Blinding
For the NR vs. placebo comparison, both researchers and participants are blinded throughout the course of the study. The relevant capsules are labelled A and B; the encoding is only known by the biostatistician in the Independent Data Monitoring Committee. As a quality check of blinding, a questionnaire item at T2 will prompt the participants as well as researchers to guess whether participants received NR or placebo, and the relationship between guessed and factual allocation will be subjected to statistical testing of randomness. Due to the nature of the intervention, the allocation of participants to MBRT or usual care will not be blinded.

6.5. Study Intervention Compliance
NR vs. placebo
- At therapy initiation, each participant will be supplied with a defined number of capsules. The residual number at T2 will be counted, and an index of compliance will be calculated

- Compliance will also be assessed by comparing the concentration of NAD+ in whole blood at T2 and T1.

MBRT vs. usual care

- The therapists will record any deviation from planned face-to-face therapies
- Within the web-based interface of Dignio®, the participants will record the number of different self-directed activities per week prompted by the designated digital resources at two time points: 25 days after T1 and at T2.
- All therapy sessions will be audio-recorded. After completion of all interventions, a random selection of 20 % of the recordings will be analyzed to assess therapeutic fidelity.
- A total of 5 % of all therapy sessions will be video-recorded (based upon separate consent from the patients), and used for continuous supervision of the therapists during the course of the study.

6.6. Dose Modification

This study is using a fixed dose of NR of 1000 mg x 2. In individuals complaining of non-serious side effects that may be attributed to the treatment, the dose can halved (NR of 500 mg x 2) at the researchers' discretion.

6.6.1. Retreatment Criteria

N/A

6.7. Continued Access to Study Intervention after the End of the Study

If one of the interventions is found to be beneficial, participants in the non-intervention group who suffer from a sustained Long COVID diagnosis will be offered the same treatment after completion of the study. Otherwise, no other access to treatments will be offered within the framework of the present study.

6.8. Treatment of overdose

For this study, any dose of NR greater than 300 mg/kg within a 24-hour time period will be considered an overdose (Marniescu 2020). In the event of an overdose, the treating physician should:

- Evaluate the participant to determine, in consultation with the Data Monitoring Committee, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities as medically appropriate and at least until the next scheduled follow-up.
- Document the quantity of the excess dose as well as the duration of the overdose.

6.9. Prior and Concomitant Therapy

Therapy initiated prior to inclusion in the present study may be continued as long as it complies with the inclusion and exclusion criteria (cf. above). During the active intervention period (from T1 to T2),

participants should not undertake any concomitant therapy for Long COVID. Therapies for other conditions should be evaluated by the investigators on a case-by-case basis. In the period from T2 to T3, concomitant therapy is generally allowed, except for the therapies tested in the present study (NR and MBRT).

6.9.1. Rescue Medicine

N/A

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant should, if at all possible, remain in the study to be evaluated at assessment points. The final decision on discontinuation will be taken by the principal investigator (PI) of the study. The Data Monitoring Committee will be notified without undue delay.

7.1.1. Liver Chemistry Stopping Criteria

N/A

7.1.2. QTc Stopping Criteria

N/A

7.1.3. Temporary Discontinuation

Discontinuation of intervention may be considered at the PI's discretion and will routinely be applied after a registered SAE.

7.1.4. Rechallenge

N/A

7.1.4.1. Study Intervention Restart or Rechallenge After Liver Stopping Criteria Are Met

N/A

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at the participant's own request for any reason (or without providing any reason).
- A participant may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued from the study intervention and the study at that time.
- The participant can withdraw consent for disclosure of future information.
- If a participant withdraws from the study, the participant may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow up

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, three telephone calls, and if necessary, a certified letter to the participant's last known mailing address). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.

8. Study Assessments and Procedures

8.1. Investigational program

8.1.1. Preparations and clinical examination

At T1, T2 and T3, all participants will undergo a structured investigational program at the MINIRICO study center at Akershus University Hospital. They will be offered local anesthetic ointment (EMLA®, AstraZeneca) to apply on the antecubital vein one hour before arriving, to avoid the pain of venous puncture. Finally, they will be instructed to bring a spot urine sample in a sterile container.

The clinical interview will include questions on country of origin/ethnicity as well a chronic diseases and permanent use of pharmaceuticals. Examination will encompass a structured review of organ systems, particularly focusing on respiratory (stridor, wheezing, retractions, crackling sounds), cardiovascular (murmur) and neurological (focal signs) abnormalities. Weight, height, blood pressures (sitting position, non-dominant arm), blood oxygen saturation (SaO_2), and tympanic temperature will be recorded. The urine sample will be assayed with a Multistix 5 (Siemens Healthcare, Erlangen, Germany); also, a pregnancy test will be performed of all women aged 18 to 50 years (T1 and T2 only).

8.1.2. Functional testing

Spirometry

Spirometry will be conducted to measure the forced vital capacity (FVC) and the forced expiratory volume in one second (FEV1) (EasyOne® Air spirometer, EasyOne Connect software, NDD Medizintechnic AG, Switzerland). The ratio of FEV1/FVC will be calculated. Procedures will be executed according to the American Thoracic Society and European Respiratory Society guidelines, and recordings that do not adhere to technical quality requirements will be excluded from the main analysis (Graham 2019). The Global Lung Function Initiative 2012 network reference values will be used to calculate the percentage of predicted values and the lower limit of normal (LLN) (Quanjer 2012).

ECG recording and autonomic cardiovascular control

A 5-minute ECG recording will be performed applying The Bittium Faro 360® device (Bittium Corporation, Oulu, Finland). During recording, participants will be laying supine in a dark room with calm surroundings.

Recordings will be analyzed using manufacturer developed software, providing automatic R-wave detection and exclusion of arrhythmias (including ectopic beats). Heart rate variability (HRV) indices will be calculated in the time domain, as well as in the frequency domain after Fast Fourier Transformation of the time series, according to international standards (Task Force 1996). Computed time domain indices include SDNN (the standard deviation of all RR-intervals), pNN50 (the proportion of successive RRIs with a difference greater than 50 ms), and r-MSSD (the square root of the mean square differences of successive RRIs). In the frequency domain, power densities will be computed in the low-frequency (LF) band (0.04-0.15 Hz) and the high-frequency (HF) band (0.15-0.5 Hz), and expressed both in absolute (LF_{abs}, HF_{abs}) and normalized units, where $LF_{norm} = LF_{abs} / (LF_{abs} + HF_{abs})$ and $HF_{norm} = HF_{abs} / (LF_{abs} + HF_{abs})$. In addition, the LF_{abs}/HF_{abs} ratio will be computed.

Vagal (parasympathetic) activity is considered the main contributor to HF-variability of heart rate, whereas both vagal and sympathetic activity contributes to LF-variability (Saul 1990; Pagani 1986). The LF/HF ratio is considered an index of sympathovagal balance.

Cognitive function tests
All cognitive function tests will be carried out by trained examiners in a separate room with calm surroundings. The Digit Span Test will be adopted from the Wechsler Adult Intelligence Scale (WAIS), 4th edition (WAIS-IV). This test is used for verbal and auditory working memory assessment. A string of random digits is read aloud by the examiner. The first string consists of two random numbers, and for every other string, one more number is added. The digit span forward mode requires the test subject to repeat the digits in the same order as they are presented; in the digit span backward mode, digits are repeated in reverse order. Each correctly repeated string is scored one point. The test is discontinued when two strings of equal length are answered incorrectly. Sum scores for digit span forward and backward, as well as total sum score, will be computed.

A test of verbal learning, delayed recall, and recognition is adopted from the Hopkins Verbal Learning Test-Revised (HVLT-R) (Benedict 1998). The examiner read aloud a list of 12 words and the participant is asked to repeat as many words as possible in three consecutive trials. An index of verbal learning memory will be computed as the sum score of remembered words (ranging from 0 to 36) across the three trials. After 20 minutes, the examiner asks the participants to report as many words as possible; an index of delayed verbal memory is computed as the number of words the test subject were able to recall correctly (ranging from 0 to 12). Finally, a total of 24 words are read aloud by the examiner, of which 12 are identical to the previous list of words; the number of correctly recognized and falsely recognized words is recorded separately (both indices ranging from 0 to 12).

A trail-making test asking the participants to draw lines between numbers and letters in increasing order will be performed. The trail-making test is primarily a test of executive functions.

8.1.3. Sampling of biological specimens and laboratory assays

Sampling and biorepository procedures
Blood samples will be drawn with participants laying in a supine position using an antecubital vein; if requested by the participants, local anaesthetic ointment (EMLA®) will be applied for at least 60 minutes but removed 15 minutes prior to sampling.

Blood samples will immediately undergo further preparations in order to obtain aliquots of plasma, serum, whole blood, RNA and viable Peripheral Blood Mononuclear Cells (PBMC)). Thereafter, blood derived material not subjected to further analyses will be transferred to a biorepository adjacent to the study centre (EpiGen laboratories, Akershus University Hospital, Norway), and stored at -80ºC or -150ºC, as appropriate.

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 150 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Inflammatory markers
EDTA whole blood samples will be placed on ice-water for 5-60 minutes. Followingly, plasma will be separated by centrifugation (2200 g, 10 min.) and frozen at –80 °C until assayed. Plasma levels of

growth-differentiation factor (GDF)-15, interleukin-6 and C-reactive protein (CRP) will be measured using an automated immunoassay from Roche Diagnostics.

SARS-CoV-2-antibodies
Sera from all participants will be screened for IgG antibodies against the receptor-binding domain (RBD, Wuhan) as well as the nucleocapsid antigen of the SARS-CoV-2 virus, using automated immunoassays from Roche Diagnostics or Abbott Diagnostics.

Routine blood analyses
Routine blood markers will be assayed at the accredited laboratory at Akershus University Hospital, Norway, and include the following: Haemoglobin; Leukocytes with differential count; Platelets; CRP; Ferritin; Alanine transaminase (ALT); Gamma-glutamyltransferase (GGT); Lactate dehydrogenase (LDH); Albumin; N-terminal prohormone of Brain Natriuretic Peptide (NT-proBNP); Troponin T; Creatine kinase (CK); Glucose; Glycated haemoglobin (HbA_{1C}); Bilirubin; D-dimer; International Normalized Ratio (INR); Urea; Creatinine; Natrium; Potassium; Calcium; Vitamin B_{12}; Folic acid; Vitamin D; Thyroid-stimulating hormone (TSH); Thyroxine; Cortisol; IgG (total); IgM (total); IgA (total); Blood gases (venous sample); SARS-CoV-2 anti-nucleocapsid, total antibody titer (IgM+IgG).

8.1.4. Questionnaires

A composite questionnaire consisting of validated inventories will be used to chart clinical symptoms, personality traits, social factors as well as basic demographic and constitutional variables. An overview is provided in Table 1. The questionnaire will be administered digitally using the "Nettskjema"-tool administered by the Services for Sensitive Data at the University of Oslo (https://www.uio.no/english/services/it/research/sensitive-data/index.html). This tool ascertains that all items are completed before submission to a dedicated and secured server area where scores are automatically computed following a predefined scoring algorithm. All participants will answer the questionnaire using a dedicated computer at our study center as part of the investigational program at baseline and follow-ups.

Table 1. Composite questionnaire overview: Constructs, inventories and scoring procedures

Construct(s)	*Name of inventory*	*Description and scoring procedures*
A. Background and Demographics		
1. Household, socioeconomic level	Not applicable	Household members; parents' occupation; the international socio-economic index (ISEI) of occupational status is used to score socio-economic level (Ganzeboom 1992)
2. Smoking, alcohol, drugs	Not applicable	Alcoholic beverages, illicit drugs, smoking; answered on a 5-point Likert scale, where 1 is "never" and 5 is "every day/almost every day".
3. Physical activity	Not applicable	Answered on a 5-point Likert scale, where 1 is "a lot less active than peers" and 5 is "a lot more active than peers".
4. Diseases	Not applicable	Chronic diseases; chronic disease among family members; undergone acute COVID-19 (only asked at follow-up)
5. Vaccines	Not applicable	Received vaccination against COVID-19 (number of dosages, manufacturer)
B. Unexpected/adverse events		
1. Events	Not applicable	A total of 13 items addressing specified adverse events (including more symptoms, more health problems in general, depressive episodes, suicidal

		thoughts, increased disability) and spontaneous contact with health services, as well as free text comments
C. SYMPTOMS AND DISABILITY		
1. Fatigue	Chalder Fatigue Questionnaire (CFQ)	A total of 11 items scored on 4-point Likert scales. In order to obtain a continuous variable, each item will be scored 0-3 where 0 is “less than usual” and 3 is “much more than usual”; then, a total sum score across all items is obtained ranging from 0 to 33, where higher scores indicate more fatigue (Chalder 1993). In addition, bimodal scoring (0-0-1-1) of each item will be performed; a total sum score across all items of 4 or higher is defined as fatigue caseness.
2. Clinical symptoms of post-COVID-19 condition and PPIS	CDC symptom inventory for Chronic Fatigue Syndrome	A total of 30 items addressing frequency of specific symptoms since falling ill from acute COVID-19 on 5-point Likert scales, where 1 is “never” and 5 is “all the time” (Wagner 2005). At follow-up, the questions will be slightly rephrased in order to address symptom frequency during the last months..
3. Post-exertional malaise (PEM)	PEM items from the DePaul Symptom Questionnaire	A total of five items addressing frequency of PEM symptoms on 5-point Likert scales, where 0 is “never” and 4 is “all the time”; answers are then averaged across all items and multiplied with 25 to get a 100 point scoring scale where higher scores indicate more PEM (Bedree 2019)
4. Sleep disturbances	Karolinska Sleep Questionnaire (KSQ)	A total of 12 items addressing frequency of sleep disturbances on 6-point Likert scales, where 1 is “never” and 6 is “all the time”; then, the scoring is reversed, and total sum score is computed across all items ranging from 12 to 72, where *lower* scores indicate more sleep disturbances (Akerstedt 2008). Accordingly, indexes for insomnia, awakening problems, and sleepiness will be computed as sum scores across relevant items.
5. Pain	Brief Pain Inventory (BPI)	A total of four items addressing different aspects of pain on 10-point Likert scales, where 1 is “no pain” and 10 is “worst pain imaginable”; total sum score is computed across all items ranging from 4 to 40, where higher scores indicate more pain. (Klepstad 2002)
6. Dyspnoea	Medical Research Council dyspnoea scale	A single item addressing dyspnea on a 5-point Likert scale, where 1 is “breathless during strenuous exercise” and 5 is “too breathless to leave the house” (Bestall 1999)
7. Depression and anxiety symptoms	Hospital Anxiety and Depression Symptoms (HADS)	A total of 14 items addressing different symptoms of depression and anxiety on 4-point Likert scales scored 0 – 3; for eight of the items, scoring is reversed, after which total sum score is computed ranging from 0 to 42, where higher scores indicate more symptoms of depression and anxiety (Zigmond 1983). Accordingly, separate indexes for depression and anxiety will be computed as sum scores across relevant items (seven each).
8. Quality of life	36-Item Short Form Survey (SF-36).	A total of 36 items, scored on Likert scales and recoded to achieve 100 point scales (higher score means better quality of life); average scores are reported. Eight subdomains: Physical functioning; Role limitations due to physical health; Role limitations due to emotional problems; Energy/fatigue; Emotional well-being; Social functioning; Pain; General health (Ware 1992)
9. Impression of change	Patient Global Impression of Change (PGIC)	A single 7-point Likert scale where patient rate their impression of change in health status from “no change/worsening” to “very much improved” (Guy 1976; Perrot 2019)
10. Miscellaneous	Not applicable	• One item addressing avoidance behavior on a 10-point Likert scale, where higher scores indicate more avoidance tendency. • One item addressing school/work absenteeism as number of totally absent days during the last month.
D. PSYCHOLOGICAL TRAITS AND SOCIAL FACTORS		
1. Neuroticism	NEO Five-Factor Inventory-30 (NEO-FFI-30)	A total of six items making up the neuroticism axis will be included and scored on 5-point Likert scales where 0 is “disagree completely” and 4 is “agree completely”; total sum score across all items will be computed ranging

		from 0 to 24, where higher scores indicate stronger neuroticism tendencies (Körner 2008)
2. Worrying tendencies	Penn State Worry Questionnaire (PSWQ)	A total of 16 items addressing worrying tendencies will be scored on 5-point Likert scales where 1 is “disagree completely” and 5 is “agree completely”; scoring will be reversed on five items, after which the total sum score across all items is computed ranging from 16 to 80, where higher scores indicate stronger worrying tendencies (Pallesen 2006)
3. Loneliness	UCLA Loneliness Scale	A total of 20 items addressing loneliness will be scored on 4-point Likert scales where 1 is “never” and 4 is “always”; scorings are reversed on nine items, after which the total sum score is computed ranging from 20 to 80, where higher scores indicate more loneliness (Russel 1980)

8.2. Administrative and General/Baseline Procedures

Recruitment and screening for eligibility

- The project will be announced at institutional website, at social media, and at collaborating health service institutions (such as general practitioners and hospital outpatient clinics) providing services for Long COVID patients. Also, Long COVID patients participating in prior COVID-19 research projects at our institution will be directly approached if permitted by the patient consent given in the particular projects and provided with general project information.
- Long COVID patient who are interested in participating will contact the MINIRICO study center by a dedicated phone number or email. A research secretary will provide general information orally and in writing, as well as conduct a standardized screening interview of eligibility of those who express a potential interest in participating in the trial. Questions in the interview include how and when the initial COVID-19 infection was established, the presence of persistent symptoms, the degree of functional impairment, co-morbidities and/or pharmaceuticals that may explain persistent symptoms, presence of permanent organ sequels after acute COVID-19, pregnancy, and command of Norwegian language. Patients that are considered eligible will be provided with the patient consent form, and a time point for baseline encounter will be agreed upon.

Inclusion and randomization

- Upon arriving for baseline assessment (T1), the eligibility of the possible participant will be assessed by the study doctor. Inclusion will be finalized by the patient signing the consent form, followed by randomization to one of the four treatment arms.

8.3. Efficacy Assessments

Efficacy assessments are described in paragraph 3. In short:

- Primary endpoint is the SF-36 general health sub score at T2, cf. Table 2 above.
- Secondary endpoints are inflammatory marker (hsCRP), executive function (Trail Making Test part B), fatigue, dyspnea, global impression of change in symptoms, function and quality of life, and incremental cost-effectiveness ratio.
- Exploratory endpoint include PROMs as well as blood biomarkers and functional test results, as specified in paragraph 3.

8.4. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA.

8.4.1. Physical Examinations

The physical examination will include assessments of all organ systems as well as height and weight at all study visits, cf. above. Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.4.2. Vital Signs

Vital signs will include tympanic temperature, systolic and diastolic blood pressure, heart rate, respiratory rate, and peripheral oxygen saturation (SaO_2). Three readings of blood pressure and heart rate will be obtained. The first reading should be rejected, and the second and third reading should be averaged to give the measurement to be recorded.

8.4.3. Electrocardiograms

A 5-minute 5-lead ECG recording will be performed applying The Bittium Faro 360® device (Bittium Corporation, Oulu, Finland), as described in paragraph 8.1 and outlined in the SoA (see Section 1.3).

8.4.4. Clinical Safety Laboratory Tests

- See paragraph 8.1 for the list of clinical laboratory tests to be performed, and the SoA (Section 1.3) for the timing and frequency.
- The investigator must review the laboratory results, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory results must be retained with source documents.
- Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 9 months after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
    - If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the participant will be referred to further investigations at the hospital (to appropriate specialists).
    - All protocol-required laboratory tests, as defined paragraph 8.1, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).
    - If laboratory values from non-protocol-specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded.

8.4.5. Pregnancy Testing

All female participants aged 18 – 50 years will have a urine pregnancy test at baseline and at 3 months (cf. the SoA, Section 1.3). Due to scarce data on embryo-fetal developmental toxicity of Nicotine Riboside, participating women of fertile age will be recommended to use contraceptives during the intervention phase.

8.4.6. Suicidal Ideation and Behavior Risk Monitoring

All participants will be monitored appropriately and observed closely for suicidal ideation and behavior (SIB) or any other unusual changes in behavior, especially at the beginning and end of the course of intervention. Participants who experience signs of SIB should undergo a risk assessment. All factors contributing to SIB should be evaluated and consideration should be given to discontinuation of the study intervention.

Both baseline assessment of suicidal ideation and behavior and intervention-emergent suicidal ideation and behavior will be assessed at baseline and follow-ups. In addition, suicidal ideation and behavior will be closely monitored during the intervention stage using the DIGNIO® digital interface. Finally, as a separate safety measure, participants scoring 15 or more on the HADS depression subscale (corresponding to possible serious depression) at baseline or follow-up will be directly approached by the investigators and asked about suicidal ideation and behavior, and eventually referred to relevant health services.

8.5. Adverse Events (AEs) Serious Adverse Events (SAEs), and Other Safety Reporting

The definitions of adverse events (AEs) and serious adverse events (SAEs) can be found in the Appendix. The definitions of unsolicited and solicited adverse events can be found in Appendix.
The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs OR AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the interventions. This includes events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).
The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix.

8.5.1. Time Period and Frequency for Collecting AE and SAE Information

All SAEs and AEs will be collected from the start of study intervention until the follow-up visit at the timepoints specified in the SoA (Section 1.3). Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as medical history/current medical conditions, not as AEs.

8.5.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. When submitted to the study, participants will be informed that they should report possible AEs and SAEs directly to the study doctors through the DIGNIO® digital interface. In addition, all participants will be reminded to report AE/SAE occurrences within DIGNIO®. Finally, AE/SAE will be charted by the questionnaire at follow-ups.

8.5.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AEs of special interest (as defined in Section 8.4.8) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to

follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix.

8.5.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the data monitoring committee of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

8.5.5. Pregnancy

- Women with a positive pregnancy test at T1 will not be included in the study. Due to scarce data on embryo-fetal developmental toxicity of Nicotine Riboside, participating women of fertile age will be recommended to use contraceptives during the intervention phase.
- Despite these precautions, if a pregnancy is reported during the course of the study, the investigator will record pregnancy information on the appropriate form.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention and be withdrawn from the study.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant will be followed to determine the outcome of the pregnancy.
- Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the local authorities as described in Section 8.4.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

8.5.6. Cardiovascular and Death Events

Cardiovascular events and death events occurring during the course of the study will be regarded as a SAE and handled accordingly.

8.5.7. Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

There are several disease-related events (DREs) in the acute face of a SARS-CoV-2 infection (eg. Acute Respiratory Distress Syndrome and clotting abnormalities). However, no present evidence suggests that DREs may appear more than six months after the acute infection (cf. inclusion criteria for the present study), and no specific DRE has been reported with Long COVID. Thus, there are no known DREs that are associated with the underlying disease in this study.

8.5.8. Adverse Events of Special Interest

N/A

8.5.9. Medical Device Deficiencies

N/A

8.5.9.1. Time Period for Detecting Medical Device Deficiencies

N/A

8.5.9.2. Follow-up of Medical Device Deficiencies
N/A

8.5.9.3. Prompt Reporting of Device Deficiencies to the Sponsor
N/A

8.5.9.4. Regulatory Reporting Requirements for Device Deficiencies
N/A

8.6. Pharmacokinetics
- Whole blood samples of approximately 2 mL will be collected for measurement of whole blood concentrations of NAD+ as specified in the SoA (Section 1.3).
- Samples will be used to evaluate the pharmacokinetics of NR. Samples collected for analyses of NAD+ concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Intervention concentration information will not be reported to investigative sites or blinded personnel until the study has been unblinded.

8.7. Pharmacodynamics
N/A

8.8. Genetics
Whole blood samples for potential later genetic analyses will be collected and stored at -80 ^{o}C. However, genetic analyses are not part of the present study, and separate approbation will be sought for future genetic analyses.

8.9. Biomarkers
A detailed overview of biomarker analyses are given in paragraph 8.1, above. In addition, biological specimens will be stored in a biorepository enabling further research projects (that would require separate approbations) as follows:

Blood samples

	Aliquots
Serum	4 x 500 µL
EDTA-Plasma	6 x 500 µL
EDTA-Whole Blood (for DNA isolation)	4 x 900 µL

CPT (for viable PBMC isolation)	4 x 1mL citrate plasma + 2 x 1 mL PBMC
PAX (mRNA isolation)	

8.10. Immunogenicity Assessments

N/A

8.11. Health Economics

Incremental cost-effectiveness ratio is defined as a secondary endpoint, using the 36-item short form (SF-36) general health sub score to determine quality-adjusted life years (cf. paragraph 3).

8.12. Registry linkage

In order to a) ascertain the diagnosis of PACS and b) to explore predictors of intervention effects (cf. paragraph 3 and 9), linkage with the following existing registries will be established: 'Norsk pasientregister', 'Vaksine-registeret Sysvak', 'Legemiddelregisteret', 'Meldesystem for smittsomme sykdommer (MSIS)' and 'Pandemiregisteret'.

For assessment of work attendance, linkage with the Norwegian Labour and Welfare Administration registry on sick leave will be established.

8.13. Qualitative substudy

A qualitative substudy will be implemented in the MINIRICO design, with the aim of exploring participants' experiences with the MBRT intervention. A total of 20 participants who have been allocated to MBRT will be recruited after completion of the intervention period (i.e., after T2). These participants will undergo semi-structured interviews which will be subsequently transcribed verbatim and subjected to qualitative thematic analyses.

The qualitative substudy is further detailed in a separate research protocol that has been approved by the Regional Ethics Committee. Inclusion in the substudy is based on separate informed consent (i.e., independent on consent to participation in MINRICO). The interviews and subsequent analyses are conducted by researchers not otherwise involved in MINIRICO.

9. Statistical Considerations

The analysis and reporting will be done on all data from all participants at the time the study ends. The statistical analysis plan will be finalized prior to unblinding and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.1. Statistical Hypotheses

In this study, there are two primary objectives:

1. To determine whether MBRT increase health-related quality of life in individuals with Long COVID compared with care as usual. Thus, the null hypothesis to be tested in relation to the first primary estimand is as follows:
   - Null hypothesis: MBRT is not different from care as usual with respect to the achievement of an increase in health-related quality of life at 3 months follow-up (T2).
     vs.
   - Alternative hypothesis: MBRT is different from care as usual with respect to the achievement of an increase in health-related quality of life at 3 months follow-up (T2).
2. The second objective is to determine whether NR increase health-related quality of life in individuals with Long COVID compared with placebo Thus, the null hypothesis to be tested in relation to the second primary estimand is as follows:
   - Null hypothesis: NR is not different from placebo with respect to the achievement of an increase in health-related quality of life at 3 months follow-up (T2).
     vs.
   - Alternative hypothesis: NR is different from placebo with respect to the achievement of an increase in health-related quality of life at 3 months follow-up (T2)..

9.1.1. Multiplicity Adjustment

For the primary endpoint analyses, the level of significance is set at α=0.05. A testing procedure that controls the family wise error rate (FWER) at the overall 5% level will be applied for efficacy evaluation of the six secondary endpoints as well as a potential interaction effects between the two interventions. However, as previous research indicates significant correlation between several PROMs in Long COVID patients (Selvakumar 2022), the Bonferroni correction method is not considered to be the best solution for FWER correction; rather, a resampling procedure such as the one suggested by Romano and Wolf will be applied (Romano 2005).

As for the exploratory endpoints, no multiplicity adjustments will be carried out.

9.2. Analysis Sets

For the purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	Description
Full analysis set (FAS)	• All randomized participants.

Participant Analysis Set	Description
Safety analysis set (SAS)	• All participants who are exposed to investigational intervention.
Per-protocol analysis set (PPAS)	• All randomized participants that completed the treatment period without any of the following protocol deviations: Interruption of therapy; Lost to follow-up (including participant withdrawal); Primary endpoint measurements missing; Diagnosed with another chronic disorder during the study period; Experiencing a severe illness or trauma during the study period; Commencing other treatment for Long COVID during the study period; Low compliance with the NR/placebo intervention; Low compliance with the MBRT intervention.

The full analysis set will be used to analyze endpoints related to the efficacy objectives and the safety analysis set will be used to analyze the endpoints and assessments related to safety. Per-protocol analyses will be reported as sensitivity analyses.

For the efficacy analyses, participants will be included in the analyses according to the planned investigational intervention; whereas for safety analyses, participants will be included in the analyses according to the investigational intervention they actually received.

9.3. Statistical Analyses

9.3.1. General Considerations

Variables will be reported with parametric or non-parametric descriptive statistics, eventually frequency tabulation, as appropriate. All statistical tests will be carried out two-sided. Generally, a p-value ≤ 0.05 is considered statistically significant.

9.3.2. Primary Endpoint Analysis

9.3.2.1. Definition of endpoint(s)

The primary endpoint is The Medical Outcome Study 36-item short form (SF-36), general health subscore. This variable is usually distributed close to a normal distribution; thus, parametric statistics are applicable.

9.3.2.2. Main Analytical Approach

A general linear model (ANCOVA) applied on the FAS will be used for analyses of treatment effect; the baseline value of the primary endpoint as well as stratification variables from the randomization procedure will be included as covariates. Two statistical tests will be carried out (one for each of the primary hypothesis related to each treatment comparison). For each statistical analysis, the net intervention effect (the mean difference between groups at T2) will be calculated from the parameters of the fitted general linear model and reported with 95 % confidence interval. Also, interaction effects will be investigated.

9.3.2.3. Sensitivity analysis

A similar analytic approach as described in 9.3.2.2. applied on the PPAS will be performed as a sensitivity analysis.

9.3.2.4. Supplementary analysis

Please cf. the Statistical Analysis Plan for details

9.3.3. Secondary Endpoints Analysis

A similar analytic approach as described in 9.3.2.2. applied on both the FAS and the PPAS will be performed as for all secondary endpoints analyses

9.3.4. Exploratory Endpoint Analysis

Exploratory endpoint analyses will depend upon variable characteristics as well as hypotheses developed form the primary and secondary endpoint analyses; thus, no detailed specification is feasible at the present stage.

9.3.5. Safety Analyses

Safety data will be summarized descriptively through appropriate data tabulations and descriptive statistics.

9.3.6. Other Analyses

9.3.6.1. Predictors of treatment effects

A prediction analysis of treatment effects will feature a methodological set-up similar to a recent observational cohort study of COVID-19 patients (Selvakumar 2022), exploring associations between a wide range of background and T1-variables (independent variables) and T2-effector variables (dependent variables) by regression analyses. The PPAS will be applied in these analyses. The independent variables include:

- Previous infectious diseases: COVID-19 diagnosed by PCR-test (date, genetic variant), other infectious events one year prior to inclusion
- Previous immunizations: Vaccination against COVID-19 (date(s), type(s)), other vaccinations one year prior to inclusion.
- Previous and current medical history: Diagnoses of other chronic diseases, current medication
- Severity of acute COVID-19: Hospitalization (days), intensive care unit admission (days), respiratory support, cardiovascular support, neurological sequels, thromboembolic events, immunological and infectious markers during hospital stay (CRP, viral replication numbers).
- Current clinical symptoms and functional disability
- Psychological traits (neuroticism, worrying tendencies) and social features (socioeconomic level, loneliness, substance abuse)

9.4. Interim Analysis

No interim analysis of efficacy will be carried out. Interim analyses of safety variables will be performed throughout the intervention period and monitored by the Data Monitoring Committee.

9.5. Sample Size Determination

Approximately 310 participants will be enrolled, randomized and assigned to investigational intervention. The sample size calculation is based on the primary efficacy estimand and its endpoint

SF-36 general health sub score. A difference of 10 points is considered clinically significant (Wyrwick 2005). The scatter of SF-36 scores among Long COVID sufferers are unknown, but a large Norwegian survey reported a Standard Deviation (SD) between 20 and 23 across all age groups (Jacobsen 2017). If SD is set to be 25 in the population under study, the study should aim to include a total of 310 participants. This yields a power of about 90 % (α=0.05) to detect a small to medium effect size, allowing up to 20 % lost to follow-up or other protocol deviations.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
  - Applicable ICH Good Clinical Practice (GCP) guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, investigator's brochure, and other relevant documents will be submitted to The Norwegian National Research Ethics Committee (REK) by the principal investigator and reviewed and approved by the REK before the study is initiated.
- Any amendments to the protocol will require REK approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following, as applicable:
  - Notifying the REK of SAEs or other significant safety findings as required by REK procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies, and all other applicable local regulations

10.1.2. Financial Disclosure

This study is financed by governmental funds, thus nothing to disclose. However, each investigator is responsible for providing information on personal financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the potential participant and answer all questions regarding the study.
- Potential participants must be informed that their participation is voluntary. They or their legally authorized representatives will be required to sign a statement of informed consent
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant.

10.1.4. Recruitment strategy

Recruitment strategy is outlined in paragraph 8.1

10.1.5. Data Protection

- Participants will be assigned a unique identifier. Any participant records or datasets that are transferred for statistical analyses will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that their medical records may be examined by authorized personnel appointed by appropriate IRB/IEC members and by inspectors from regulatory authorities.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. The present project will utilize the Services for Sensitive Data (TSD) at the University of Oslo for all data management (https://www.uio.no/english/services/it/research/sensitive-data/index.html). The TSD adheres to the most strict requirements for data protection.

10.1.6. Committees Structure

MINIRICO is conducted at Dept. of Paediatrics and Adolscent Health at Akershus University Hospital, Norway. Professor/Head of Research Vegard Bruun Bratholm Wyller is Principal Investigator. Researcher Maria Pedersen manages the trial on a day-to-day basis. MINRICO is a separate work package in the overarching research initiative "Long-term effects of SARS-CoV-2 infection: An interdisciplinary observational and interventional study program", lead by professor Torbjørn Omland. There is close collaboration with profs. Silje Endresen Reme and Henrik Børsting Jacobsen at the Mind-Body Lab, Dept. of Psychology, University of Oslo.
The Steering Committee (SC) of MINIRICO consists of Wyller, Pedersen, Omland, Reme and Jacobsen, and meets on a quarterly basis. The SC is responsible for all major decisions regarding design, management structure, protocol amendments, safety concerns, publication and dissemination strategy, etc.
As described in section 9.4, MINIRICO has employed an independent data monitoring committee (IDMC), consisting of three senior academics not otherwise involved in the study. The IDMC will receive reports on all AEs/SAEs as well as key variables during the course of the study and may recommend unblinding/withdrawal of individual participants and eventual termination the study in case of safety concerns. The final decision regarding unblinding/withdrawal and termination is taken by the SC. The role and responsibilities of the IDMC is outlined in detail in a separate charter.
The established Consumer Advisory Group of the Collaborative on Fatigue Following Infections (COFFI, www.coffi-collaborative.com) provides regular consumer input on different facets of the present project as well.

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must permit study-related monitoring, audits, REK review, and regulatory agency inspections and provide direct access to source documents.
- Records and documents, including signed ICFs, pertaining to the conduct of this study will be retained by the investigator for 10 years after study completion. No records may be destroyed during the retention period without the written approval from the study leaders. No records may be transferred to another location or party without written notification to the study leaders.

10.1.8. Source Documents.

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

10.1.9. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants. The first act of recruitment is the first telephone conversation between the study center research secretary and a potential Long COVID sufferer interested in participation.

10.1.10. Publication Policy

- The results of this study may be published or presented at scientific meetings.
- The researchers will comply with the requirements for publication of study results.
- Results will be published in international scientific journals; publication of negative as well as positive results will be pursued.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.2.1. Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Definition of Unsolicited and Solicited AE

- An unsolicited AE is an AE that was not solicited using a participant diary (through Dignio®) and that is communicated by a participant/participant's parent(s) who has signed the informed consent. Unsolicited AEs include serious and nonserious AEs.
- Potential unsolicited AEs may be medically attended (ie, symptoms or illnesses requiring a hospitalization, emergency room visit, or visit to/by a healthcare provider). The participants/participant's parent(s) will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant/participant's parent(s) concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.
- Unsolicited AEs that are not medically attended nor perceived as a concern by the participant/participant's parent(s) will be collected during an interview with the participants/participant's parent(s) and by review of available medical records at the next visit.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease, or more severe than expected for the participant's condition)
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events <u>not</u> Meeting the AE Definition

- Any abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen

10.2.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

a. Results in death

b. Is life threatening

The term *life threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Is a suspected transmission of any infectious agent via an authorized medicinal product

g. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as important medical events that that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
    - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, convulsions not resulting in hospitalization, or development of intervention dependency or intervention abuse.

10.2.3. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- All AE/SAE will be reported to the steering committee as well as the independent data monitoring committee.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

- Mild: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.
- A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes. There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data.

- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the steering committee and the independent data monitoring committee with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to the steering committee and the independent data monitoring committee within 24 hours of receipt of the information.

10.2.4. Reporting of SAEs

SAE Reporting

- The primary mechanism for reporting an SAE to the steering committee and the independent data monitoring committee and other relevant authorities will be by emails and telephone calls.
- A designated form for SAE reporting has been developed, containing assessment of causality on a 7-point Likert scale; for each SAE, this form will be completed by the study physician and attached to the notifying emails.
- All SAEs and related information will be filed at the designated project server area within the TSD.

10.3. Appendix 3: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the table of contents (TOC).

Amendment #1, 26.01.2023: Minor adjustments of assessment program, inclusion criteria, lifestyle restrictions, randomization procedures, therapeutic fidelity assessment, and sample size calculations.

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Amendment #2, 20.12.20243: Minor adjustments of study rationale, outcome measures, safety monitoring routines, compliance assessment, screening procedures, analysis set definition, committee structure and SAE reporting; addition of a qualitative substudy.

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

11. References

Airhart SE, Shireman LM, Risler LJ, Anderson GD, Nagana Gowda GA, Raftery D, et al. An open-label, non-randomized study of the pharmacokinetics of the nutritional supplement nicotinamide riboside (NR) and its effects on blood NAD+ levels in healthy volunteers. PloS one. 2017;12(12):e0186459.

Ajaz S, McPhail MJ, Singh KK, Mujib S, Trovato FM, Napoli S, Agarwal K. Mitochondrial metabolic manipulation by SARS-CoV-2 in peripheral blood mononuclear cells of patients with COVID-19. Am J Physiol Cell Physiol 2021; 320: C57-65.

Akerstedt T, Ingre M, Broman JE, Kecklund G. Disturbed sleep in shift workers, day workers, and insomniacs. Chronobiol Int 2008;25:333-48

Almutairi B, Langley C, Crawley E, Thai NJ. Using structural and functional MRI as a neuroimaging technique to investigate chronic fatigue syndrome/myalgic encephalomyelitis: a systematic review. BMJ Open 2020; 10: e031672.

Bagby RM, et al. The twenty-item Toronto Alexithymia Scale – II. Convergent, discriminant, and concurrent validity. J Psychosom Res 1994;38:33-40.

Bedree H, et al. The DePaul symptom questionnaire – 2: A validation study. Fatigue 2019; 7: 166-79

Berg SK, Nielsen SD, Nygaard Y, et al. Long COVID symptoms in SARS-CoV-2-positive adolescents and matched controls (LongCOVIDKidsDK): a national, cross-sectional study. Lancet Child Adolesc Health 2022; 6: 240-248.

Bestall JC, et al. Usefulness of the Medical Research Council (MRC) dyspnea scale as a measure of disability in patients with chronic obstructive pulmonary disease.Thorax 1999; 54: 581-6.

Blomberg J, Gottfries C-G, Elfaitouri A, Rizwan M, Rosen A. Infection elicited autoimmunity and myalgic encephalomyelitis/chronic fatigue syndrome: an explanatory model. Front Immunol 2018; 9: 229.

Brakedal B, et al. The NADPARK study: A randomized phase I trial of nicotinamide riboside supplementation in Parkinson's disease. Cell Metab 2022; 34: 396-407.

Buchwald DS, Rea TD, Katon WJ, Russo JE, Ashley RL. Acute infectious mononucleosis: characteristics of patients who report failure to recover. Am J Med 2000; 109: 531-7.

Chalder T, Berelowitz G, Pawlikowska T, et al. Development of a fatigue scale. J Psychosom Res 1993;37:147-53.

Chandrasekaran K, Anjaneyulu M, Choi J, Kumar P, Salimian M, Ho CY, et al. Role of mitochondria in diabetic peripheral neuropathy: Influencing the NAD(+)-dependent SIRT1-PGC-1alpha-TFAM pathway. Int Rev Neurobiol. 2019;145:177-209.

Chandrasekaran K, Choi J, Arvas MI, Salimian M, Singh S, Xu S, et al. Nicotinamide Mononucleotide Administration Prevents Experimental Diabetes-Induced Cognitive Impairment and Loss of Hippocampal Neurons. Int J Mol Sci. 2020;21(11).

Crook H, Raza S, Nowell J, Young M, Edison P. Long covid-mechanisms, risk factors, and management. BMJ. 2021;374:n1648.

EFSA Panel on Nutrition, Novel foods and Food allergens (NDA). Safety of nicotinamide riboside chloride as a novel food pursuant to Regulation (EU) 2015/2283 and bioavailability of nicotinamide from this source, in the context of Directive 2002/46/EC. EFSA Journal 2019; 17: e05775.

Gloster AT, et al. The empirical status of acceptance and commitment therapy: A review of meta-analyses. Journal of Contextual Behavioral Science 2020; 18: 181-192.

Grizzle R. Wechsler Intelligence Scale for Children, Fourth Edition. In: Goldstein S, Naglieri JA, eds. Encyclopedia of Child Behavior and Development. Springer US; 2011:1553-1555.

Guy W. ECDEU Assessment Manual for Psychopharmacology, Revised. Rockville: National Institute of Mental Health, 1976.

Hanevik K, Wensaas KA, Rortveit G, Eide GE, Morch K, Langeland N. Irritable bowel syndrome and chronic fatigue 6 years after giardia infection: a controlled prospective cohort study. Clin Infect Dis 2014; 59: 1394-400.

Havdal LB, et al. Neurological involvement in COVID-19 among non-hospitalized adolescents and young adults. Front Neurol 2022; *in press*.

Henningsen P, Gündel H, Kop WJ, Löwe B, Martin A, Rief, W, Rosmalen JGM, Schröder A, Fez-Cornelis C, van den Berg O. Persistent physical symptoms as perceptual dysregulation: A neuropsychobehavioural model and its clinical implications. Psychosom Med 2018; 80: 422-31.

Hickie I, Davenport T, Wakefield D, Vollmer-Conna U, Cameron B, Vernon SD, et al. Post-infective and chronic fatigue syndromes precipitated by viral and non-viral pathogens: prospective cohort study. BMJ. 2006;333(7568):575.

Hughes A, et al. An attention and interpretation bias for illness-specific information in chronic fatigue syndrome. Psychol Med 2017; 47: 853-65.

Hulme K, Hudson JL, Rojczyk P, Little P, Moss-Morris R. Biopsychosocial risk factors of persistent fatigue after acute infection: A systematic review to inform interventions. Journal of psychosomatic research. 2017;99:120-9.

Hurst H, Bolton J. Assessing the clinical significance of change scores recorded on subjective outcome measures. J Manipulative Physiol Ther 2004;27:26-3

Jacobsen EL, et al. Norwegian reference values for the Short-Form Health Survey 36: development over time. Qual Life Res 2018; 27: 1201-12.

Jacobsen HB, et al. Processes in acceptance and commitment therapy and the rehabilitation of chronic fatigue. Scandinavian journal of psychology 2017; 58(3): 211-220.

Jacobsen HB, Klungsøyr O, Landrø NI, Stiles TC, Roche BT. MINDflex training for cognitive flexibility in chronic pain: a randomized controlled, cross-over trial. Front Psychol 2020; 11: 604832.

Janse A, Work-Smeitink M, Bleijenberg G, Donders R, Knoop H. Efficacy of web-based cognitive behavioural therapy for chronic fatigue syndrome: randomized controlled trial. Br J Psychiatry 2018; 212: 112-8

Jason LA, Cotler J, Islam MF, Sunnquist M, Katz BZ. Risks for developking myalgic encephalomyelitis/chronic fatigue sydnrome in college students following infectious mononucleosis: a prospective cohort study. Clin Infect Dis 2021;73:e3740-6

Katz BZ, Reuter C, Lupovitch Y, et al. A validated scale for assessing the severity of acute infectious mononucleosis. J Pediatr 2019;209:130-3.

Keijmel SP, Delsing CE, Bleijenberg G, van der Meer JWM, Donders RT, Leclercq M, et al. Effectiveness of Long-term Doxycycline Treatment and Cognitive-Behavioral Therapy on Fatigue Severity in Patients with Q Fever Fatigue Syndrome (Qure Study): A Randomized Controlled Trial. Clin Infect Dis 2017;64(8):998-1005.

Klepstad P, et al. The Norwegian brief pain inventory questionnaire: translation and validation in cancer patients. J Pain Symptom Manage 2002;24:517-25.

Kristensen MS, Stabursvik J, O'Leary E, et al. Clinical synmptoms and markers of disease mechanisms in adolescent chronic fatigue following Epstein-Barr virus infection: an exploratory cross-sectional study. Brain Behav Immun 2019;80:551-63

Kuut TA, Müller F, Aldenkamp A, et al. A randomsied controlled trial testing the efficacy of Fit after COVID, a cognitive therapy targeting severe post-infectious fatiguel following COVID-19 (ReCOVer): study protocol. Trials 2021; 22: 867.

Kuut TA, et al. Efficacy of cognitive behavioural therapy targeting severe fatigue following coronavirus disease 2019: Results from a randomized controlled trial. Clin Infect Dis 2023; 77: 687-95.

Lee HJ, Yang SJ. Supplementation with Nicotinamide Riboside Reduces Brain Inflammation and Improves Cognitive Function in Diabetic Mice. Int J Mol Sci. 2019;20(17).

Lien K, Johansen B, Veierod MB, Haslestad AS, Bohn SK, Melsom MN, et al. Abnormal blood lactate accumulation during repeated exercise testing in myalgic encephalomyelitis/chronic fatigue syndrome. Physiol Rep. 2019;7(11):e14138.

Magnani ND, Marchini T, Calabro V, Alvarez S, Evelson P. Role of mitochondria in the redox signaling network and its outcomes in high impact inflammatory syndromes. Front Endocrinol 2020; 11: 568305

Marinescu AG, Chen J, Holmes HE, et al. Safety assessment of high-purity, synthetic Nicotinamid Riboside (NR-E) in a 90-day repeated dose oral toxicity study, with a 28-day recovery arm. Int J Toxicol 2020; 39: 307-20.

Martens CR, Denman BA, Mazzo MR, et al. Chronic nicotinamide riboside supplementation is well-tolerated and elevates NAD+ in healthy middle-aged and older adults. Nat Commun 2018; 9: 1286.

Maynard ME, Redell JB, Zhao J, Hood KN, Vita SM, Kobori N, et al. Sarm1 loss reduces axonal damage and improves cognitive outcome after repetitive mild closed head injury. Exp Neurol. 2020;327:113207.

Mehandru S, Merad M. Pathological sequelae of long-haul COVID. Nat Immunol 2022;23:194-202.

Mehmel M, Jovanovic N, Spitz U. Nicotinamide Riboside-The Current State of Research and Therapeutic Uses. Nutrients. 2020;12(6).

Montoya J, Holmes TH, Anderson KN, Maecker HT, Rosenberg-Hasson Y, Valencia IJ, et al. Cytokine signature associated with disease severity in chronic fatigue syndrome patients. Proc Natl Acad Sci USA 2017; 114: E7150-8.

Myhre PL, Prebensen C, Strand H, et al. Growth Differentiation Factor 15 Provides Prognostic Information Superior to Established Cardiovascular and Inflammatory Biomarkers in Unselected Patients Hospitalized With COVID-19. Circulation. 2020;142(22):2128-2137.

Naviaux RK, Naviaux JC, Li K, Bright AT, Alaynick WA, Wang L, et al. Metabolic features of chronic fatigue syndrome. Proceedings of the National Academy of Sciences of the United States of America. 2016;113(37):E5472-80.

Newman M. Chronic fatigue syndrome and long covid: moving beyond the controversy. BMJ 2021; 373: n1559

Nguyen CBTT, Alsøe L, Lindvall J, Sulheim D, Fagermoen E, Winger A, Kaarbø M, Nilsen HL, Wyller VB. Whole blood gene expression in adolescent chronic fatigue syndrome: An exploratory cross-sectional study suggesting altered B cell differentiation and survival. J Transl Med 2017; 15: 102

Nijhof SL, Bleijenberg G, Uiterwaal CS, Kimpen JL, van de Putte EM. Effectiveness of internet-based cognitive behavioural treatment for adolescents with chronic fatigue syndrome (FITNET): a randomised controlled trial. Lancet. 2012;379(9824):1412-8.

O'Reilly A, Roche B, Gavin A, Ruiz M, Ryan A, Campion G. A function acquisition speed test for equivalence relations (FASTER). Psychol Rec 2013; 63: 707–724.

Obrador E, Salvador R, Marchio P, Lopez-Blanch R, Jihad-Jebbar A, Rivera P, et al. Nicotinamide Riboside and Pterostilbene Cooperatively Delay Motor Neuron Failure in ALS SOD1(G93A) Mice. Mol Neurobiol 2021;58(4):1345-71.

Pallesen, S, et al. A Norwegian adaption of the Penn State Worry Questionnaire: factor structure, reliability, validity and norms. Scandinavian Journal of Psychology 2006, 47, 281–291

Pedersen M, Asprusten TT, Godang K, Leegaard TM, Osnes LT, Skovlund E, et al. Predictors of chronic fatigue in adolescents six months after acute Epstein-Barr virus infection: A prospective cohort study. Brain, behavior, and immunity. 2019;75:94-100.

Peluso MJ, Lu S, Tang AF, et al. Markers of immune activation and inflammation in individuals with postacute sequelae of severe acute respiratory syndrome coronavirus 2 infection. J Infect Dis 2021;224:1839-48

Perrot S, Lantéri-Minet M. Patients' Global Impression of Change in the management of peripheral neuropathic pain: Clinical relevance and correlations in daily practice. Eur J Pain. 2019;23(6):1117-28.

Reitan RM. Validity of the trail making test as an indicator of organic brain damage. Percept Mot Skills 1958; 8: 271-6.

Romano JP, Wolf M. Exact and approximate stepdown methods for multiple hypothesis testing. Journal of the American Statistical Association. 2005; 100 (469): 94–108.

Romppel M, et al. A short form of the general self-efficacy scale (GSE-6): Developoment, psychometric properties, and validity in an intercultural non-clinical sample and a sample of patients at risk for heart failure. Psychosoc Med 2013; 10: Doc01.

Russell D, et al. The revised UCLA loneliness scale: concurrent and discriminant validity evidence. Journal of Personality and Social Psychology 1980, 39(3), 472–480

Sandler CX, Wyller VBB, Moss-Morris R, et al. Long COVID and post-infective fatigue syndrome: a review. Open Forum Infect Dis 2021; 8: ofab440.

Selvakumar J, Havdal LB, Brodwall E, et al. Prevalence and predictors of post-COVID-19 condition among non-hospitalised adolescents and young adults: a controlled prospective observational study. *Submitted*

Shaw WS, Reme SE, Linton SJ, et al. 3rd place, PREMUS best paper competition: development of the return-to-work self efficacy (RTWSE-19) questionnaire – psychometric properties and predictive validity. Scand J Work Environ Health 2011; 37: 109-19.

Soriano JB, Murthy S, Marshall JC, et al. A clinical case definition of post-COVID-19 condition by a Delphi consensus. Lancet Infect Dis 2022; 22: e102-e107.

Stephenson T, Pereira SMP, Shafran R, et al. Physical and mental health 3 months after SARS-CoV-2 infection (long COVID) among adolescents in England (CLoCk): a national matched cohort study. Lancet Child Adolesc Health 2022; February 7.

Sweetman E, Kleffmann T, Edgar C, de Lange M, Vallings R, Tate W. A SWATH-MS analysis of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome peripheral blood mononuclear cell proteomes reveals mitochondrial dysfunction. Journal of translational medicine. 2020;18(1):365.

Task Force of the European Society of Cardiology the North American Society of Pacing Electrophysiology. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Circulation 1996; 93: 1043-1065

Trammell SA, Schmidt MS, Weidemann BJ, Redpath P, Jaksch F, Dellinger RW, et al. Nicotinamide riboside is uniquely and orally bioavailable in mice and humans. Nat Commun. 2016;7:12948.

Van den Bergh O, et al. Symptoms and the body: Taking the inferential leap. Neurosci Biobehav Rev 2017. https://doi:10.1016/j.neubiorev.2017.01.015.

Vono M, Huttner A, Lemeille S, et al. Robust innate responses to SARS-CoV-2 in children resolve faster than in adults without compromising adaptive immunity. Cell Rep 2021;37:109773.

Wagner D, et al.Psychometric properties of the CDC symptom inventory for assessment of chronic fatigue syndrome. Popul Health Metr 2005;3:8

Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992; 30: 473-83.

White PD, Goldsmith KA, Johnson AL, Potts L, Walwyn R, DeCesare JC, et al. Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. Lancet. 2011;377(9768):823-36.

Wortinger LA, Endestad T, Melinder A, Øie MG, Sulheim D, Fagermoen E, Wyller VB. Emotional conflict processing in adolescent chronic fatigue syndrome: a pilot study using fMRI study. J Clin Experiment Neuropsychol 2017; 39: 355-68.

Wortinger LA, Endestad T, Sevenius A, Melinder A, Øie MG, Wyller VB. Aberrant resting-state functional connectivity in adolescent chronic fatigue syndrome. PLoS One 2016; 11: e0159351.

Wortinger LA, Øie MG, Endestad T, Wyller VB. Altered right anterior insular connectivity and loss of associated functions in adolescent chronic fatigue syndrome. PLoS One 2017; 12: e0184325.

Wyller VB, Eriksen HR, Malterud K. Can sustained arousal explain the chronic fatigue syndrome? Behav Brain Funct 2009; 5: 10.

Wyrwich KW, Thierney WM, Babu AN, et al. A comparison of clinically important differences in health-related quality of life for patients with chronic lung disease, asthma, or heart disease. Health Serv Res 2005; 40: 577–92

Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054-62.

Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand. 1983;67(6):361-370.

