

# **Short-time behavioural intervention in post-Covid syndrome (SIPCOV): A pragmatic randomised controlled trial**

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## 1. Introduction

### Persistent post-infectious symptoms (PPIS) after Covid-19, often referred to as *post-Covid syndrome*, may be considered as an epidemic in its own right

The Covid-19 pandemic is an unprecedented threat to health and welfare globally. It is increasingly clear that Covid-19 may result in disabling long-term sequelae often referred to as *post-Covid syndrome* or “*Long Covid*”, being equally common among hospitalized and non-hospitalized patients.<sup>29,30</sup> Evidence suggests that most post-Covid syndrome cases fit within the label of *Persistent post-Infectious Symptoms (PPIS)*, encompassing chronic fatigue, pain and other symptoms, but with scarce findings on standard clinical examination.<sup>6,24,27,31</sup>

PPIS is a common sequel after several acute infections with a diverse array of pathogens, ranging from infectious mononucleosis (IM) caused by Epstein-Barr virus, to Q-fever caused by the bacterium *Coxiella burnetii*, and gastroenteritis caused by the parasite *Giardia lamblia*,<sup>10,12</sup> or as an adverse effect following vaccination.<sup>9</sup> PPIS is a pathogen-independent phenomenon that phenotypically appears as an abnormal perpetuation of the acute sickness response (ASR), which is a stereotyped collection of physiological, behavioral and psychological manifestations to an infectious event.<sup>1</sup> 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 chronic fatigue syndrome (CFS) (often also referred to as myalgic encephalomyelitis (ME)).<sup>5,10,12,23,28</sup> Although late recovery may occur chronic disability is common, with strong negative impact upon employment prospects and family networks, and with high societal costs.<sup>13</sup> Given the total number of Covid-19 cases globally (approximately 140 million by April 2021),<sup>37</sup> *post-Covid syndrome may be considered as an epidemic in its own right* (Fig. 1).

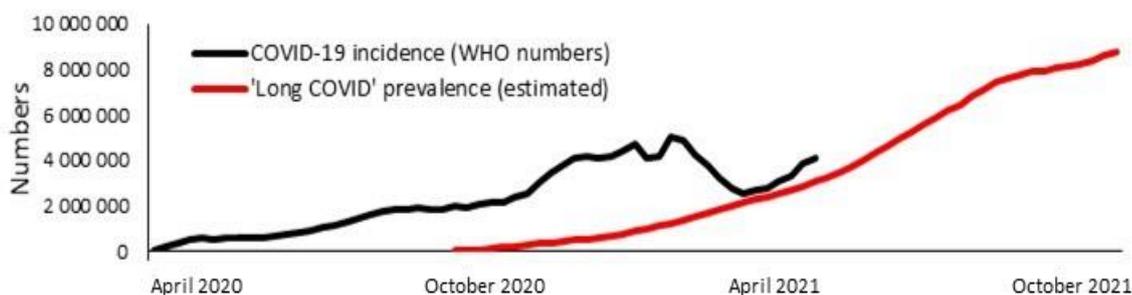


Figure 1. Covid-19 weekly incidence<sup>37</sup> and a conservative estimate of post-Covid syndrome prevalence (based on 10 % and 5 % case rate, respectively, 6 and 12 months after the acute infection).<sup>12</sup> Recent evidence suggests that the numbers may be even higher.<sup>35</sup>

### Functional brain alterations may be a central disease mechanism of post-Covid syndrome

The underlying disease mechanisms of post-Covid syndrome remain poorly understood. However, studies of PPIS following other infections have revealed a complex blend of genetic/epigenetic<sup>25</sup> and psychosocial<sup>7</sup> vulnerabilities, in concert with autonomic,<sup>40,41</sup> hormonal,<sup>22</sup> and immunological<sup>21</sup> alterations.

A prominent model of PPIS consider *functional brain alterations* to be a central pathophysiological element, possibly explaining other documented aberrations.<sup>11,26,42</sup> This assumption is supported by functional brain imaging studies,<sup>38,39</sup> clinical trial outcomes,<sup>17,32</sup> and fundamental neurobiological concepts,<sup>3,18</sup> and is also intimately related to more comprehensive theories on sustained activation of biological stress responses.<sup>33,42</sup>

### A rehabilitation program aiming to counteract functional brain alterations in post-Covid syndrome may be effective, but has not been systematically studied

If functional brain alteration is important in the pathogenesis of PPIS (including post-Covid syndrome), it is conceivable that mental and behavioural interventions may have a beneficial effect. Indeed, cognitive behavioral therapy (CBT) is of documented value in PPIS following other infections.<sup>15,17</sup> As for more extensive and multidisciplinary rehabilitation, little is known regarding

efficacy. To the best of our knowledge, no specific rehabilitation program has been systematically studied among post-Covid syndrome sufferers.

### **1.1 Needs description**

**The present study addresses urgent needs for the health care services as well as the scientific community**

- *Patient treatment.* This project directly addresses a strong need to develop effective treatment strategies for a large patient group suffering from post-Covid syndrome disability. Thus, it significantly improve health care services. Of note, the pragmatic approach ensures strong external validity and generalizability of the results.
- *Relevance and benefit to society.* This project addresses a highly challenging health problem nationally and internationally, which may have substantial negative impact upon employment issues, social security systems, family networks etc.
- *Scientific relevance.* The project addresses a prominent knowledge gap. Also, as the intervention builds upon a specific pathophysiological model, the study results will provide increased insight in disease mechanisms, and may eventually foster similar studies in PPIS following other infections.

## **2. Hypotheses, aims and objectives**

**We hypothesise that a short-time outpatient-based rehabilitation program will be beneficial as compared to usual care in post-Covid syndrome**

The aim of the present study is to assess the efficacy of a short-time outpatient-based rehabilitation program (the intervention) as compared to usual care (non-intervention) in post-Covid syndrome. The objectives are:

- a) To determine the effect on physical functioning immediately after completion of the intervention. We hypothesises better physical functioning in the intervention group than in the non-intervention group.
- b) To determine the effect on other post-Covid syndrome symptoms (such as fatigue, cognitive difficulties, dyspnoea, pain, sleeping problems) and quality of life (QoL) immediately after completion of the intervention. We hypothesise a beneficial effect of the intervention across all these domains.
- c) To determine adverse effects of the intervention. We hypothesis no differences in the frequency nor seriousness of adverse effects in the intervention group as compared to the non-intervention group.
- d) To determine the effect of the intervention on a long-term basis. We hypothesise that a beneficial effect of the intervention is sustained six months after its delivery.
- e) To explore predictors of intervention effect, including differential effects across subgroups. We hypothesise that time since diagnosis of acute Covid-19 and hospitalization is negatively associated with intervention effect. Furthermore, we hypothesise equal effect of the intervention in the subgroup fulfilling diagnostic criteria for chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME).
- f) To determine the cost-benefit and cost-effectiveness of the intervention. We hypothesise cost-benefit and cost-effectiveness to be better in the intervention as compared to the non-intervention group.

## **3. Project methodology**

### **3.1. Project arrangements, method selection and analyses**

#### **Design, recruitment, inclusion/exclusion**

The proposed study is a 2-arm pragmatic randomised controlled trial (RCT) in which 310 patients who suffer from post-Covid syndrome are randomised to either a short-time outpatient-based rehabilitation program (the intervention) or care as usual in a 1:1 ratio (Fig. 2). Assessments will take

place immediately before randomisation (T0), after intervention or care as usual (T1), and 12 months after T0 (T2). Of note, the timing of T1 will vary in the intervention group, due to the individualized therapy approach (cf. below); T1 in the non-intervention group will be matched accordingly. Patients will be recruited from General Practitioners (GP's) as well as social media and self-referral to the involved institutions, and included based upon the criteria listed in Table 1.

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**Table 1. Criteria for inclusion and exclusion**

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| <i>Inclusion criteria</i>  | <i>Exclusion criteria</i>  |
|--|--|
| Fulfills pragmatic diagnostic criteria of idiopathic post-Covid syndrome (Sandler 2021):   | Other chronic illnesses or demanding life situations that might explain persistent symptoms and disability |
| <ul style="list-style-type: none"> <li>Confirmed acute Covid-19 by a positive PCR or self-test for SARS-CoV-2.</li> <li>Persistent symptoms at least 3 months following acute Covid-19 without symptom-free interval.</li> <li>Functional disability to an extent that interrupts all or a majority of normal activities (such as work/school attendance, physical exercise, social activities, etc.)</li> </ul> | Sustained organ damage (lung, heart, brain) following acute, serious Covid-19                              |
| Age $\geq$ 16 years  | Bedridden  |
| Lives in one of the following Norwegian counties: Oslo, Viken, Innlandet, Vestfold og Telemark, Agder  | Insufficient command of Norwegian language   |
| Informed consent to participation  |  |

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### Randomisation and blinding

Patients eligible for the present study are randomized to either intervention or care as usual in a 1:1 probability by a computer-based routine for block randomization; block size will vary randomly between 4 and 6. Allocation will be stratified by severity of illness during the acute stage of Covid-19, operationalized as (1) no admission to hospital, (2) admission to hospital. Allocation concealment will be ensured using sequentially numbered, opaque, sealed envelopes. It is not possible to blind for treatment due to the nature of the intervention. However, during endpoint-evaluation, the responsible researchers will be blinded for group allocation.

### Intervention

The intervention consists of an individualized numbers of outpatient encounters (min. 2, max. 8) with medical doctors and physiotherapists at Kysthospitalet. The first meeting is always with a medical doctor. At least one of the encounters has to be face-to-face; the remaining encounters may be organized by video link for patients living far away. The encounters aim to foster a two-stage rehabilitation process:

- Stage 1: This first meeting is with a medical doctor. The intervention aims to eliminate serious pathology with a good anamnesis and clinical examination and to give patients' knowledge and understanding of their condition. The main focus is psychoeducation, based upon the theoretical framework of the Cognitive Activation Theory of Stress (CATS) and the Sustained Arousal-model of PPIS development. These models regard PPIS to be a product of functional brain alterations, which initially are an integrated part of the physiological acute sickness response,<sup>1</sup> but may become inappropriately sustained because of mechanisms such as unconscious expectancies/predictions, worrying tendencies and associative learning processes.<sup>18,33,34,42</sup> This sustainment causes persistent changes of autonomic nervous activity, hormonal activity and immunological responses, which in turn may explain patients' symptoms and occasional findings (such as high heart rate). Thus, the symptoms and functional disability of patients does not indicate a chronic infectious or autoimmune disorders, and efforts are made to counteract patients' worries.
- Stage 2: The individual follow-up with physiotherapists starts with a repetition of the information given in stage 1, based on patients understanding of their condition and experienced symptoms.

The aim is to counteract patients' worries and subsequent symptom monitoring, and to reassure them that desired activities and graded exercise are both beneficial and safe. Over time, the overall aim is to increase activity levels and normalize activity tolerance by 'uncoupling' an unconscious association between activity and neurobiological stress response activation. The use of both cognitive talking therapy and behavioral modifications (included graded exercise) are important intervention components, and all the health care workers providing the intervention are educated in cognitive behavioral therapy (CBT). Stage 2 is highly individualized based upon the patients' symptom burden and personal preferences. A total of 120 patients' with post-Covid syndrome have received the intervention so far. The number of encounters needed as well as the interval between encounters is highly individual. It is considered important that the number of encounters is based on patients' individual needs, as a fixed number may delay recovery because of unnecessary treatments and result in overuse of health services.

The intervention share some resemblance with Cognitive Behavioral Therapy (CBT) for PPIS.<sup>15,17</sup> The rationale behind the intervention is explained in detail to the patients' family doctors, ensuring compliant follow-up in primary health care. The cost (in monetary units) will be calculated for both stages of the intervention.

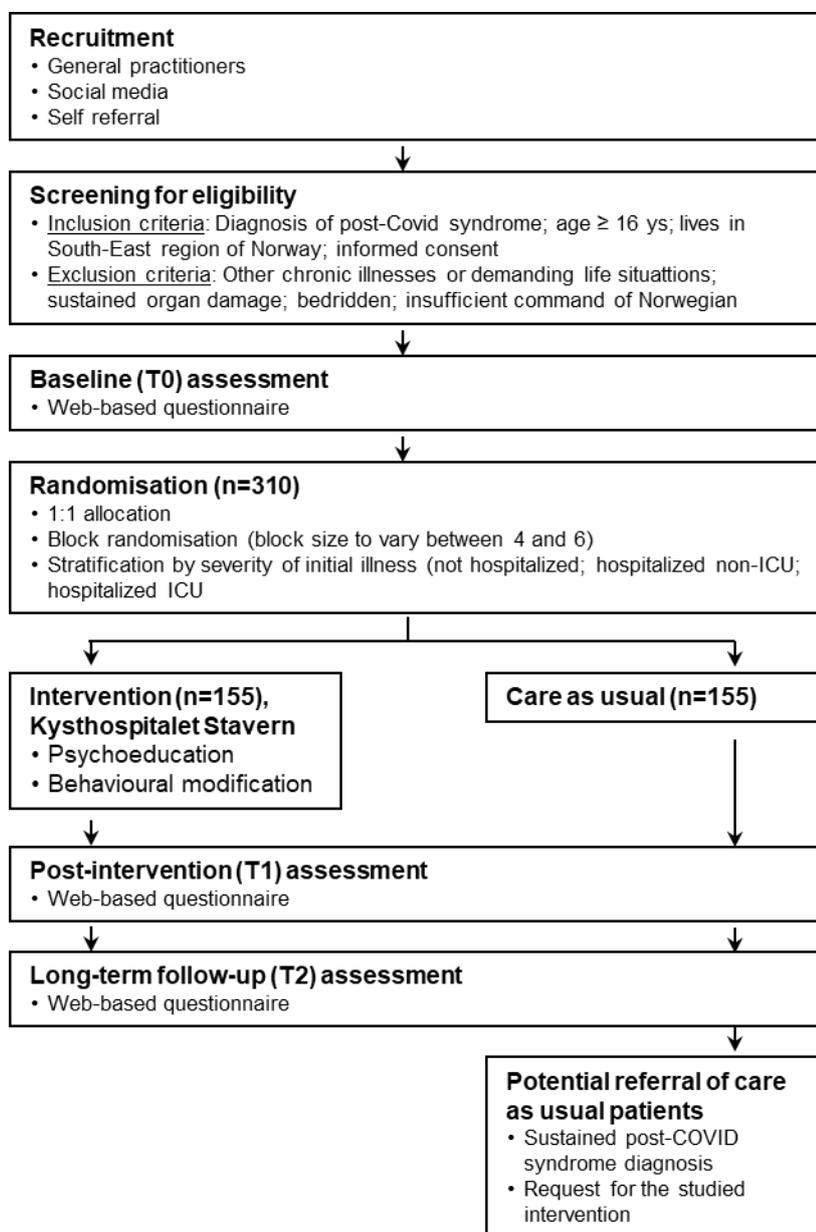


Figure 2. Overview of study design.

### **Effect monitoring**

Effect monitoring is primarily based on patient reported outcome measures (PROM), applying a web-based questionnaire composed of several validated instruments. The questionnaire will be distributed to the participants at T0, T1 and T2. It will chart clinical symptoms as well as background, psychological and social variables, and will be used for subgrouping according to different case definitions of CFS/ME. The most important inventories are (cf. appendix 1 for a complete overview):

- *The 36-Item Short-Form Survey (SF-36)* comprises a total of 36 items on subjective mental, social and physical health, which are assigned to 8 dimensions. Scale ranging from 0 (poor quality of life) to 100 (best).<sup>36,43</sup> The SF-36 instrument was recently recommended as a useful tool to assess rehabilitation needs in post-Covid syndrome sufferers, and is generally recognized as a valid and reliable measurement for intervention trials.<sup>20</sup>
- *The Chalder Fatigue Questionnaire (CFQ)* charts subjective experience of physical and mental fatigue. In this study, the CFQ total linear score (i.e. the sum across all 11 items, each item scored on a zero to three Likert scale) will be applied. Furthermore, fatigue caseness is defined as a CFQ total dichotomous score of 4 or higher (each item scored 0-0-1-1).
- *The Hospital Anxiety and Depression Scale (HADS)* is a validated questionnaire for charting symptoms of depression and anxiety. It consists of 14 items rated zero to three on Likert scales, allowing computation of sub-scores for depression and anxiety symptoms. In the present study, these sub-scores as well as total sum score will be applied.
- *Adverse effects:* A self-invented questionnaire will address possible adverse effect related to the intervention.

In addition, employment status, usage of social security-systems (i.e. short and long-term sick leave), and usage of health care services (i.e. the number of GP and specialist contacts, hospitalisations, medications, usage of rehabilitation services, etc.) will be charted through register linkage (cf. below) as well as questionnaires to the study participants.

### **Unexpected findings of other health problems**

The questionnaire may reveal unexpected findings of other health problems, such as serious depressive symptoms, substance abuse, etc. We will implement Standard Operating Procedures to ensure that such health problems are identified and that appropriate measures are instituted, such as immediate notifying of the patient's general practitioner/family doctor.

### **Linkage with health registries**

In order to explore predictors of intervention effects (point 2.e), above), linkage with existing health registries will be considered, such as 'Norsk pasientregister', 'Mor-Barn-studien', 'Vaksine-registeret Sysvak', 'Reseptregisteret', 'Intensivregisteret' og 'Pandemiregisteret'. Also, previously recorded medical information from hospital and family doctor records will be exploited for the same purpose. A primary prediction analyses will use the following variables, based upon previous evidence from other studies of PPIS:<sup>10,12,23</sup>

- *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).

Other possible predicting factors, such as genetic traits, will not be explored under the current protocol.

### **Population and sample size calculation**

As of July 2021, a total of approximately 103,000 Covid-19 cases have been reported from the geographical areas (five Norwegian counties) from which patients are recruited to the present study. Assuming a 5 % case rate of post-Covid syndrome (cf. Figure 1) of whom 1/5 is eligible and willing to participate, a total of 1,300 patients could potentially be included.

The SF-36 subscale Physical Functioning (SF-36-PFS) will serve as the primary endpoint in the present study. A difference of 10 points is considered clinically significant.<sup>43</sup> Similarly, in a study of CFS/ME which shares similarities with post-Covid syndrome, the minimally clinically important difference of SF-36-PFS was reported to be 10.<sup>4</sup> The scatter of SF-36-PFS scores among post-Covid syndrome sufferers are unknown, but two large Norwegian surveys reported a Standard Deviation (SD) of 20 across all age groups.<sup>8,14</sup> If SD is set to be 25 in the population under study, and assuming 20 % drop-out rate, the study should aim to *include a total of 310 participants*. This yields a power of 90 % ( $\alpha=0.05$ ) to detect a small to medium effect size.

### **Statistical analyses**

The ‘full analysis set’ (all randomized participants) will be used for intention-to-treat analyses of efficacy. Missing values will be imputed applying multiple imputation techniques. The ‘per protocol analysis set’ is defined as all patients in the ‘full analysis set’ that completed the treatment period without any of the following protocol deviations: Interruption of therapy; Lost to follow-up; 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 post-Covid syndrome during the study period.

Variables will be reported with parametric or non-parametric descriptive statistics, eventually frequency tabulation, as appropriate. General linear models (ANCOVA) will be used for analyses of treatment effect; the baseline values of each efficacy endpoint will be included as covariates. For each statistical analysis, the net intervention effect (the mean change in the intervention group minus the mean change in the usual care group) will be calculated from the parameters of the fitted general linear model and reported with 95 % confidence interval. All statistical tests will be carried out two-sided. A p-value  $\leq 0.05$  is considered statistically significant. Safety data will be summarized descriptively through appropriate data tabulations and descriptive statistics. No interim analysis will be carried out. A statistical analysis plan will be developed.

## **3.2. Participants, organization and collaborations**

### **Principal investigator and research group**

The present project is hosted by the PAEDIA research group at Akershus University Hospital (Ahus), which has extensive experience in translational as well as clinical research on post-Covid syndrome and other PPIS, and a strong track record of result dissemination and implementation. The group has established a well-working infrastructure for patient flow and data acquisition, and a large collaborative network with national and international experts on various methodological aspects.

The PAEDIA research group is headed by Prof. Vegard Wyller, who is also the PI of the present project, and Chair of the COFFI collaborative (cf. below). Prof. Wyller is the most published and cited PPIS researcher in Norway. Other members of PAEDIA include two postdoctoral fellows, six PhD fellows, two master students, and three clinical consultants. The local research support staff consists of one laboratory engineer, two research nurses and two research secretaries. An internal learning program for PhD fellows has been established, encompassing a) one-to-one supervision sessions; b) regular in-group discussions; c) invited lecturers; d) oral presentation training and practice; e) seminars on selected topics (statistics, ethics). A total of five PhD fellows have successfully graduated over the past four years.

### **Steering Committee, collaborating partners and networks**

A Steering Committee consisting of Prof. Vegard Wyller (Head, University of Oslo); Prof. Guri Rørtveit (University of Bergen); Prof. Signe Flottorp (Norwegian Institute of Public Health); Profs.

Silje Endresen Reme and Henrik Børsting Jacobsen (Dept. of Psychology, University of Oslo) and Drs. Annika Jordbru, Andreas Horsdal, Gro Aasland, and Tom Farnen Nerli (Kysthospitalet Stavern) will oversee all stages of the project. The main collaborating partner is Kysthospitalet Stavern, where the intervention under study has already been established for other patient groups. In addition, the project will be intimately linked to an international consortium of researchers on post-infectious complications (Collaborative of Fatigue Following Infection, COFFI), encompassing highly reputed research groups from five countries (US, UK, Australia, The Netherlands and Norway), and with Prof. Wyller as the chair of the consortium ([www.coffi-collaborative.com](http://www.coffi-collaborative.com)). A total of 15 post-infectious cohort studies (including 3 COVID-19 cohorts) have joined the collaborative so far, summing up to a total of about 6000 patients.

Important measures to ensure integration between all collaborators encompass a) Regular meetings (video link) to discuss scientific and strategic challenges; b) Hosting of seminars and workshops; and c) Face-to-face meetings.

### **The work tasks of a potential PhD fellow**

A PhD fellow in the present project will be included in the team of researchers and managers responsible for participant investigations and data gathering. Thus, he will get first-hand knowledge of all parts of the investigational program described above. Furthermore, in close collaboration with his supervisors and the rest of the research team, he is expected to carry out data analyses, interpret the results and draft a total of four scientific papers.

### **Infrastructure**

As the intervention under study has already been developed, the necessary research infrastructure is primarily related to a) administrative and coordinating tasks regarding patient flow, allocation, data management, etc; and b) patient recruitment from GPs. For the former, the project will exploit already established routines and personnel within the PAEDIA research group. For the latter, the project will benefit from using ‘Praksisnett’ – a collaborative network of GPs providing established routines and payment procedures for the recruitment of patients in clinical trials.

### **3.3. Plan for activities, visibility and dissemination**

**A PhD-dissertation can be completed within three years from project onset; the entire project period is estimated at a maximum of 10 years**

A PhD-fellow focusing on research questions a) – c) will be able to complete a dissertation within approximately three years from project onset. However, extensive analyses related to research questions d) – f) are estimated to take longer time, and is also dependent on external funding of additional researchers (PhD and/or postdoctoral positions). Thus, the total project period is estimated at a maximum of 10 years.

### **Results will be disseminated widely; scientific dissemination is prioritized**

Given the seriousness of post-Covid syndrome and the urgent need for scientific knowledge, rapid and continuous dissemination of project results will receive high attention. The target for dissemination is not restricted to the scientific community, but includes a wide range of health-care workers, politicians, policy makers, health care administrators, and the general public.

Several means of dissemination will be exploited, including scientific papers; popular science newspaper articles; giving interviews; meetings with politicians, public health providers and other stakeholders; social media. Dissemination to researchers and the scientific community includes publications in international, peer-reviewed, open access medical journals. The main results will be offered to journals of high impact. Negative findings will also be reported.

### **3.4. Plan for implementation**

Based upon the research results, the Steering Committee will contribute actively to the establishment for clinical guidelines for post-Covid syndrome, in strong collaboration with health administrators,

patients' organizations, and other stakeholders. A Working Group of should be established with the specific task of scrutinizing existing guidelines, revising them, and disseminating the revised guidelines.

## 4. User involvement

### **An advisory board of two user representatives is the most important user involvement**

For the present project, an advisory board of users will formally established, consisting of a) One representative from the Consumer Advisory Committee at Ahus; and b) One representative from the organization Recovery Norway, consisting of individuals having recovered from PPIS and similar conditions. The advisory board will meet quarterly with the PI; important themes for discussions are results' interpretation and practical impact, ethical issues, considerations regarding further research, and dissemination/implementation strategies.

## 5. Ethical considerations

### **Ethics**

Participation in the project is based upon informed consent, and thorough information will be provided orally as well as in writing to the participants. All data will be treated and stored without personal identifying information, and in accordance with national directives. Generally, investigational methods are neither harmful nor painful. Approval will be sought from the Regional Committees for Medical and Health Research Ethics. If the intervention is found to be beneficial, participants in the non-intervention group who suffer from a sustained post-Covid syndrome diagnosis will be offered a referral to Kysthospitalet for treatment after completion of the study (Fig. 2).

### **Gender perspectives**

Severe COVID-19 appears to be more common in males than in females. post-infectious complications, however, such as PPIS, are more common among females than males, the ratio being about 3:1. Thus, such complications strongly impact on women's health, but have traditionally received low attention. In this project, possible gender differences will be scrutinized in the analyses.

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## Appendix

### Overview of inventories

| Category  | Inventory  | Characteristics  | References   |
|---|--|--|--|
| <b>BACKGROUND/DEMOGRAPHICS</b>                          |  |  |  |
| Household, socioeconomic level                          |  | Household members; parents work/education; chronic disease in family   |  |
| Smoking, alcohol, drugs                                 |  | Alcoholic beverages, illicit drugs, smoking; 5-point Likert scale (never to each day)  |  |
| <b>SYMPTOMS AND FUNCTIONS</b>                           |  |  |  |
| Fatigue   | Chalder Fatigue Scale                            | 11 items; 4-point Likert scale; each item scored 0-3; total sum score range 0 to 33.   | Chalder T, Berelowitz G, Pawlikowska T, et al. J Psychosom Res 1993;37:147-53. |
| Chronic Fatigue Syndrome diagnosis and related symptoms | CDC symptom inventory for CFS                    | 28 items addressing frequency of symptoms on 5-point Likert scale; each item scored 1-5 (never to each day/always).  | Wagner D, et al. Popul Health Metr 2005;3:8                                    |
| post-exertional malaise (PEM)                           | PEM items from DePaul Symptom Questionnaire      | 5 items addressing frequency of symptoms on 5 point Likert scale; each item scored 0-4 (never to each day/always). Average, then multiply with 25 to get a 100 point scoring scale.          | Bedree H, et al. Fatigue 2019; 7: 166-79                                       |
| Sleep disturbances                                      | Karolinska sleep questionnaire (KSQ)             | 12 items addressing frequency of sleep related problems; 6-point Likert scale scored 1 – 6; lower score means <i>more</i> symptoms. Indexes for insomnia, awakening problems, and sleepiness | Akerstedt T, Ingre M, Broman JE, Kecklund G. Chronobiol Int 2008;25:333-48     |
| Pain  | Brief Pain Inventory (BPI)                       | 4 items; 10 point Likert scale score 1 - 10 (no pain to worst pain possible)   | Klepstad P, et al. J Pain Symptom Manage 2002;24:517-25.                       |
| Dyspnoea  | Medical Research Council dyspnoea scale          | 1 item; 5 options (from “breathless during strenuous exercise” to “too breathless to leave the house”).  | Bestall JC, et al. Thorax 1999; 54: 581-6.                                     |
| Depression/Anxiety symptoms                             | Hospital Anxiety and Depression Symptoms (HADS)  | 14 items; 4 point Likert scale scored 0 – 3 (8 items with reversed scoring). Indexes for anxiety symptoms and depressive symptoms, also total sum score range 0 to 42.                       | Zigmond AS, Snaith RP. Acta Psychiatr Scand 1983;67:361-70.                    |
| Negative affect   | Positive and Negative Affect Schedule (PANAS-SF) | 5 items addressing negative affects (ashamed, anxious, nervous, hostile, upset); 5-point Likert scale scored 1-5. Total sum score range 5-25   | Thompson ER. J of Cross-Cultural Psychology 2016; 38: 227-42.                  |

|                                     |   |   |  |
|-------------------------------------|---|---|--|
| Illness perception                  | Brief Illness Perception Questionnaire        | 8 items; 10 point Likert scale, scoring 1 – 10.   | Broadbent E, et al. J Psychosom Res 2006;60:631-7  |
| Work related self-efficacy          | Return-to-work self-efficacy scale (RTWSE-11) | 11 items; 6-point Likert scale, scored 1-6 (reverse scoring item 2 and 6). Total sum score range 11 to 66 (higher scores means high work-related self- efficacy).   | Shaw WS, Reme SE, Linton SJ, et al. Scand J Work Environ Health 2011; 37: 109-19.                              |
| Quality of life                     | 36-Item Short Form Survey (SF-36).            | 36 items, scored on Likert scales and recoded to achieve 100 point scales (higher score means better health); average score 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 JE, Sherbourne CD. Med Care 1992; 30: 473-83.   |
| Health related quality of life      | EuroQoL 5L (EQ-5D-5L)                         | 5 items; 5 point Likert scale, scored 1 to 5. A summary index with a maximum score of 1 (best health status) can be derived from these five dimensions by conversion with a table of scores. In addition: 200 mm VAS scale for assessment on global health status. A score of 100 indicates best health status.                                   | Herdman M, Gudex C, Lloyd A, Janssen MF, Kind P, Parkin D, et al. Quality of Life Research. 2011; 20: 1727-36. |
| Interoception                       | Body Vigilance Scale (BVS)                    | 4 items; 11 point Likert scales 0 – 10. Score on item 3 should be divided by 10. Scores on item 4: average among 15 sensations. Total sum score range 0 to 40.  | Schmidt NB, et al. J Consult Clin Psychol 1997; 65: 214-20.  |
| Miscellaneous/hypotheses generating |   | a) 1 item addressing avoidance behavior: “To what degree do you avoid everything that may worsen your symptoms”?<br>b) 1 item addressing school/work absenteeism.   |  |
| <b>CONSTITUTIONAL</b>               |   |   |  |
| Neuroticism                         | NEO-FFI-30                                    | 6 items making up the neuroticism axis; 5-point Likert scale scored 0 – 4. Total sum score range 0 – 24.  | Körner A, et al. Psychother Psychosom Med Psych. 2008; 58: 238-245   |
| Worrying tendencies                 | Penn State Worry Questionnaire (PSWQ)         | 16 items; 5-point Likert scale scored 1 – 5 (reversed scoring of item1,3,8,10,11). Total sum score range 16 to 80   | Pallesen, S, et al. Scandinavian Journal of Psychology 2006, 47, 281–291                                       |
| Emotional awareness                 | Toronto Alexithymia Scale (TAS-20)            | 7 items making up the index of Difficult identifying feelings. 5-point Likert scale scored 1-5, total sum score range 7 to 49.  | Bagby RM, et al.. J Psychosom Res 1994;38:33-40.   |

|               |   |  |   |
|---------------|---|--|---|
| Loneliness    | UCLA loneliness scale                   | 20 items; 4-point Likert scale scored 1 – 4 (reverse scoring of item 1,5,6,9,10,15,16,19,20). Total sum score from 20 to 80. | Russell, D., et al. Journal of Personality and Social Psychology 1980, 39(3), 472–480 |
| Self-efficacy | General Self-Efficacy Scale, short form | 6 items; 4-point Likert scale scored 1 – 4. Total sum score from 6 to 24.  | Romppel M, et al. Psychosoc Med 2013; 10: Doc01.                                      |