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COMPARING EFFECTIVENESS OF TELEREHABILITATION VERSUS INSTITUTION-BASED ADAPTED PHYSICAL ACTIVITY AND THERAPEUTIC EXERCISE PROGRAM ON FATIGUE, PHYSICAL FUNCTIONING, AND EPISODIC DISABILITY FOR CHRONIC FATIGUE SYNDROME IN LONG COVID-19: PROTOCOL FOR A RANDOMIZED CONTROL TRIAL

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Abstract

Background: Adaptive pacing improved fatigue and physical functioning in non-COVID patients with chronic fatigue syndrome. Safe long COVID-19 rehabilitation recommends patient-centred, customised, and safer approaches. There is a research gap on the effectiveness of telerehabilitation versus institution-based Adapted Physical Activity and Therapeutic Exercise Program (APTE) on long COVID-19 patients with chronic fatigue syndrome (CFS).

Methods: We planned a three-arm prospective randomised control trial on 124 long COVID-19 cases with chronic fatigue syndrome to determine the effectiveness of APTE in institution-based care versus the telerehabilitation approach compared to active control. Participants will be

recruited from a population based on the inception cohort and assigned to three groups with the concealed location process with an enrollment ratio of 1:1:1. Between May and July 2023, Participants will be assessed by blinded assessors and during the baseline evolution posttest. After two months and follow-up after six months post-intervention, the Chalder Fatigue Scale will measure primary outcome fatigue. SF-36 and the DALYs will measure the secondary outcome of physical functioning and episodic disability.

Discussion: Previous studies suggest that adapted physical activity effectively manages fatigue symptoms in CFS cases in 12 sessions. In Long COVID-19, chronic fatigue syndrome is a prominent symptom that causes episodic disability and impacts a person's physical functioning, activities, and participation. To manage patients with long COVID-19, Telerehabilitation is a widely accepted process. This study will fill the research gap to determine the appropriate approach to APTE compared to active control. The future direction of the study will guide the determination of interventions in long COVID-19 rehabilitation.

Trial registration: The trial is registered prospectively from a primary Clinical Trial Registry side of WHO CTRI/2023/03/050808 [Registered on: 17/03/2023]

Keywords: Long COVID, Chronic Fatigue Syndrome, Adapted physical activity and Therapeutic exercise program, Telerehabilitation

Introduction:

Long COVID-19 is a group of persistent symptoms after 12 weeks of the initial diagnosis of SARS-COV-2, ongoing for at least 2 months, and cannot be explained by any other clinical diagnosis [1]. The standard diagnosis criteria by the World Health Organization defines the specificity and symptoms responses that are categorised as long COVID. The integrated classification of long COVID [2] states any persistent symptoms after 4 weeks as post-acute COVID-19 after 12 weeks as post-COVID-19 symptoms. The Global prevalence of long COVID is 43 % among the persistent symptoms of SARs CoV-2, and the Asian Prevalence was found to be 51%, slightly higher than the global prevalence [3]. Bangladesh had a large-scale household inception cohort study that found long COVID-19 symptoms with a prevalence of 16.1% [4]. Another study finds long COVID symptoms from the delta variant found to be slightly higher for Bangladeshi people at 24% [5]. The long COVID symptoms ranged from 7% to 43% [2-4]. Among all the symptoms, fatigue is prominent in Global [3], Asian, Southeast Asian, and Bangladeshi studies [4,5]. Nearly one-third of the Global population with long COVID suffers from fatigue and painful symptoms [3-5].

Chronic Fatigue Symptoms (CFS), also called myalgic encephalomyelitis, is a persistent multisystem disease openly characterised as fatigue associated with painful conditions that impact cognitive, immune, and autonomous nervous system involvement [6,7]. Several pieces of evidence suggest that CFS has a disease severity that significantly reduces activity levels progressively, and it is a persistent condition that has poor progression [8]. CFS is a highly prevalent condition among long COVID cases. The global prevalence of CFS is nearly 45.2% [9]. CFS also evidently affects personal and social life and hurts a person’s physical and psychological status [9]. Evidence

suggests CFS has a clinical presentation of fatigue and pain associated with decreased physical functioning, depression, and reduced quality of life [10]. Another study suggests that CFS has additional symptoms such as headache, photophobia, painful symptoms, problems in short-term memory, reduced ability to multitask functions, brain fog, and difficulty in working with digital media like using the computer or watching television [11].

The medical management of CFS is mostly symptomatic, depending on the symptoms of brain fog, pain, fatigue, sleep disruption, muscle disorder, and postural tachycardia syndrome (POTS) [12,13]. A wide variety of medications used for treating CFS as amphetamine, methylphenidate, naltrexone, duloxetine, gabapentin, intravenous solution, Dexedrine, fludrocortisone, trazodone, clonazepam, tricyclic antidepressants, ketotifen, montelukast, diphenhydramine, and metoprolol [12,13]. Physiotherapy is one of the non-pharmacological management of CFS. Physiotherapy management of CFS includes exercise therapy, cognitive behavioural therapy, adaptive pacing, aerobic exercise, and different indicative approaches [14,15]. The management is aimed at improving the cardiorespiratory status, managing painful symptoms, improving adaptive coping for fatigue, energy consumption, and restoration, ensuring adequate use of energy and appropriate pacing, improving physical and psychological well-being, and improving sleep for CFS patients [14]. There are many components of exercise therapy for CFS; adapted physical activity and Therapeutic exercise programs are more effective is more effective than passive control, cognitive behavioural therapy (CBT), adaptive pacing, or oral antidepressant to improve overall symptoms, physical functioning, depression, and sleep for non-COVID patients [14,16]. For long COVID-graded exercise, therapy is not recommended to use according to NICE Guidelines [17,18]

Several studies examined the effect of exercise therapy on patients with chronic fatigue syndrome in non-COVID patients. Studies find exercise therapy may reduce fatigue symptoms in CFS cases, and the effect persists from 12 to 26 weeks of intervention [14,21]. But, after 52 to 70 weeks, the effect of treatment becomes uncertain [19,20]. Moreover, the improvement of physical functioning due to exercise therapy had a moderate improvement in CFS, even after 12 to 24 weeks of the interventions. In this case, the outcome also becomes uncertain after 52 to 70 weeks [15,16,19-21]. In summary, the effect of exercise therapy on chronic fatigue syndrome for non-COVID patients finds positive outcomes in fatigue and physical functioning that persist nearly 2 years after the intervention, and after 2 years, the results become uncertain. Evidence supports the Adapted Physical Activity and Therapeutic Exercise Program (APTE) as more effective than patient education or active control for non-COVID cases [22]. There is no study eliciting the outcome of APTE on CFS in long COVID cases. We hypothesised that APTE prescribed in an institution-based approach and telerehabilitation might effectively reduce fatigue and improve physical functioning for chronic fatigue syndrome (CFS) cases with long COVID. The study aims to determine the effectiveness of Adapted physical activity and Therapeutic exercise program (APTE) through Institution-based care (APTE-I) versus Tele-rehabilitation (APTE-T) compared to active control (AC) on fatigue, physical functioning, and episodic disability for long COVID-19 patients with chronic fatigue syndrome. The Objectives are to (1) determine the baseline

compatibility among APTE-I, APTE-T, and AC, (2) elicit the among the group, among observation outcomes on fatigue, physical function, and episodic disability for long COVID patients having CFS, (3) present the post-hoc within-group, within observation outcomes.

Methodology

Study design

According to WHO working group criteria, the proposed study will be a three-arm randomised control trial (RCT) of long COVID patients having CFS [1]. One hundred twenty-four long COVID cases having chronic fatigue syndrome (CFS) will be randomised into three groups: adapted physical activity and therapeutic exercise provided in institution-based care (APTE-I), adapted physical activity and therapeutic exercise provided by Telerehabilitation (APTE-T), and active control (AC) group. Participants will be enrolled from a population-based inception cohort[5] with defined eligibility criteria.

Sample size calculation

Sample size calculation has been performed through the software ClinCalc [23], estimating the key outcome as the score of the Chalder fatigue scale (CFS) [24]. Sample size has been calculated as the anticipated minimal clinically important differences (MCID) of CFS were estimated as 9.14±2.73 (0-33 Scale) with a baseline of 15% minimal clinical improvement, enrolment ratio 1:1:1, 80% power, and with the alpha value 0.05, the total sample stands as of 124.

Study duration

Participants will be recruited between May and July 2023. Baseline compatibility, intervention, and outcome evaluation will be conducted from July 2023 onwards. The blinded assessor will assess participants during the baseline evaluation during the baseline, post-test, and follow-up evaluation. The post-treatment assessment will be performed after two months of initial recruitment, and follow-up will be undertaken after six months of post-intervention assessment.

Study population and samples

The long COVID cases with CFS will be screened from the inception cohort [5] of post-COVID conditions and will be determined as the population. Sample criteria from the population to the trial will be performed through stratified random sampling. Respondent is eligible to be enrolled in the study with (1) Age 18 years or above, (2) diagnosis of long COVID according to WHO working group criteria [1], (3) diagnosis of chronic fatigue syndrome(CFS) according to the 2006 Canadian consensus criteria [25], (4) respondents meeting with persistent or relapsing chronic fatigue and post-exertion malaise or fatigue criteria of the Canadian consensus guideline, and (5) willing to participate with the trail with the consent of adherence to the intervention. Exclusion criteria will be (1) any preexisting clinical condition with fatigue as cardiovascular or neurological disability, (2) Any preexisting condition of the respiratory system (COPD) where exercise therapy needs special attention, (3) any red flags or signs that were explained in safe long COVID

rehabilitation guideline [26], (4) patients who were unwilling to continue the treatment, (5) patient who is drop out within the 1st week of inclusion.

Study procedure

From eight (08) strata, two divisions will be randomly selected, and from those two divisions, respondents will be recruited for institution-based interventions and the Tele Rehabilitation group. From both divisions, the respondents will be categorised as active control and assigned to the standard control group. The concealed allocation process will continue until the estimated number of samples reaches each group. So, a blocked randomisation process will be employed if any group fulfils the number of participants earlier than any other group to ensure representative sampling. Fifty participants will be enrolled for each group, and we will follow the standard criteria for maintaining the protocols as standard protocol items: Interventional Trails 2013 (SPIRIT guidelines) to ensure the rigour of designing the trial protocol (Figure 1).

Time point	**Enrolment**	**Allocation**	**Post-allocation**		
	$-T_1$	T_0	T_1	T_2	T_3
Enrolment					
Eligibility screen	X				
Informed consent		X			
Demographic assessment			X		
Group allocation		X			
Intervention					
APTE-I				X	
APTE-T				X	
AC				X	
Assessment					
CFS			◆—	—◆	
SF-36			◆—	—◆	
DALY			◆—	—◆	

APTE-I= Institution base Adapted physical activity and Therapeutic exercise program; APTE-T= Telerehabilitation base Adapted physical activity and Therapeutic exercise program; AC= Active control; CFS= Chalder Fatigue Scale; SF-36= Short Form 36 Health Survey Questionnaire; DALY= Disability-adjusted life years; T_0=Group allocation; T_1=Baseline before the intervention; T_2=Measurement taken in 2-months after T_1; T_3= Measurement taken after 6-months of T_2.

Figure 1: SPIRIT protocol for the study

Study settings

The CFS patients will be recruited and treated in three specialised Physiotherapy and Rehabilitation setups. In Dhaka division, BRB Hospital Limited Dhaka, and specialised physiotherapy hospital will be the study set-up for APTE-I. The Department of Physiotherapy and

Rehabilitation at Jashore University of Science and Technology will be the APTE-T center. The AC group will be from any of the centres. We expect similar criteria of patients from different parts of Bangladesh as the respondents were recruited from a single household screening procedure of a population-based inspection cohort in Bangladesh [5]. As APTE-I and APTE-T are being provided in different set-ups and respondents of AC will be residing at homes in different parts of the country, it will ensure that there is no cross-contamination of data.

Interventions

Both the APTE-I and APTE-T participants will receive treatment according to the e-Delphi consensus from a Bangladeshi research group [27], Malaysian Ministry of Health guidelines for managing Post COVID-19 conditions [28], Cochrane review [10], previous RCTs [22] and a systematic review from a research group in Norway [29]. The adapted physical activity and therapeutic exercise (APTE) will be composed of breathing exercises and breathing control exercises [29], exercises to improve flexibility and motor control [10], exercises to improve aerobic capacity [10,28,29], and interventions to maintain a healthy lifestyle [27,28]. All the interventions will be provided according to the guidelines recommended by Safe Long COVID rehabilitation [26]. According to the guideline, the steps of prescribing the interventions will be firstly screening of the red flag sign or deteriorating sign, then personalised intervention design for every individual by a registered physiotherapist. The execution of the interventions will be with a patient-centred care approach. Moreover, psychological support will be provided, and the team will report any adverse effects, such as post-exertional dyspnea or any other symptoms. There will be no added treatment to ensure the true effect of the interventions.

Institute-based adapted physical activity and therapeutic exercise (APTE-I)

For an institution-based Adapted Physical Activity and Therapeutic Exercise Program (APTE-I), the interventions will be provided under the supervision of a consultant physiotherapist. They will be performed by a physiotherapist with a minimum graduate degree and practising in Bangladesh. The interventions will be provided at the centre for a 45-minute session by one with one approach to the therapist. The treatment will be provided with home exercise interventions and continuous communication will be maintained according to the person-to-person approach.

Adapted physical activity and therapeutic exercise through telerehabilitation (APTE-T)

Registered physiotherapists will also provide adapted physical activity and Therapeutic exercise programs through telerehabilitation (APTE-T) under the supervision of a consultant physiotherapist through digital media such as Zoom, WhatsApp, or Facebook Messenger as per the patient's convenience. It will also be a 45-minute session one by one approach, by the therapist and the patients performing at home. The therapist will explain and demonstrate the procedure through the camera, and patients will perform, and the therapist will monitor and give feedback through the camera. The intervention procedure will be maintained from person to person. Communication and reporting of any adverse intervention will also be documented after the everyday session.

Active Control (AC)

Participants of AC will also receive the interventions as the other two groups with a booklet at home; they might get support for some pharmacological interventions from the physicians or proceed with any alternative care as per their choice. But if they receive any intervention or no interventions, a physiotherapist will record everything, who will continuously monitor the control group.

Treatment progression

The participants' Adapted physical activity and Therapeutic exercise program will perform the treatment twice a week for eight weeks. In case of any adverse event, additional sessions will be employed. The overall treatment will be provided for two months; after two months, treatment will stop, and after six months, follow-up will be taken.

Outcome Measures

Fatigue is the primary outcome of the study. We will use the Chalder fatigue scale (CFS) [24,30] to measure fatigue. CFS has 11 questionnaire items, and each item's responses are 4-point Likert scale [30]. The total score is calculated between 0 and 33; more scores indicate the severity of fatigue [30]. CFS has good core reliability and an agreeable internal consistency (omega coefficient 0.78 -0.96) [31]. The secondary outcome will be physical functioning and determining episodic disability. The physical functioning will be measured by SF-36 [32-34], and episodic disability will be measured by calculating Disability-adjusted life years (DALYs). SF-36 is a self-reported tool for measuring health status; it has 8 sub-domains. One sub-domain of SF-36 is physical functioning, having ten items of the questions [35]. Scores on this scale range from 0-100 in the physical functioning section of the SF-36 questionnaire [36,37]. In this scale, higher scores reflect performing all physical activities, including heavy activities, and a lower score indicates limiting a lot of performance in all physical activities [38]. SF-36 has a good reliability of 0.80, and the physical function section reliability score is more than 0.90 [36].

Participant timeline

Recruitment and Randomization

We will perform a stratified random sampling of the long COVID cases having CFS in the Dhaka and Khulna divisions. During the allocation procedure, we will use a concealed allocation process. Only the control group will be employed from the unwilling participants who will not consent to participate in any experimental group. To ensure the prospect of the trial, a randomised block design will be employed.

Study Guideline

The study will follow the consolidated standard of reporting trials (CONSORT) guidelines. The summary of CONSORT is illustrated in Figure 2.

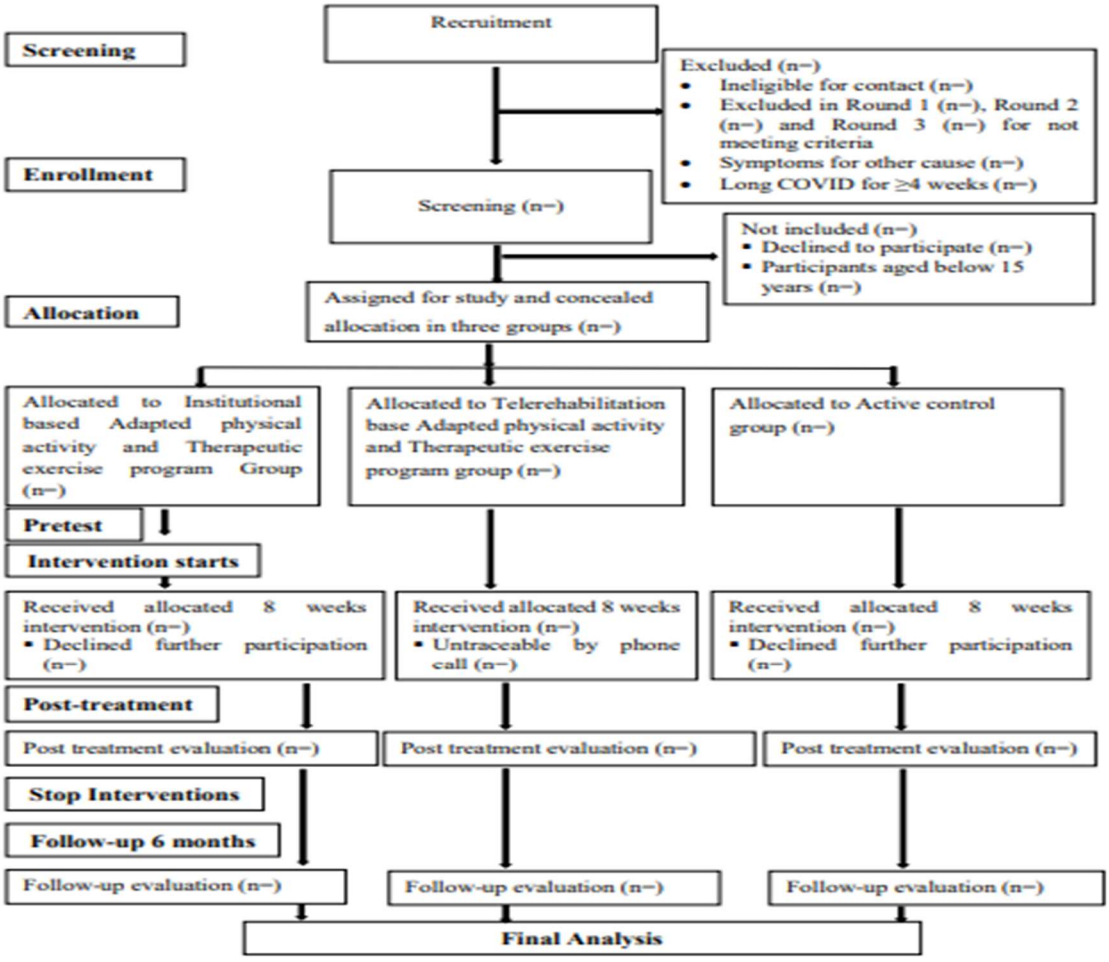

Figure 2: CONSORT flow diagram of the trial

Baseline, Posttest, and Follow-up

Baseline, post-test, and follow-up will be documented by three independent blinded assessors in both divisions. After completing the baseline assessment, the intervention team will provide interventions according to the treatment protocol. All the primary and secondary outcome measures will be taken during the baseline, post-test, and follow-up evaluation. Online Google forms and verbal approaches for the telerehabilitation groups will document the outcome.

Minimisation of bias and process

The respondents of the APTE-I and APTE-T groups will be blinded to the group allocations. Only the control group will be chosen according to patient interest or not receiving any exercise interventions. The treatment providers will also be blinded to the group; they will be aware of the treatment and treatment components, but they'll be blinded to which group is the intervention group. Participants will not pay for the interventions, or they will not be given any sort of financial compensation. Their participation will be voluntary. The research team will not be an active part of any of the interventions or the assessment group as there will be separate assessors, a separate

treatment provider, an evaluation team, and one trial manager to coordinate the entire trial procedure.

Monitoring Team

There will be a monitoring team consisting of two graduate physiotherapists who are not a part of any other evaluation in the trial. So, they will monitor the interventions provided by the physiotherapist, the patient's home exercise chart, and the patients' adverse event chart, and execute the blocking process of the trial procedure. They will directly report to the trial manager. Also, they will preserve the field-up questionnaire and the online version. They will audit the data, and they can carry out the interface analysis as per the trial requirements. The monitoring team will notify any kind of changes in the trial.

Safety measures and monitoring managing adverse effects.

We anticipate no major adverse event except post-exertional dyspnea to maintain a separate monitoring team. Also, will follow all guidelines for safe long COVID rehabilitation [26] maintain the subjective, objective analysis and plan note (SOAP note), and inform the plan manager. Before the intervention, the patients will report what kind of discomfort they might feel, and they will report verbally and through a blank format provided by the research team. All the adverse events will be monitored, documented, and published during the final publication of the study.

Ethics approval and consent to participate

Screening participants will be informed about the study's aims, objectives, and intervention process and provided a written informed consent form. For online patients, informed consent will be obtained using Google forms and a verbal procedure. The entire trial is part of a doctoral study and obtains ethical permission from the University of Malaysia Sabah (UMS) UMS/FPSK6.9/100-6/1/95 [12/08/2022]. Also, the trial is registered to the Clinical Trial Registry India (CTRI), the primary trial site of the World Health Organization CTRI/2023/03/050808 [Registered on: 17/03/2023]. We will follow the Helsinki Declarations' ethical guidelines per the rules provided by the ethical approval bodies. Before enrolling, we'll provide written informed consent and ensure the participation is voluntary, and they can withdraw the trial anytime during the trial. Also, the participants will be ensured that withdrawal from our study will not change their treatment process. The trial manager, principal investigator, and data auditors will have access to the final trial data set. After completing the trials, all the authors will have equal access to the anonymous data. All The hard copies and soft copies of data collection will be kept to the principal investigator, and there will not be any disclosure or access to the identification of trial patients. There will be post-trial care only if any adverse effects are noted during the trial.

Data analysis

Data will be analysed through social science SPSS version 23.00 statistical packages for Windows. Normality distribution will be examined through the Bells curve, Kolmogorov- Simonov, and

Shapiro–Wilk tests [39]. Descriptive analysis will be performed using the arithmetic mean and the standard deviation for continuous data and frequency and percentage for categorical data. Baseline compatibility will be performed using One-way ANOVA or Friedman's ANOVA according to the nature of the data. Based on the data distribution, group changes and observation changes will be determined using MANOVA or the Multivariate Krushkal Walis test. Within-group changes, among three measurements, or three groups will be performed using one-way ANOVA or Friedman's ANOVA, and subsequent post-test will be conducted by Paired sample "t" test or Wilcoxon test [40]. We will use the intention to treat the analysis process for the respondents who completed at least one month of interventions in the post-test. The level of significance will be set as alpha<.05, In the case of the post hoc test, Bonferroni correction will be made as P<0.0125.

Study Status

This trial version number 1 and formulated this protocol on 11 April 2023. This trial is not recruiting participants yet.

Dissemination

After the end of the trial, the result will be presented to the relevant stakeholders in the seminar in Bangladesh and Malaysia. The final research paper will be submitted to an indexed journal for publication. There will be a training session for physiotherapy professionals on managing long COVID through the grading exercise process regarding the adopted trial results. The trial results will be published as open access to ensure the maximum visibility and reproducibility of the original research.

Statement of Reporting Guidelines

We followed the Standard Protocol Items: Recommendations for Interventional Trials guideline for the study protocol. The study implication will follow Consolidated Standards of Reporting Trials guidelines.

Discussion

Chronic fatigue syndrome has an existing disease burden, and researchers estimate that the overall disease burden of CFS in the USA is double that of HIV and half of the disease burden of breast cancer [41]. From the global prevalence, it is estimated from 52 studies with a sample size of more than 127,000 long COVID cases, 45.2% of survivors had chronic fatigue syndrome (95% CI; 34.1%- 56.9%) [10]. So, it is assumed that chronic fatigue syndrome's disease burden will significantly increase after the COVID-19 pandemic.

The study reveals chronic fatigue syndrome is associated with painful conditions, fatigue, impairments, and physical functioning [29]. These physical issues gradually affect mental health status and progress to depression and problems in sleep [26-29]. Pharmacological management has a limited impact [20], and non-pharmacological interventions such as exercise therapy have a

relatively short-term outcome in non-COVID cases [14-16, 19, 21]. The proposed study will cover a significant research gap in estimating the outcome of exercise therapy progress by both patient and therapist to improve the fatigue status and physical functioning of people with long COVID having chronic fatigue syndrome. Limited studies evaluated the outcome of telerehabilitation for post-COVID cases and found it to have a positive impact on functional capacity and physical functioning [42], however, the stated research recommended further studies to address the long-term issues and multi-systemic outcomes in post-COVID cases. This study integrates the research gap from existing studies [42,43] and is expected to add new knowledge on the outcome of Adapted physical activity and Therapeutic exercise program (APTE) for long COVID cases parallel to the previously published results of non-COVID cases [14-16,19-21,29].

We use a safe long COVID-19 rehabilitation approach to treat patients with CFS in both institution-based care and telerehabilitation [26]. The exercise interventions were taken from consensus guidelines on a long COVID-19 in the Bangladeshi context [27], a national protocol from the Ministry of Health of Malaysia [28], and existing available best-quality literature drawn from the non-COVID era [14-16,19-21, 44] to ensure an equal level of care to be provided in both groups. We are providing similar treatment approaches and concepts in institution-based and tele-rehabilitation-based approaches. We expect the study findings will help us determine the best possible approach to deliver long COVID-19 rehabilitation for patients with chronic fatigue syndrome. The standard control group is non-adherence to therapeutic exercises. Hence, they are free to choose any approach, and after the intervention, they will be advised to take exercise interventions free of cost after the end of the trial.

The study procedure will follow the standard protocols SPIRIT and CONSORT, and different layers of blinding and masking will be applied. The study will also adopt approaches to prevent cross-contamination of the data and choose valid and reliable tools to measure fatigue, physical functioning, and episodic disability. The study also adopted the standard translation process for the questionnaire, which is not available in the Bangla language and also is planning to provide a couple of training programs for the stakeholders of the trial. The study process is complicated, but it is well-designed, synchronised, and well-planned to be executed. We expect the result will cover a glimpse of the paradigm shift of treatment approaches for CFS, and how the future implication of long COVID rehabilitation will be implemented. The study's strength is covering a recommended research gap, ensuring representative sampling, following standard protocols and guidelines, adequate planning for adequate samples, the appropriate timeframe of post-test (2 months) and follow-up (6 months), and proper blinding and masking procedures. Future studies with a larger timeframe covering the long-term (more than one year) outcome of exercise therapy compared to other available interventions such as pacing, cognitive behavioural therapy (CBT), and aerobic exercise alone will guide to a complete guideline for long COVID-19 cases having CFS. The result of the trial will be confined to two different divisions in Bangladesh; hence, the

actual generalisation will be a challenge, but we hope the findings will guide us to good clinical practice for the long COVID-19 patients having chronic fatigue syndrome.

Conclusion:

This is a clinical protocol for doing the randomised control trial. This study will be started very soon, according to the trial.

Abbreviations

CFS: Chronic fatigue syndrome; CBT: Cognitive behavioural therapy; APTE: Adapted physical activity and Therapeutic exercise program; AC: Active control; MCID: Minimal clinically important differences; DALYs: Disability-adjusted life years;

Consent for publication

Not applicable.

Availability of data and material

There is no available data as this is a trial protocol.

Competing interests

The authors declare no conflict of interest.

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Author Contributions

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