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Controlling the Management of a Multimodal Stress-Controlled Therapy for Post-COVID-19-Patients

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Abstract

Background: For the medical treatment of Post-COVID-19 syndrome, no medical treatment or causal therapy based on evidence-based criteria is currently recommended. As an interlinking of digital modules and classic on-site therapy, we developed a cross-sector, doctor-led blended therapy that is aimed at the main syndromes of fatigue/immunometabolic depression and sensorimotor instability (easily manageable real-time cognitive parameters). The real-time recording and analysis of the corresponding parameters become an important environmentally stable and control training item.

Methodology: Changing the leading syndromes of fatigue and sensorimotor instability through stress-controlled standardized training therapy and intensified cognitive behavioral therapy were the overarching goals of the intervention and observation study over a 3-year period (Q1-2021 - Q2-2024). The outcome assessment was based on the Post-COVID-19-key symptoms and motor fatigue parameters. A secondary psychosomatic syndrome that emerged during the course of treatment was examined using cognitive fatigue parameters. The analysis of participation, quality of life and mental health was carried out using validated questionnaires. The patients' health behavior was evaluated using a guideline-supported expert interview.

Results: With blended therapy, improvements in Post-COVID-19-key symptoms as well as motor and cognitive fatigability parameters were achieved. The timing of the start of the individual sections of the treatment path had an influence on the outcome. The intensification of cognitive behavioral therapy also had positive effects, achieving an increasing development of the patients' own activity and their self-control. With the results of the guideline-supported expert interview, the social-cognitive process model of health action was specified.

Conclusion: Cross-sector blended therapy with central data storage can coordinate the structured exchange of information between the individual actors in the treatment process with an impact on the success of the therapy. A delay in the start of therapy is counteracted, service provision and coordination is accelerated at a central and peripheral level, and an effective, efficient, safe and scalable intervention is implemented.

Keywords: Post-COVID-19-syndrome; Fatigue; Multimodal blended therapy; Cognitive behavioral therapy; Health behavior

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Introduction

Since the beginning of the SARS-CoV-2 pandemic, by the end of September 2024, over 700 million people worldwide have been infected with an immunogenic virus [42], which causes (long-term) health consequences of varying severity and duration (Figure 1). Following a SARS-CoV-2 infection, similar to other infectious diseases, persistent symptoms can occur in various organ systems (lungs, heart, brain, gastroenteron and other secondary organs) and/or various new symptoms can arise that persist over a longer period of time [2-5].

In the specialist literature, the term Post-COVID-19-Syndrome (PCS) has become established for symptoms that occur or persist twelve weeks after a SARS-CoV-2 infection [6-8]. The frequency of occurrence of PCS is between 10 and 35% [9]. Using the Delphi consensus method, the WHO defined PCS as follows [10-12]:

- Symptoms must still be present 12 weeks (3 months) after a SARS-CoV-2 infection and must last at least two months
- there is no other etiological explanation
- the course may be persistent, recurrent or fluctuating

There is currently no causal therapeutic approach based on evidence-based criteria for the treatment of Post-COVID-19/Syndrome (PCS). The S2k guidelines of the German Society for Neurology (DGN) advocate that Post-COVID-19/sufferers with sensory, sensorimotor, cognitive and/or emotional changes receive adequate neurological evaluation and, if necessary, neurorehabilitative care be supplied. The need for treatment arises either immediately after the acute treatment or during the course (e.g. after 3 - 6 months).

There are over 100 symptoms behind PCS with different pathogenetic entities. However, neuropsychiatric symptoms such as cognitive impairments (concentration, memory, executive functions, sensorimotor stability), central peripheral paralysis, autonomic dysfunction, smell/taste disorders, sleep disorders, depressive symptoms, anxiety disorders, make up a large part of the Post-COVID-19/Syndrome from [13,14]. Fatigue is characterized by a subjectively often severely limiting physical (especially motor), cognitive and/or psychological exhaustion that is disproportionate to the previous exertion and cannot be eliminated by sleep [15-20]. The focus is on the stress reactions of a somatic, cognitive and emotional nature that are triggered by low objective stress due to performance requirements, the extent of which is often not foreseeable in advance for the person affected (crash or post-exertional malaise: PEM). From

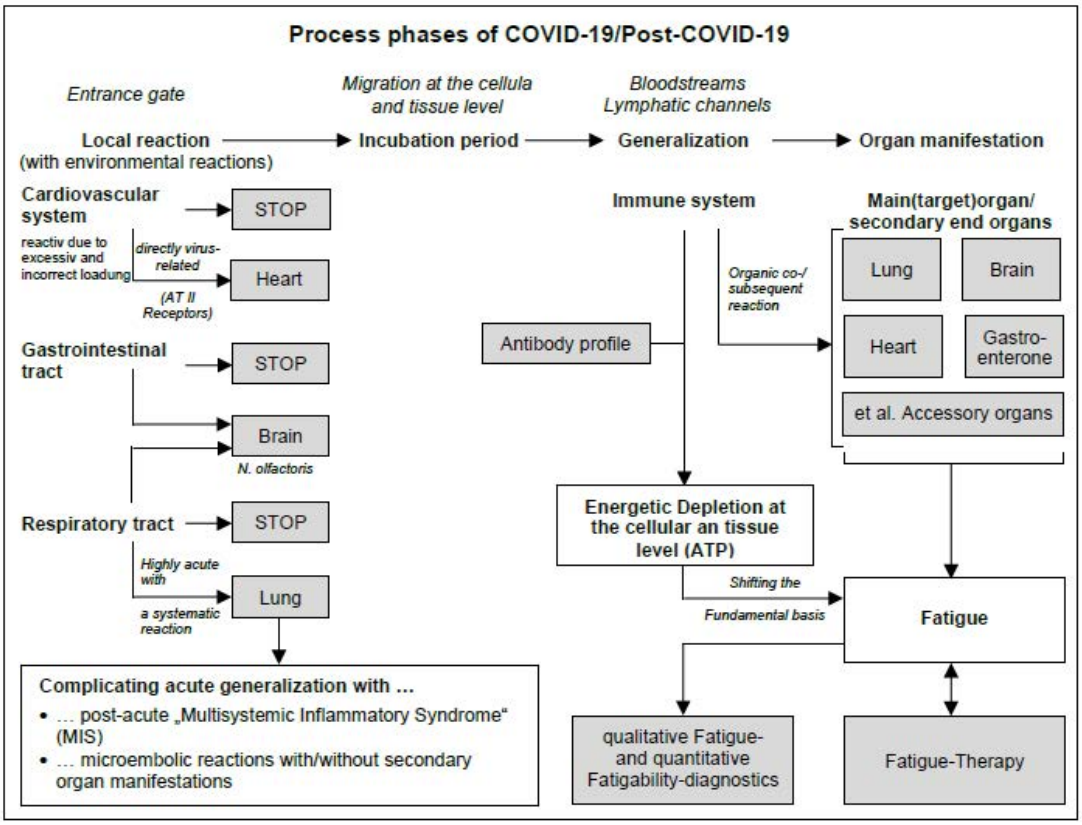

Figure 1: Process phases COVID-19/Post-COVID-19.

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the perspective of psychiatry, the depressive illnesses that occur in immunologically triggered patients are referred to as immunometabolic depression because they have a rather atypical symptom constellation for classic depression, such as fatigue [21].

Fatigue (neurology, neurocardiopulmology) and immunometabolic depression (psychiatry, psychosomatics, immunology) bridge the affected disciplines in the investigation of immunologically triggered energy deficit-related network disorders in various organ systems. The nervous system as a whole is most often affected [22]. It is accepted that, on the one hand, a variety of organ damage can occur during the process phases of COVID-19, for example in the lungs, heart, brain or peripheral nervous system (see Figure 1) and, on the other hand, psychological comorbidities in individually different combinations the development of fatigue are significant [18]. The following pathophysiological mechanisms are discussed [9]:

- Virus persistence (not likely)
- persistent overactivation of the immune system, including autoimmune phenomena
- progressive thrombus formation in the microvascular system and other tissue hypoxemia

As an important aspect in the classic treatment of fatigue/immunometabolic depression (e.g. in multiple sclerosis, in hemato-oncology and currently in immunotherapy), training and physiotherapy were considered strictly contraindicated just a few months ago. It was about protection in the convalescence phase (rest, relaxation techniques, avoiding stress and excessive demands). The greatest effects on fatigue are now seen with balance training and motor exercise therapies, followed by cognitive behavioral therapy aimed at fatigue [23].

Due to the diversity and medical range of Post-COVID-19-key symptoms, the patient's health status must be recorded and assessed by experts from different disciplines [24,25]. Such a multidisciplinary connection can take place within the framework of an interdisciplinary care network with the implementation of a multimodal blended therapy structure (Figure 2). Blended therapy concepts use digital intervention options to supplement analog forms of therapy [26]. For example, patient groups with little mobility or at great geographical distances can be reached, service providers can be integrated at a central and peripheral level, and the patient's treatment plan can be coordinated through shared data use.

The digital intervention in the blended therapy concept enables a real-time analysis of load, performance and strain as

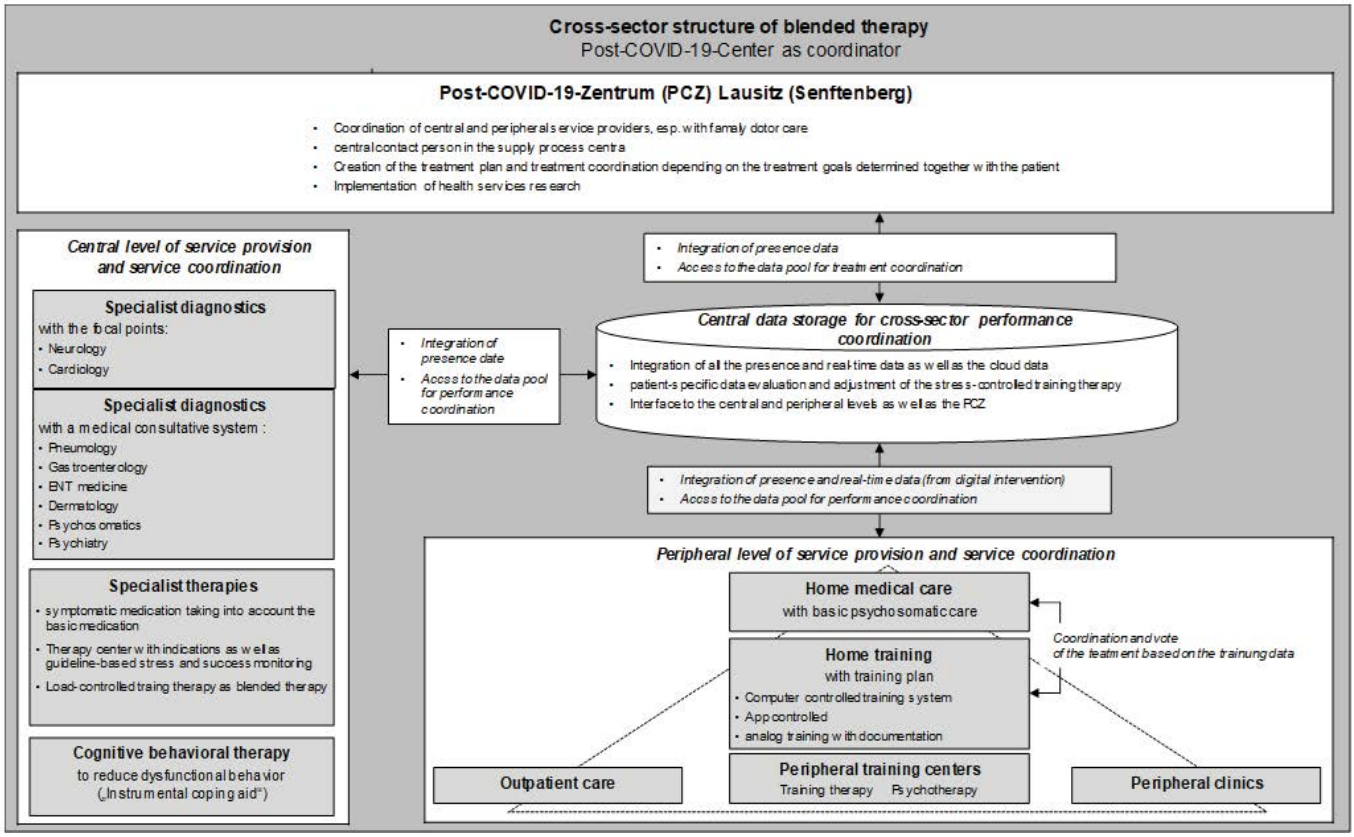

Figure 2: Cross-sector structure of blended therapy.

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well as the transition from treatment control to a close-meshed information technology control [1,12,27]. The technological basis for this is the "Reha-Planet"/System developed by the research group [28]. The implemented applications realize the following functions (Figure 4):

- Implementation of individual stress-controlled training to build performance while specifically avoiding overload and crashes
- Integration of a therapist known to the patient from the therapy center and other therapy members
- Creating an emotional connection to the system in order to create closeness despite the spatial distance to the proportionate practice at home

Methodology

The SARS-CoV-2/Pandemic has shown that medical management functions stably, even with a large number of patients, if it can rely on established structures that are stably networked in routine operations. For example, specific treatment resources were available for stroke care in Germany, which linked the medical practice with the local university structures and could be used immediately for pandemic care. The implementation, control and evaluation of the multimodal blended therapy took place within the framework of a cross-sector care network, the implementation structure of which is shown in Figure 2.

Implementation structure of blended therapy

As can be seen in Figure 2, the coordination of blended therapy in the cross-sector care network is carried out by the Post-COVID-19-Zentrum (PCZ) Lausitz (Senftenberg). Central data storage of all the data exchanged during the treatment process between the service providers at a central and peripheral level benefits, among other things: management, treatment satisfaction and treatment results of patients, but also the central and peripheral levels of service provision as well as service coordination between the actors involved.

In the PCZ, a monocentric stress-controlled training therapy (analog and digital intervention) was implemented to treat the key syndromes "fatigue" and "sensorimotor instability", as well as a need for secondary psychosomatic treatment in the form of fatigue, which often arises in the Post-COVID-19-Process with fatigue Intervention and observation study realized from Q1-2021 to Q2-2024. The combination of analog and digital forms of therapy (blended therapy) achieves a high level of flexibility in therapy design as well as better patient adherence [23,29,30]. The guidelines §3 (4) number 4 of the Federal Joint Committee (G-BA) recommend the use of digital therapy offers that take into account different symptoms of the basic assessment and individual levels of stress [24,31].

407 vaccinated nucleocapsid-positive patients were available for screening in the PCZ (Table 1). The nucleocapsid protein was determined through a blood sample and laboratory examination in the period from Q1-2021 to Q1-2023. At the same time, a functional status survey was carried out using a method developed by Klok et al. [32] validated scale with five levels of severity, ranging from grade 0 = no functional limitation to grade 4 = severe functional limitation [2]. The 78 patients with reduced sensorimotor performance and fatigue (Table 1) were admitted after a standardized diagnosis in accordance with guidelines and taking into account the following exclusion criteria:

- irreconcilable communication problems
- vestibular dysfunction (video head impulse test)
- Pacemaker
- non-compensatory visual limitations
- orthopedic deficits of the lower extremities
- Inability to stand independently without the use of assistive devices

All patients were of legal age and gave written informed consent before inclusion in the study. The implemented study design and the computer-controlled training system used were approved by the ethics committee of the TU Dresden (reference numbers EK 378092016, EK 356092017).

The treatment plan of the intervention- and observation-study at the PCZ consisted of two phases (Figure 3):

- **Treatment phase 1 (intervention study):** Stress-controlled training therapy to improve quantified sensorimotor parameters and post-COVID-19 key symptoms (Q1-2021 - Q2-2023).
- **Treatment phase 2 (intervention and observation study):** Intensified cognitive behavioral therapy to improve fatigue and secondary psychosomatic symptoms (Q2-2023 - Q4-2023), evaluation of the patients' health behavior with a guide-supported expert interview as well as the questionnaire-supported assessment of participation (IMET), health-related quality of life (VR- 12), generalized anxiety disorders (GAD-7) and depressive disorders (PHQ-9) in Q2-2024.

Control of blended therapy

The blended therapy in treatment phase 1 of the intervention study is based on the building blocks "presence", the "computer-aided training system" and the "mobile application". On the one hand, it took place in a training center belonging to the PCZ and, on the other hand, in the patient's home in order to achieve sufficient training density (at least 2 training units per week). A computer-supported training

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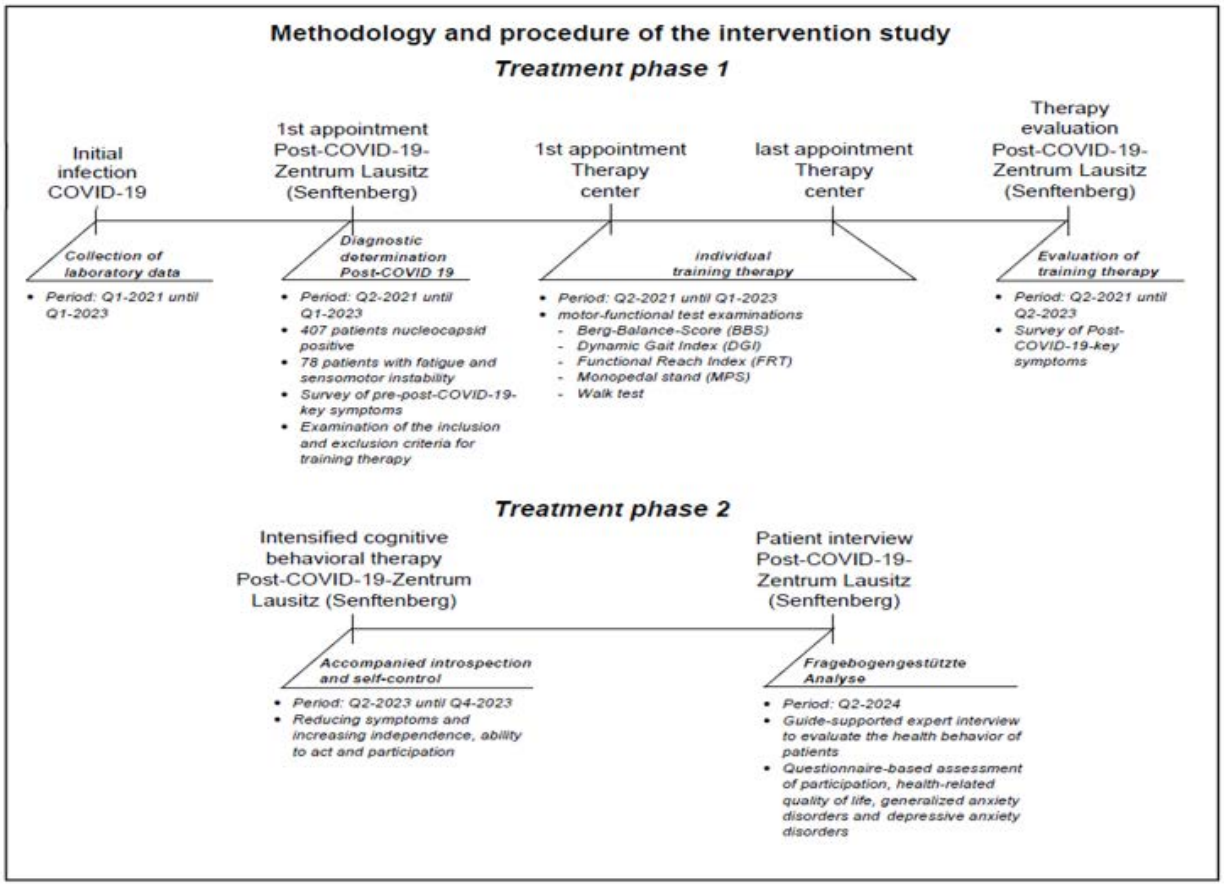

Figure 3: Methodology and procedure of the intervention- and observation-study.

system was used in the training center (in-person) as well as in the home. The system structure and the methodology used in blended therapy are based on three steps (Figure 4):

1. Initial determination of the severity of functional limitations in the training center
2. Digital intervention of stress-controlled training therapy in the training center and at home
3. Load control and monitoring of training therapy

Patients for whom a computer-controlled training system could not be used at home due to spatial and/or technical restrictions either a) carried out the exercises independently with measurement of the pulse rate (ECG recordings if necessary) via a smartwatch and documentation of the results, or b) used the computer-aided training system based on a mobile application with the following functionalities:

- Training plan with video instructions for carrying out the standardized exercises
- regular training reminder
- Digital trainer that optimizes exercise complexity and length through user feedback
- Overview of the practice times with review
- Recording and recording quality of life using the SF 36 questionnaire
- Point system to increase motivation and adherence
- Meditation tool with guided relaxation exercises

In the experience of Post-COVID-19-sufferers, increasing thought dysfunction can develop over time (including during the course of therapy at the PCZ) from stress insufficiency experienced in everyday work and at home [4,33]. The aim was to improve self-management of reduced resources and the often significantly limited participation in social and professional life.

Evaluation of blended therapy

The stress-controlled training therapy was evaluated based on the Post-COVID-19-key symptoms (fatigue, sensorimotor instability, cardiopulmonary/autonomic dysfunction, neuropsychiatric symptoms, secondary psycho-somatic symptoms and pain) as well as the motor fatigue parameters (Berg Balance Scale, Dynamic Gate Index, Functional Reach Test, Monopedal Stand and 10 Meter Walk Test). Motor

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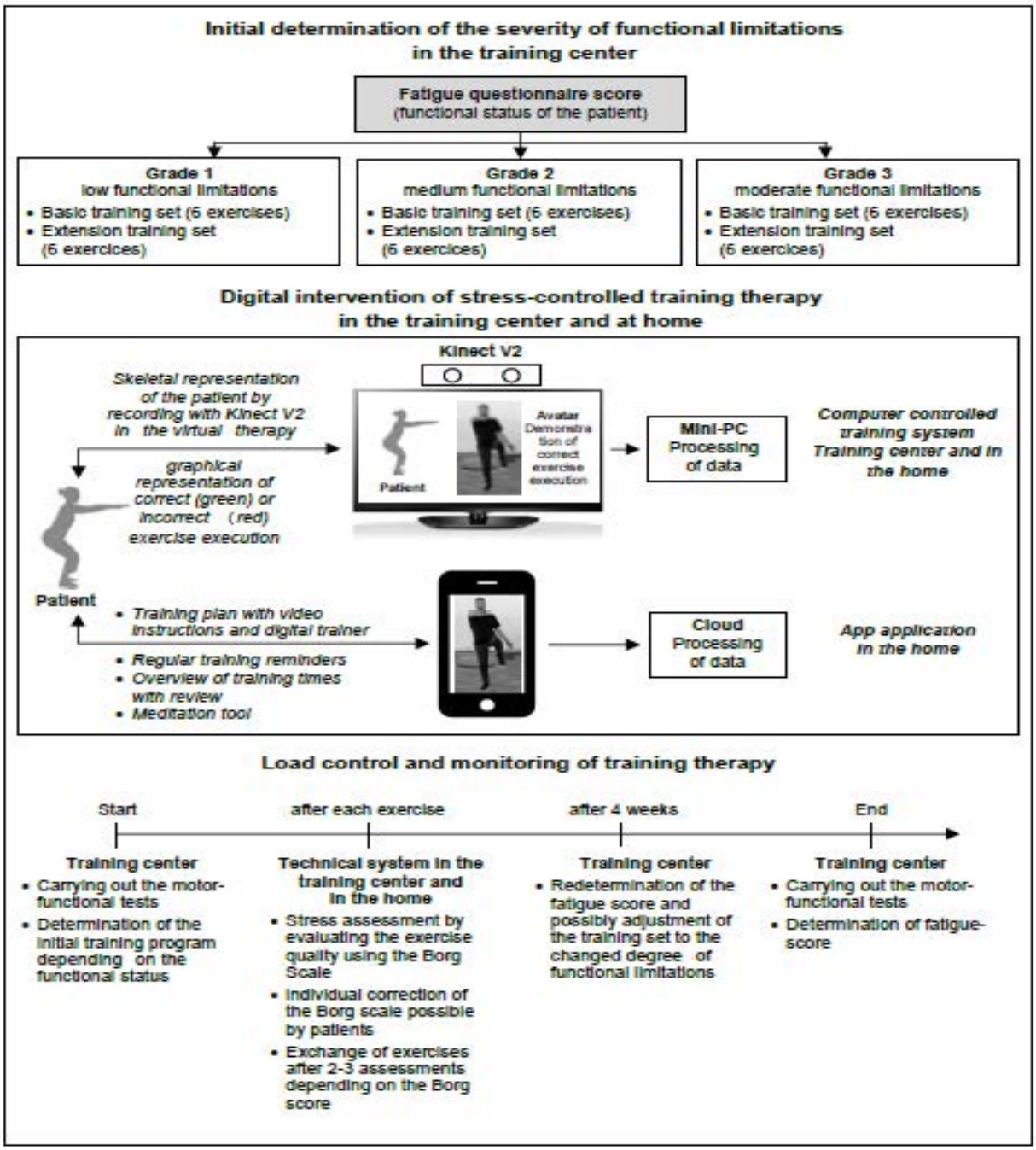

Figure 4: System structure and methodology of blended therapy.

fatigability represents an objectively measurable indicator of motor performance and allows for a higher medical assessment of the effectiveness of therapy [6, 26,34-36].

As part of treatment phase 2 of the intervention study (Figure 3), intensified cognitive behavioral therapy was carried out for the group of therapy participants with "secondary psychosomatic symptoms". A connection between the organic and psychological-emotional sides is the patient's self-control (control of thoughts, feelings and behavior) [21]. With the intensification of cognitive behavioral therapy (structured, present-oriented short-term psychotherapy) in the period Q2-2023 to Q4-2023, the changes in the secondary psychosomatic syndromes were examined (cognitive fatigue parameters).

In Q2-2024, an assessment of participation (IMET), health-related quality of life (VR-12), generalized anxiety disorders (GAD-7) and depressive disorders (PHQ-9) was carried out. On the other hand, the patients health behavior

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was recorded using a guideline-supported expert interview. The interview results were integrated into the social-cognitive process model of health action (HAPA) and shows possibilities for doctors and therapists to influence health behavior.

Results

An example of a cross-sector blended therapy was implemented, which puts the post-COVID-19-syndromes fatigue and sensorimotor instability at the center of the considerations. The therapy evaluation is based on the qualitative and quantitative evaluation parameters presented as well as the analysis of the management process of the stress-controlled intervention. There were no strong gender differences. Deviations exist in individual sub-phases and have an impact on the timing of the management process as well as on the outcome.

Post-COVID-19-key symptoms

The overall analysis with N=78 (Table 1) produced the following results:

- Improvement in "fatigue" by around 71%, "sensorimotor instability" by around 56%, "neuropsychiatric symptoms" by around 72%, "cardiopulmonary/autonomic dysfunction" by around 76% and "pain" by around around 14% through pre-post survey of Post-COVID-19-key symptoms
- Worsening of "secondary psychosomatic symptoms" by around 72%

In the men (N = 37), all values improved compared to the women except for "pain" (no improvement). One reason may be the faster process flow in the period "Initial infection-1. Appointment PCZ" and "1. Appointment PCZ- 1st appointment therapy center" can be seen. Women showed a very strong deterioration in the "secondary psychosomatic symptoms". The slower process flow in the above-mentioned cases can be the cause. Periods compared to men, overestimation of (residual) performance or evasive behavior, especially in hyperdynamic young women in the form of dysfunctional psychological reactions.

The Wilcoxon test was carried out to evaluate the effectiveness of therapy because there was no normal distribution in the pre- and post-data sets. The specific effect of the training therapy on the respective fatigue parameter is determined using the Cohen's d value (Table 1).

Table 1: Presentation of the total results.

Nucleocapsid positive patuents (vaccinated)								
	< 25 Years	25-34 Years	35-44 Years	45-54 Years	55-64 Years	> 64 Years	M (Years)	SD (Years)
Total (N = 407)	9	16	46	79	123	134	58,26	14,79
Men (N = 169)	5	4	16	25	51	68	60,41	14,80
Women (N = 238)	4	12	30	54	72	66	56,74	14,6
Cohort intervention study (fatigue and sensorimotor instability)								
	< 25 Years	25-34 Years	35-44 Years	45-54 Years	55-64 Years	> 64 Years	M (Years)	SD (Years)
Total (N = 78)	0	0	8	12	26	32	59,1	12,76
Men (N = 37)	0	0	4	2	12	19	62,2	11,91
Women (N = 41)	0	0	4	10	14	13	56,6	13,01

Motor fatigability-parameters (treatment phase 1 of intervention study)						
		Berg-Balance-Score (BBS)	Dynamic Gait Index (DGI)	Functional Reach Test (FRT)	Monopedalstand (MPS)	10 m-Walk testm
Total (N = 78)	**Pre**	M = 48,5	M = 21,8	M = 32 cm	M = 88,8 sec.	M = 6,6 sec.
	Post	M = 51	M = 22,9	M = 36,7 cm	M = 100,8 sec.	M = 6,3 sec.
	Significance (Wilcoxon-Test 2-sided)	**< 0,001**	**< 0,001**	**< 0,001**	**0,036**	**0,017**
	Improvement	**5,1 %**	**4,6 %**	**14,7 %**	**13,6 %**	**4,5 %**
	Effekt size (Cohens d)	**- 0,48** (low)	**- 0,42** (low)	**- 0,61** (medium)	**- 0,22** (low)	**0,201** (low)
Men (N = 37)	**Pre**	M = 49	M = 21,9	M = 33,7 cm	M = 75 sec.	M = 6,21 sec.
	Post	M = 51,7	M = 23	M = 37,7 cm	M = 96,8 sec.	M = 6,24 sec.
	Significance (Wilcoxon-Test 2-sided)	**< 0,001**	**0,020**	**0,001**	**0,044**	**0,551**
	Improvement	**5,5 %**	**5 %**	**11,8 %**	**29 %**	**0,5 %**
	Effekt size (Cohens d)	**- 0,7** (medium)	**- 0,38** (low)	**- 0,56** (medium)	**- 0,30** (low)	**0,02** (very low)

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Motor fatigability-parameters (treatment phase 1 of intervention study)						
Women (N = 41)	**Pre**	M = 48,1	M = 21,8	M = 30,4 cm	M = 99,3 sec.	M = 7,0 sec.
	Post	M = 50,5	M = 22,8	M = 35,8 cm	M = 104,4 sec.	M = 6,3 sec.
	Significance (Wilcoxon-Test 2-sided)	**0,017**	**0,007**	**< 0,001**	**0,382**	**0,005**
	Improvement	**5 %**	**4,6 %**	**15,1 %**	**5,1 %**	**10 %**
	Effekt size (Cohens d)	**- 0,38** (low)	**- 0,45** (low)	**- 0,64** (medium)	**- 0,12** (very low)	**0,4** (low)

Secondary psychosomatic syndromes (treatment phase 2 of the intervention study)			
	Total	**Men**	**Women**
Therapy evaluation at the PCZ (end of phase 1) = start of intensification of cognitive behavioral therapy (start of phase 2)	N = 19 (100 %)	N = 4	N = 15
after 3 quarters of intensive cognitive behavioral therapy (end of phase 2)	N = 9 (47,4 %)	N = 2	N = 7
Improvement	**N = 10** (52,6 %)	**N = 2** (50 %)	**N = 8 (53,3 %)**

Development of further health parameters (observational study)					
	IMET	**VR-12** physical health	**VR-12** mental health	**GAD 7**	**PHQ-9**
without intensive cognitive behavioral therapy	M = 31,2	M = 38,45	M = 38,89	M = 10,5 (moderate symptoms)	M = 11,5 (mild symptoms)
with intensive cognitive behavioral therapy	M = 35,6	M = 36,25	M = 34,64	M = 15 (severe symptoms)	M = 17 (moderate symptoms)

Overall (N = 78), a therapeutic effect was demonstrated for all motor fatigue parameters. The Functional Reach Test (FRT) achieved a medium effect size. There was a small effect size for all other motor fatigability parameters.

In men, no treatment effect could be demonstrated for the 10 m walk test. The Berg Balance Score (BBS) and the FRT showed medium effect sizes. Small effect sizes were found for the dynamic gait index (DGI) and monopedal stance (MPS).

In the women's cohort (N = 41), there were no treatment effects for the dynamic gait index (DGI) and monopedal stance (MPS). The FRT achieved a medium effect size. Small effect sizes were found for the BBS and 10 m walking test.

Cognitive fatigability parameters

Table 1 shows the development of the study participants with fatigue and secondary psychosomatic symptoms after the end of phase 1 and the subsequent intensified cognitive behavioral therapy over 3 quarters (phase 2: Q2-2023 to Q4-2023). The positive effect of self-observation with accompanied self-control can be seen both in the overall view (improvement around 53%) and in the gender-specific analysis (improvement for men: 50%; improvement for women: around 53%).

Questionnaire-based analysis of participation, quality of life and mental health

The survey with the validated individual questionnaires took place in Q2-2024 and at the earliest 3 months after the stress-controlled training therapy and, if necessary, additional intensified cognitive behavioral therapy. Restrictions on participation were recorded with the IMET, health-related quality of life was measured with the VR-12 and aspects of mental health were recorded with the GAD-7 and PHQ-9. Of the 78 participants in the intervention study, 26 participants took part. As can be seen in Table 1, the participants with intensive cognitive behavioral therapy (treatment phase 2) continue to have severe anxiety symptoms and moderate depressive symptoms. Psychotherapeutic treatment should therefore continue to take place in order to improve participation and physical and mental health.

Questionnaire-based analysis of participation, quality of life and mental health

The results of the guideline-supported expert interview were integrated into the health action process approach (HAPA)-model in order to explain health-promoting and health-damaging behaviors. As can be seen in Figure 5, the trusting doctor-therapist-patient relationship as well as a central contact person or guide for all topics of the recovery process form the bracket around the motivational and volitional phase.

In the motivating phase, the respective influencing factors on risk perception, action outcome expectations and self-efficacy expectations of patients with Post-COVID-19 as well as fatigue and sensorimotor instability are presented. Risk perception includes the individual perception and subjective assessment of the severity of the disease as well as one's own vulnerability. In order for blended therapy to be implemented,

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behavioral alternatives must be known to reduce perceived risks. Perceived self-efficacy is the patient's subjective belief that they can carry out new behaviors based on their existing competence. The moderating variables in each case are shown in Figure 5. The individual assessment of risk perception, action outcome expectations and self-efficacy expectations flow into the patient's goal intention and completes the pre-intentional stage. The stronger this intention is, the more likely it is that behavioral changes will occur in the sense of a quick start to the load-controlled training therapy.

The volitional phase begins with action and coping planning, where the patient decides on the framework conditions for the desired behavior. In the pre-actional stage, this concerns the planning of the start and the regular implementation of the stress-controlled training therapy (when, where and how), but also the development of personal activities. In the actional stage, therapy is carried out and maintained. The extent of self-efficacy expectations affects the intensity and persistence of goal pursuit. Optimistic attitudes promote persistent goal pursuit even in the face of

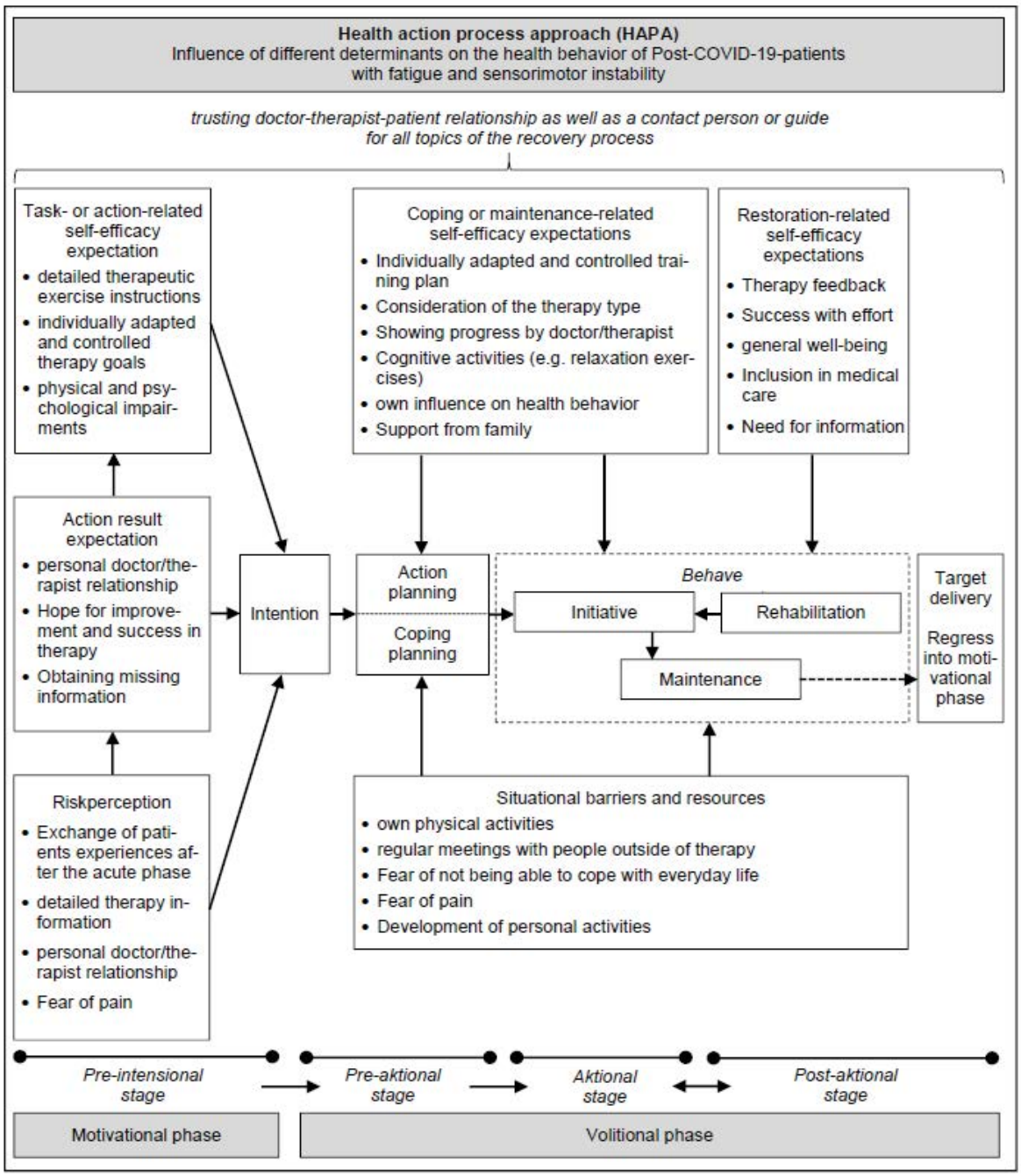

Figure 5: Health action process approach (HAPA)-model specified for Post-COVID-19-Patients with fatigue and sensorimotor instability.

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setbacks (e.g. being exhausted by successes with effort). In the final post-actional phase, the patient evaluates the action in terms of the success/failure of the therapy. In order to be successful, the treatment plans must therefore be planned constructively together with the doctor/therapist in order to set achievable goals, create rewards in the spirit of success and regulate unpleasant emotions (e.g. depressive and helpless moods) [37].

Discussion

The SARS-CoV-2-pandemic has shown that medical management functions stably, even with a large number of patients, if it can rely on established structures that are stably networked in routine operations. For example, specific treatment resources were available for stroke care in Germany, which linked the medical practice with the local university structures and could be used immediately for pandemic care. At the beginning of the pandemic, however, these were only available with the necessary precision at intersections, such as TU Dresden and BTU Cottbus-Senftenberg. This was the reason for the initially implemented mono-center design of the intervention study. This must be seen as a limitation for the overall conclusion of the study.

As part of the multimodal blended therapy of post-COVID-19 patients with fatigue and sensorimotor instability, it was demonstrated that individual stress-controlled training and, to some extent, cognitive skills accompanying the main medical process at the post-Covid-19 center tive behavioral therapy (treatment phase 1) as well as intensified cognitive behavioral therapy with a focus on self-control at home (treatment phase 2) the Post-COVID-19-key symptoms “fatigue”, “sensorimotor instability”, “neuropsychiatric symptoms”, “cardiopulmonary/autonomic dysfunction”. “, “Secondary psychosomatic symptoms” and “pain” could be reduced.

The digital interventions integrated into blended therapy in the form of a computer-supported training system and a mobile application support physical health. They improve the ability to maintain everyday activities and are independent of the location and time of the provision of analogue therapies by medical providers. At the same time, they prove to be particularly effective in dealing with fatigue symptoms. In order to increase adherence and effect strength among patients, digital therapy offers must be individually tailored to patients and their symptoms [10,24,38-42]. With hybrid training therapy, it is possible to implement a high training density.

The analysis of the gender-specific motor fatigability parameters showed that a timely implementation of the individual process stages of the therapy can lead to a better outcome. By integrating different service providers, 19 study participants (Table 1) with fatigue and secondary psychosomatic symptoms were integrated into a subsequent intensified cognitive behavioral therapy (treatment phase 2) after the end of treatment phase 1. The outcome was significantly improved.

With the results of the guideline-supported expert interview, the social-cognitive process model of health action for Post-COVID-19-patients with fatigue and sensorimotor instability was specified. Recommendations for action are therefore given to doctors and therapists in order to positively influence therapy behavior and thus the outcome.

With the cross-sector structure of blended therapy, the goal of a low-threshold i. d. General medical screenings can be carried out in order to determine at an early stage the persistence of predominantly neurological and neurocardiological manifestations of a COVID-19 disease requiring treatment, or the need for treatment in Post-COVID-19-patients with neurological functional disorders after an initially non-severe course [7]. As shown in Figure 1, the structured exchange of information between the individual actors can be coordinated via central data storage in order to achieve the best possible treatment success. This counteracts any delay in the start of therapy and accelerates the provision and coordination of services at the central and peripheral levels.

Compliance with Ethical Guidelines

Conflict of interest: All authors declare that they have no conflict of interest.

This article does not contain any studies on humans or animals.

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