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Comprehensive Home-based and Remotely Supervised Physiotherapy Programme within Interdisciplinary Treatment Approach in Patients with Pulmonary Arterial Hypertension

Summary of the Doctoral Thesis for obtaining a doctoral degree "Doctor of Science (*PhD*)"

Sector – Health and Sport Sciences
Sub-Sector – Sports Medicine and Rehabilitation

Riga, 2023

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Abbreviations used in the Thesis

6MWT	six-minute walk test
AI	Autonomy Indoors IPA sub-scale
AO	Autonomy Outdoors IPA sub-scale
BNP	brain natriuretic peptide
BP	blood pressure
CI	95 % confidence interval
CRP	high-sensitivity C-reactive protein
ERS	European Respiratory Society
ESC	European Society of Cardiology
FR	Family Role IPA sub-scale
GSE	The General Self-Efficacy Scale
HR	heart rate
IPA	The Impact on Participation and Autonomy Questionnaire
IP_{submax}	submaximal static inspiratory mouth pressure test
mPAP	mean pulmonary arterial pressure
PAH	pulmonary arterial hypertension
PH	pulmonary hypertension
PSQI	The Pittsburgh Sleep Quality Index
SL	Social Life and Relatioships IPA sub-scale
WE	Work and Education IPA sub-scale
FIZIO-I	The developed and investigated physiotherapy programme
MED-TH	The stable PAH medical therapy based on the current guidelines of pharmacological treatment, under supervision of cardiologist specialized in PH
TG	training group
CG	control group

Introduction

Pulmonary arterial hypertension (PAH) is a progressive and life-threatening disease that refers to one of the five subgroups of PH. According to the 2022 ESC/ERS guidelines, PH is defined as an increase in mean pulmonary arterial pressure > 20 mmHg at rest and assessed by right heart catheterization. The term PAH designates a group of patients with PH that is hemodynamically characterized as precapillary PH. PAH is characterized by a progressive course of the disease with increased pulmonary vascular resistance and pulmonary arterial pressure, leading to overload and failure of the right ventricle (Galie et al., 2016; Humbert et al., 2022; Lan et al., 2018).

The initial clinical symptoms of PAH are commonly induced by exertion and can include shortness of breath, excessive fatigue and weakness, chest pain, and episodes of syncope. The symptoms of PAH are nonspecific and therefore early diagnosis often remains a challenge (Galie et al., 2016). Pathologic processes in the pulmonary arteries alter oxygen uptake and consumption in the body, decreasing SpO2 and restricting the ability to perform physical activities. The above-mentioned indices decline described as progressive worsening of exercise capacity and combined with muscular weakness and secondary sleep disorders, symptoms of depression, and inability to adapt to continuous insecurity caused by severe, chronic, and life-threatening disease (Grünig et al., 2019; Halimi et al., 2021; Rawlings et al., 2020).

PAH refers to a group of rare diseases. By the European Union, rare diseases are defined as life-threatening or chronically debilitating diseases with low prevalence, affecting less than 5 in 10 000 (Moliner & Waligora, 2017). The prevalence rate of PAH in the United States and Europe is between 15 and 50 cases per million people (Levine, 2021), while in Latvia in 2016, according to data from the pulmonary hypertension registry, 45.7 cases (Skride, 2018). Rare diseases present unique challenges in terms of structuring healthcare processes,

while delays in developing clinical algorithms result in long diagnostic pathways, limited and unequal treatment. In addition, these complex care coordination problems impose a heavy burden on a patient and his family, contributing to personal, professional, and social life difficulties, and, consequently, worsening the quality of life in general.

With the development of PAH pathogenetic therapy, patient survival, clinical stability, and quality of life have improved significantly; however, clinical symptoms, limited exercise capacity, sense of insecurity, and isolation often remain, bringing to the fore such treatment aspects that are not related to basic medical treatment of the disease. Considering the negative impact of PAH on the ability to perform physical activities, research has focused on physical exercise studies over several years which has allowed one to significantly change the point of view about its practical applicability: from prohibition and recommendations to avoid, to goal-oriented usage with a view to improving functional condition. Recent studies have shown that physical training can improve exercise capacity, muscle function, quality of life, and possibly right heart function and pulmonary hemodynamic. However, approval of exercise methodology (type, intensity, form of supervision and delivery) has not yet been achieved, which might allow putting forward specific evidence-based recommendations (Galie et al., 2016; Grünig et al., 2019).

In the 6th Symposium on Pulmonary Hypertension (Nice, 2018) the conference section involving patient perspectives on life with PH was first supported. Bringing a broader patient perspective into understanding the outcome of treatment allows us to discover that symptoms, exercise capacity, and hemodynamic parameters are only a visible part of an iceberg, and therefore, the overall negative impact caused by PAH on patient life highlights the need for a comprehensive and interdisciplinary treatment approach. Along with the objectives of risk stratification and mitigation, the outcome of treatment should

include meeting the changing needs of the patient to improve and maintain maximum the ability to participate in his daily life the way he wishes, thus living a meaningful life.

It is necessary to combine specialized healthcare services and long-term interventions in the treatment of patients with PAH, aiming at improving chronic disease management and dynamic adaptation. This highlights the need to develop comprehensive physiotherapy interventions aimed not only at improving physical functions, but also at promoting self-management and creating healthy daily habits. The challenge of ensuring specialized healthcare services and long-term interventions at the same time shows that the need for telehealth interventions becomes relevant. At the same time, remotely supervised service delivery is relevant in the context of financial and geographical accessibility and the potential cost-effectiveness of the above-mentioned interventions.

Objective of the Thesis

The aim of the study was to investigate the effectiveness of the comprehensive home-based and remotely supervised physiotherapy programme within the interdisciplinary treatment approach to improve and maintain participation in everyday life activities, along with exercise capacity and inspiratory muscle strength, perceived self-efficacy, daily physical activity, and sleep quality in patients with PAH.

Tasks of the Thesis

1. To prepare the methodology of the innovative physiotherapy programme to use it in an interdisciplinary treatment approach in the specific target group: patients with PAH.
2. To evaluate and analyse the dynamic of the perceived opportunity to participate in activities of daily life, because one's health condition, in the studied sample.

3. To evaluate and analyse the dynamic of physical functional parameters: exercise capacity with walking distance and desaturation during the six-minute walk test, and inspiratory muscle strength with submaximal inspiratory pressure test, in the sample studied.
4. To evaluate and analyse the dynamic of perceived self-efficacy in the sample studied.
5. To evaluate and analyse the dynamic of daily physical activity, based on accelerometery data from seven consecutive days, in the sample studied.
6. To evaluate and analyse the dynamic of perceived sleep quality in the studied sample.

Hypotheses of the Thesis

The comprehensive home-based and remotely supervised physiotherapy programme within the interdisciplinary treatment approach in patients with PAH improves physical functions, perceived self-efficacy, and encourages the creation of healthy daily habits, thus allowing one to improve and maintain the perceived opportunity to participate in everyday life as one wants to in the context of one's health condition.

Novelty of the Thesis

This study appears to be the first to develop and investigate a comprehensive structured physiotherapy programme, which is expected to be implemented in an interdisciplinary treatment approach in patients with PAH in Latvia.

The novelty of the prepared programme is its integration into the daily life of the patient, providing an opportunity to adapt it to the needs and contextual factors of every patient. At the same time, the implementation of a home-based and remotely supervised physiotherapy programme is still a novelty in the target population, because only in the latest publications there are data on the applicability and initial research of such interventions. Meanwhile, in the context of Latvia, remotely supervised structured physiotherapy programmes have not been implemented or studied so far.

The novelty of this study in the context of the target population appears in the follow-up assessment three months after the end of the intervention to evaluate long-term benefits of the applied comprehensive intervention.

The novelty of the Thesis obviously shows in the approach used in the study to assess the quality of life of patients with PAH, including the perceived opportunity to live as one wants to in the context of one's health condition, thus opening opportunities to shed more light on the perspective of the patient on one's life with a rare, chronic, and life-threatening disease. Patients' perceived opportunity to participate in everyday life as an outcome measurement has not been used in the research studies of the target group so far, at the same time the selection made justified itself, allowing to approve benefits of the applied intervention, by stimulating the patient to use both internal and external resources, thus developing an optimal adaptation.

Structure of Doctoral Thesis

The Doctoral Thesis is written in Latvian and includes four main chapters: a review of the literature, methods, results, and discussion, along with conclusions and practical proposals. The Thesis consists of 122 pages, including 10 tables, 15 images, and three annexes. The work includes a bibliography of

219 sources referenced in this paper. The work presented here was carried out during the author's time as a *PhD* student. The author is aware and understands the university's plagiarism policy and certifies that this Thesis is her own work, except where indicated by referencing.

1 Material and Methods

1.1 Study design and procedure

The experimental design referred to as prospective, randomized, controlled trial was used. A diagram of the sequenced study procedure is presented in Figure 1.1.

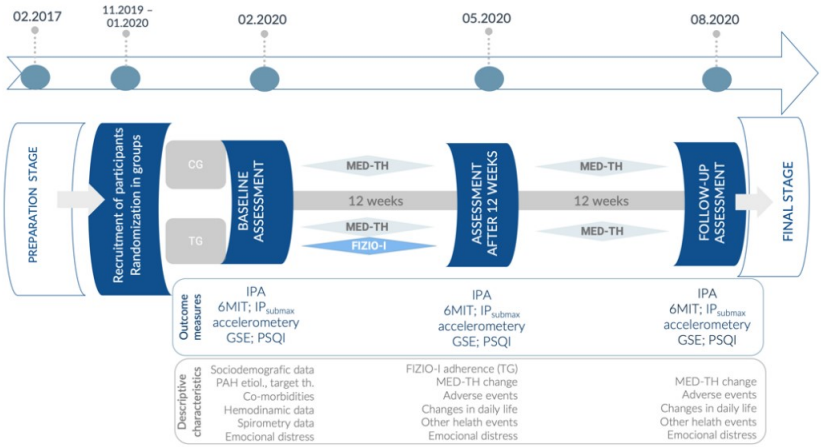

Figure 1.1 **Study procedure diagram**

Preparation stage

In the beginning of this stage, the review of the literature on previous studies was performed and the summary of the conclusion of previous evidence was carried out, giving a basis for the development of the initial intervention methodology, which was verified in a pilot study within the author's master thesis. The results of this pilot study were reported in conferences and a manuscript was prepared, submitted, and published (see section Publications). The presentation of the results and conclusions of the pilot study promoted discussions and exchange of ideas between other researchers and clinicians. The insights gained from the discussions along with up-to-date research findings on

effectiveness, potential benefits and effects of physiotherapy methods allowed improving and complementing the initial methodology, thus allowing the development of the innovative physiotherapy programme (abbreviation FIZIO-I) according to the first task of the dissertation (see detailed description in Chapter 1.3).

At the same time, during the preparation stage, patients self-reported outcome measure questionnaires were chosen and prepared for use. The translation from English to Latvian language and initial verification of a translation obtained was performed, as well as the reliability of Latvian translation was tested in a target population (see Chapter 1.4.1.1). Also, the reliability of available GSE and PSQI Latvian translations was tested in the target population (see Chapter 1.4.1.2).

Simultaneously, the protocol for assessment and evaluation of daily physical activities by combination of accelerometery from seven consecutive days and diary monitoring data was prepared (see Chapter 1.4.1.2). The initial approbation of this protocol was done based on the University initiative of the vertical integration of research by engaging and supervising two students from the RSU Physiotherapy programme within their bachelor thesis projects. The results of this approbation study were reported at the conference (see Publications).

The recruitment of participants and data collection

A detailed description of the recruitment process and the selection of participants, based on the criteria applied in the study, is given in Chapter 1.2. All participants were recruited from the Latvian PH registry in a period from November 2019 to January 2020, at the end of which the study sample was created and all participants were assigned to TG or CG according to a simple randomization principle. Data collection was started in February 2020 when the

baseline assessment was carried out for all participants. Subsequently, FIZIO-I was started for TG participants, but both groups continued with MED-TH. Repeated assessments were performed after 12 weeks in May 2020 and at follow-up after 24 weeks from the start in August 2020. In each assessment, all outcome measures were used, and data collected, in addition, data on descriptive characteristics were collected, as seen in Figure 1 and detailed description is given in Chapter 1.4.1 and Chapter 1.4.2. All three assessments were performed by an independent assessor ("blinded") during the on-site visit at Paula Stradins Clinical University Hospital with prior agreement on time with the participant. The assessment was started by asking each participant to complete all three self-reported questionnaires (IPA, GSE, PSQI), followed by performing the IP_{submax} test, and subsequently 6MIT was carried out. Additionally, at the end of on-site assessment, an accelerometer sensor was attached and installed to record seven consecutive days, agreement was found on removal and return management of the sensor with each participant. Data obtained in each assessment were recorded in a protocol of each participant, but accelerometer data was collected in the database of the accelerometry software. At the final stage, all data were summarized in the MS Excel computer programme. Accelerometer data initially were processed and analysed in the *IDEEQ software*, which was then converted to MS Excel. After summarizing, data were analysed with mathematical statistics methods, using IBM SPSS Statistics (v.23.0) and G-Power software (see detailed description in Chapter 1.5).

Simultaneously with data collection, a provisional analysis of preliminary data was performed and prepared, submitted, and published article. At the final stage after completing the data analysis, a manuscript on the main findings (primary outcomes and part of secondary outcomes) was prepared, submitted, and published. An additional manuscript with a more detailed focus on two

secondary outcomes - daily physical activity and exercise capacity, was prepared, submitted, and accepted for publication (see Publications).

Ethical Considerations

The study was carried out in accordance with ethical principles in accordance with the Declaration of Helsinki, the Code of Ethics for Science, and other regulatory documents. Throughout the entire research process and thesis development, an ethical action was implemented against both the participants and other involved persons. Respect for any human being, the values of every person and respect for free choice formed the basis of ethical conduct. The research objective was never placed above the interests and rights of the individual participant or other stakeholders. Confidentiality was ensured during both data collection and during the processing and dissemination of the results. At all stages of the development of the study, the protection of personal data was ensured, in accordance with the Personal Data Processing Law and the General Data Protection Regulation. Potential participants were engaged based on voluntary and informed consent. Informed consent from all eligible patients was obtained and signed prior to their participation. The study was approved by the Institutional Ethics Committee of Rīga Stradiņš University (protocol code: 3/08.09.2018, date of approval: 8 September 2018).

1.2 Study population

Patients with PAH were included in the study from the Latvian PH registry, according to the study inclusion criteria: the patient has a confirmed diagnosis of PAH based on right heart catheterization, corresponds to pulmonary hypertension functional class, according to World Health Organization: WHO-FC II or III, age $\geq$ 18 years, clinically stable and on optimized medical target therapy for at least 3 months prior to entering the study. As the exclusion

criteria were applied: non-compliance with any of the above inclusion criteria, during the study, the failure to attend the intended evaluation at one site during the study, refusal to participate.

Before the recruitment of participants, the current Latvian PH registry was reviewed in November/December 2019 to select patients with PH Group 1 (PAH) approved by right heart catheterization. The recruitment of potential participants was carried out in two phases. In the first phase, the registry data was screened and the initial evaluation by the cardiologist involved in the study was carried out, based on which communication with potential participants began. In the second phase, an on-site visit and evaluation with the cardiologist involved in the study was carried out, to assess the current clinical condition of the potential participant. At the same time, at this stage, potential participants who corresponded and agreed to participate in the study received and signed informed consent, thus becoming participants. The flow chart of the recruitment of participants and the study sample are shown in Figure 2.1 (See Chapter 2.1).

1.3 The intervention (FIZIO-I)

The development of the FIZIO-I analysed in the study of the Doctoral Thesis was based on the needs of the target group, previous evidence of the effectiveness of physiotherapy methods or potential benefits/mechanisms of action, as well as taking into account the insights gained from the pilot study (Butane et al., 2019), which examined the usability, safety and results of the initially created programme in the target group, which was already mentioned in the previous chapter (see Chapter 1.1).

The following *underlying principles* were included in the formation and realisation of the FIZIO-I within an interdisciplinary treatment approach:

1. The dynamic cooperation between the cardiologist, physiotherapist, patient, and his family are essential for realisation of FIZIO-I.
2. FIZIO-I can be initiated and safely performed if the patient with PAH receives an optimized MED-TH.
3. PHYSIO-I supervision is provided by a physiotherapist specializing in PAH.
4. The intervention can be adaptable to the needs and contextual factors of each patient.

PHYSIO-I is a comprehensive intervention and includes four basic elements consisting of several components, which are illustrated in Figure 1.2.

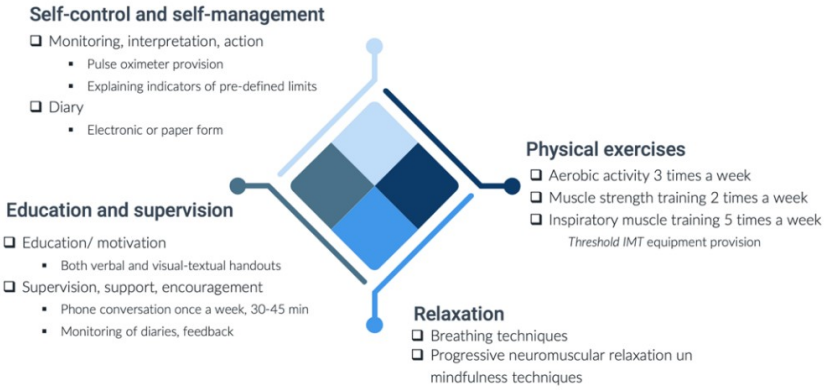

Figure 1.2 **FIZIO-I basic elements and its components**

1.3.1 Physical exercises

Based on current evidence of the effectiveness of complex exercise programmes in patients with PAH (Waller et al., 2020), it was chosen to use three basic types of exercises: aerobic activity, muscle strength, and breathing training.

As an essential principle, an approach was established that all exercises should be incorporated as much as possible into the daily rhythm of life of each patient, thus improving adherence to the programme and promoting long-term exercise performance and contributing to behavioural change. The exercise programme in FIZIO-I was developed specifically for patients with PAH who receive stable MED-TH. Both physical functional state and abilities, possibilities, and needs were considered in the choice of exercises, together with the fact that the exercise programme was entirely home-based with close self-control and telehealth elements, and the latest research evidence (Babu et al., 2019; Brown et al., 2018), including the pilot study of the Thesis author (Butane et al., 2019), has confirmed sufficient safety of home-based exercise programmes in the target group.

The exercises were adapted individually and clearly explained for each patient. The physical exercise programme in PHYSIO-I included three training modalities, and in the following the characteristics of each component will be described.

Aerobic activities (exercises)

Rationale: In previous studies, particularly aerobic activities (exercises) have been the most studied physical exercises in patients with PAH and have been shown to be effective not only in improving exercise capacity and quality of life, but also in improving hemodynamic characteristics and function of the right ventricle (Waller et al., 2020; Zeng et al., 2020).

Type: The type of aerobic activity was chosen based on the capabilities of each patient and those he liked, but as a prerequisite it was to correspond to the possibility of providing aerobic training, that is, cyclic activity that involves large muscle groups, but is not a load on both the upper and lower extremities at the same time. It was recommended to choose an outdoor activity if possible.

Examples include dosed walking, stationary exercise bike, marching in place near an open window.

Intensity: In studies described in the literature, the intensity of aerobic activities in patients with PAH is most often used between 50 and 85 % of the maximum aerobic capacity (VO_2max), performed in periods of 30 to 60 minutes 3–7 days a week (Arena, 2011; Zeng et al., 2020). Considering that the exercise programme in FIZIO-I is designed to be performed entirely at home (with self-control and telehealth elements), but in most studies described in the literature, exercise programmes are fully or partially performed under direct supervision mainly at hospital facilities with a basic instrument for dosing aerobic load using HR 50–85 % of VO_2max (Babu et al., 2016), it was chosen to use a lower intensity of aerobic activities. Already, the results of the pilot study (Butane et al., 2019) showed that the use of relatively lower intensity aerobic activities could not only provide additional safety, but also obtain an equivalent increase in exercise capacity: in the pilot study mentioned above (Butane et al., 2019), the increase in the 6MIT distance was 60 m, which is comparable to the results of the systematic review done in year 2016 (Babu et al., 2016) on increase of 17 – 96 m after hospital-based exercise programmes with a higher intensity applied . Thus, there was a basis for the hypothesis that aerobic activity at relatively lower intensity also improves exercise capacity in patients with PAH.

Given that the results of the same pilot study (Butane et al., 2019) approved the manifestation of reduced chronotropic response during 6MIT as a characteristic feature in the studied patients with PAH, with simultaneous provocation of desaturation, a combined approach was used for the prescription and monitoring of intensity of aerobic activity.

a. As primary measure for intensity, SpO2 was established: during exercise, it should not decrease by more than 5 % of the initial level at rest or reach 85 % or lower.

b. As the second measure, the perceived exertion (effort) was evaluated on the 10-point Borg scale: “weak effort to moderately low effort" (4 to 5 points) as the basic target intensity, along with short time intervals with "remarkable effort to hard" (6 to 7 points) (e.g. if the total duration of the activity is 30 minutes (effort 4 to 5 Borg scale points), then it includes two intervals with periods of five (seven) minutes, in which the effort is 6 to 7 points of the Borg scale).

c. As a third measure for intensity HR was used, which could be applied by fulfilling the first two conditions mentioned above. Most often, HR was possible to apply for intensity prescription and monitoring after the fourth week of PHYSIO-I. Given that there was a reduced chronotropic response, in intensity prescription the target HR was calculated as an increase in 20 beats per minute from a rest HR obtained at the beginning of 6MIT and if there is a recovery of HR within 5 minutes after cessation of activity and the maximum HR during activity does not exceed 120 beats per minute (De Man et al., 2009; Mereles et al., 2006; Zeng et al., 2020).

d. In addition to participants who demonstrated an inadequate response in arterial blood pressure during 6MIT, measures of blood pressure were included in the prescription and monitoring of the intensity of aerobic activities, determining individual target indicators.

In the developed exercise programme included in FIZIO-I, aerobic activities were scheduled 3 times a week, at least 30 minutes period, which could be divided into two bouts (for example 15 minutes in the morning, and 15 minutes in the afternoon).

Progression: The first increase in the intensity of aerobic activity was prescribed after four weeks during on-site consultation for the adjustment considering the results of the re-evaluated 6MWT and the analysis of the diaries

(monitored data during activity and recovery period: HR, SpO_2, perceived exertion (effort) and subjective symptoms of exercise intolerance, overall subjective feeling, BP if indicated). In cases where no desaturation, inadequate response of HR or BP, or provocation of the threshold symptoms (see the detailed description of self-control in Chapter 1.3.3) were detected, the intensity of aerobic activity was augmented by increase of total time of activity accomplishment in the day of performance and / or increasing number of repetitions for short time intervals with a higher intensity. The next increase in intensity could occur every four weeks, based on the data from the diaries as mentioned above. In cases where HR was also used as an intensity measure, progression could also be made by increasing the target HR by another 10 beats per minute, but not exceeding 120 beats per minute, and maintaining adequate recovery within 5 minutes after cessation of activity.

Muscle strength training

Rationale: In previous studies, aerobic exercise is commonly applied along with muscle strength training, since this combination significantly improves exercise capacity with better results in the 6MWT distance and VO_{2max} in patients with PAH (Waller et al., 2020). In studies, muscle strength training is performed most often 2 to 3 times a week, including 8 to 10 exercises, with 10 to 15 repetitions and one set for each exercise, alternately for the upper and lower extremities (Arena, 2011; Grünig et al., 2019).

Type: In the FIZIO-I exercise programme, muscle strength exercises for the upper and lower extremities were included, which at the beginning of the programme were scheduled on separate days, making a total of two performance days a week, an average of five exercises per day. Before each exercise session, it was intended to perform two to three warm-up exercises, to prepare the body for the load, to sense and take the correct posture for the exercise performance.

Sitting on the table and standing postures were used for exercise performance, bilateral movements were not included, and free breathing and optimal position of the proximal segments were emphasized during execution. In exercises for the upper extremities, diagonal movements were emphasized that involved muscles' synergies and promoted the facilitation of extensors, along with extension of the thoracic spine and scapular retraction. In exercises for the lower extremities, activation and strengthening of *m. quadriceps femoris, m. gluteus max, m. triceps surae* were accentuated. In the execution of the exercises, carrying of a slow and smooth movement was emphasized both moving against gravity (for concentric muscle work), holding the end position (for isometric muscle work), and returning to the starting position (for eccentric muscle work), thus allowing one to achieve maximum muscles' activation.

Progression: Initially, the exercises were performed using own body weight, so the resistance was made by gravitational force, while the progression was carried out by increasing the number of repetitions (up to 10 times) and the duration of holding the end position (up to 5 seconds). The second step of progression was carried out after four weeks, when the type of exercise was changed, increasing its degree of difficulty, if maximum progression was achieved using own body weight, then additional weights were added using dumbbells or water bottles (0.5 - 1 kg), and the progression mentioned above increased the number of repetitions and the duration of hold, respectively. The third step of progression was applied in cases where maximum progression was achieved in the two above-mentioned steps, then in this step in a one-day training session both exercises for the upper and lower extremities were included, maintaining two days of training per week.

Inspiratory muscle training

Rationale: The results of studies described in the literature approve evidence on the benefits of adding inspiratory muscle training to combined physical exercise programmes (Waller et al., 2020).

Type: A breathing training device PHILIPS Threshold IMT (manufactured by Philips Respironics, USA; device was provided for each TG participant) was used, which provides consistent resistance for inhalation, regardless of how quickly or slowly one breath is taken and allows one to set an individually adjustable specific pressure (cm H_2O), thus allowing for controlled training within a target resistance. Device graduation: 9–41 cmH_2O. The submaximal strength (IP_{submax}) of the inspiratory muscles was assessed prior to training (see Chapter 1.4.2). Training was scheduled five times a week, with a target intensity measured by both the amount of resistance and the number of repetitions. Remarks on a correct body position during training performance were emphasized, that is, a sitting position with relaxed shoulders, slight extension of the thoracic spine and slight scapular retraction, neutral position of the cervical spine and head. The correct use of the device was also taught.

Progression: Initially, based on the baseline assessment, a target resistance 30 % of IP_{submax} was applied and three breaths in three sets with a one-minute pause between (3 × 3) were prescribed. The number of sets gradually increased to seven, reaching three breaths in seven sets (3 × 7), when the target resistance increased by five cmH_2O. With this resistance, the number of sets gradually increased, respectively, followed by a corresponding increase in resistance, overall progressing to 65–70 % of IP_{submax}.

All physical exercises included in FIZIO-I were taught by the physiotherapist at the on-site consultation at the beginning and after four weeks, when the type of exercises was changed. Additionally, each participant received the handout material (paper or online based on preference of participant) with

visual and textual description of all scheduled exercises and individual adjustments to type, intensity, and specific remarks.

For *safety considerations* with respect to physical exercise monitoring and analysis of self-control indicators (SpO2, HR, BP, subjective symptoms) along with screening for levels of two biomarkers BNP and CRP in blood serum were carried out. Self-control indicators and their monitoring and analysis are detailed described in further text (see Chapter 1.3.3 and Chapter 1.3.4). To explain more about the biomarkers analysed as safety indicators, note that both biomarkers were detected in peripheral blood serum at E. Gulbis Laboratory, but the blood sample was taken by a nurse at Pauls Stradins Clinical University Hospital, at the beginning and after completion of FIZIO-I (12 weeks). Absolute values of both biomarkers were analysed relative to the high-risk reference level (BNP > 300 ng/l; high-sensitivity CRP > 5 mg/l) and a significant increase in these indicators, which could indicate inadequate exercise intensity applied, as well as disease progression (Gali e et al., 2016; Quarck et al., 2009; Waller et al., 2020).

1.3.2 Relaxation

Rationale: The 2019 ERS Working Group Report on Physical Exercise for PH Patients additionally updates the usefulness and additional benefits of relaxation techniques (Grünig et al., 2019). Recent studies have shown the effectiveness of relaxation techniques based on the concepts of body awareness and mindfulness to improve the individual's ability to sense themselves, their own possibilities and boundaries, and to consciously control breathing, tension, thus reducing the feeling of anxiety and improving the breathing pattern, in general increasing the sense of control over the situation (Courtois, Cools, & Calsius, 2015; Hopper et al., 2019; Klainin-Yobas et al., 2015; Li et al., 2019).

Breathing techniques

As the first of the breathing techniques included in FIZIO-I was *diaphragmatic breathing*, the execution of which emphasized the lateral expansion of the lower part of the chest during inhalation, which could be facilitated by manual contact, while maintaining relaxed shoulders and not involving accessory inspiratory muscles. Initially, diaphragmatic breathing was recommended to be conducted in the sitting or lying position, but by improving understanding and skills, in standing and during movements. Furthermore, the diaphragmatic breathing technique was included and taught as part of an action strategy based on predefined limits as a self-management tool to restore the optimal breathing pattern and reduce overactivity of the sympathetic nervous system.

As a second of the breathing techniques included in FIZIO-I was *purse-lip breathing*, the execution of which requires slow controlled breath that produces inhalation through the nose and exhalation through the mouth with lips having a pursed appearance, thus creating a small amount of positive end-expiratory pressure and the exhalation is prolonged when compared to the inhalation to exhalation ratio in normal breathing. The purse-lip breathing technique was included and taught as part of the action strategy to control the symptoms of dyspnoea. Such a breathing technique can relieve shortness of breath by restoring breathing pattern and improving the efficiency of breathing, as well as it can promote regain a sense of control over one's breathing and increasing relaxation (Vatwani, 2019).

As the third type of breathing technique was *breathing awareness and voluntary control*, which initially was focused on sense and observe the flow of the breath, recognize the own breathing stereotype in different situations, and gradually progressed to voluntary control, such as control of the inhalation to exhalation ratio in the breathing pattern, for example, lengthening of the

exhalation, control of respiratory movements that improve the expansion in the lower part of the chest during inhalation while relaxing the shoulder region. This breathing technique was combined with other methods of body awareness and was performed at the beginning of the progressive neuromuscular relaxation session.

Progressive neuromuscular relaxation and mindfulness techniques

Progressive neuromuscular relaxation was based on the Jacobson relaxation technique (Jacobson, 1987). It is an actively engaging relaxation technique which requires contracting muscles to create tension, sense this tension, and then releasing this, sense of this release, and gradual involvement of individual muscle or muscle groups is carried out. A starting body position for progressive neuromuscular relaxation was recommended and an individually adjusted supine or side-lying, or maximally supported sitting posture was chosen, focusing on relaxed and supported shoulders, thoracal spine and upper body positioned above the level of heart.

In addition, the conscious sensation of the body's support points in the starting position was taught and scheduled to use both before progressive neuromuscular relaxation and as a separate technique (for example, incorporating in the physical exercise programme, daily activities).

Relaxation was scheduled five times per week, but gradually, as the performance skills of the techniques improved, certain elements of them could also be carried out daily according to individual feeling to reduce anxiety and regain internal balance. Furthermore, as mentioned above, breathing techniques were practiced and utilized as self-management tools. All relaxation techniques included in FIZIO-I were taught by the physiotherapist at the on-site consultation, and additionally, each participant received the handout material

(paper or online based on the preference of the participant) with a visual and textual description and individual remarks.

1.3.3 Self-control and self-management

Monitoring, interpretation, action

Rationale: One of the prerequisites to ensure clinical safety of a home-based physical exercise programme is adequate self-control skills (Butane et al., 2019; Waller et al., 2020). At the same time, self-control skills together with an appropriate action strategy allow optimal self-management of a chronic disease to be achieved, contributing to better overall treatment outcomes and long-term prognosis (Graarup, Ferrari & Howard, 2016; Ivarsson et al., 2018; Riegel et al., 2021).

Type: To acquire and develop skills of self-control and self-management, knowledge and comprehension of what, how, and why to do, as well as the skills to act, are essential and was considered when planning the elements in this FIZIO-I component.

a. As self-control indicators or measurements were explained and taught to perform, the following were included: HR and SpO_2 using a pulse oximeter; evaluation of the subjective sense of effort based on the Borg scale; recognition of subjective symptoms; and in isolated cases BP measurement was included in self-control, using an electronic automatic arm sphygmomanometer. For each participant in the TG, a *Beurer PO 60 pulse oximeter* (manufactured by Beurer, Germany) was provided.
b. To facilitate the ability to interpret the results of self-control measurements and to promote the acquisition of an appropriate action strategy, indicators of two limits were defined and explained: 'warning', which indicated the need to reduce the intensity of activity

or postpone its commencement; ‘alarm or threshold', which indicated the immediate need to stop activity. The choice of indicators in both limits was based on previous studies (Arena, 2011; Butane et al., 2019; Grünig et al., 2019; Waller et al., 2020; Zeng et al., 2020). As an activity was defined, both the physical exercises included in PHYSIO-I and any other daily activity. For each defined limit, recommendations on appropriate action were explained and taught.

Diary

One of the most used self-management interventions for patients with chronic diseases is the use of diaries or their principles (Riegel et al., 2021). FIZIO-I included completion of the diary, recording self-control data, such as: HR, SpO_2, perceived exertion on Borg scale, symptoms, performance of intended physical exercises and relaxation elements or reasons for non-performance, and comments on everyday life and wellbeing. Diaries were created for each week, providing the possibility of choosing the form of a paper or electronic online document diary.

1.3.4 Education and supervision

Education / motivation

Rationale: As mentioned above, education of patients is a prerequisite to acquire and develop self-control and self-management skills, as well as reduces anxiety and insecurity, promotes health behaviours, and improves adherence to the overall treatment process, thus allowing optimal treatment outcomes to be achieved (Rawlings et al., 2020; Riegel et al., 2021).

Types: The education in PHYSIO-I was carried out in both verbal and visually textual form. The physiotherapist began a patient education already during the first one-site consultation and continued in every communication with a patient, both in each weekly phone conversation and in the other two one-site consultations intended in FIZIO-I. In verbal education, attention was equally focused on providing information and on the way of communication, applying an empathetic and supportive approach. Educational content consisted of improving general knowledge of PAH and its treatment and explaining the effects and action of the interventions included in PHYSIO-I. Additionally, education on secondary prevention and health promotion in general was included and based on the specific needs of the individual patient additional explanations could also be included. The patient's personal and contextual factors were considered in the education to promote the understanding of information, the attribution to oneself, and thus the use of knowledge.

The educational content in FIZIO-I was created in cooperation with the patients' representatives from Pulmonary Hypertension Society of Latvia to better understand the specific needs of the patients, as well as, as far as possible, members of the association were involved in peer-support of the study participants. As mentioned above, in addition to verbal education, an informative booklet was created, which included both an explanation of the specific elements of PHYSIO-I and other information aimed at encouraging and supporting the patient's health behaviours and self-management, which could ground for an optimal life with a chronic disease, allowing to accomplish own goals of life.

Supervision, support, encouragement

Rationale: For the implementation of safe physical exercise interventions in patients with PAH, a prerequisite is stable targeted therapy and ensuring optimal monitoring and supervision (Waller et al., 2020). Support and

encouragement of healthcare professionals is essential for patients with chronic disease, which is also noted by patients with PAH, pointing to changing needs and challenges during treatment (Rawlings et al., 2020).

Types: FIZIO-I included a weekly *phone conversation* between the physiotherapist and the patient, with a time set in advance and a duration of an average of 30–45 minutes. The aim of this weekly communication included both supervision and support and encouragement. Conduct supervision conversation included topics on the execution of FIZIO-I during the week, self-control indicators, other events, ambiguous questions, and / or concerns about execution of the programme. To support and encourage conversation included feedback on each individual's achievements, such as the ability to fit into the optimal intensity or the quality of performing individual exercises, active listening to everyday events, worries and what is important for each patient, and support in making a decision on solving various problem situations, for example, in relation to a health condition that requires consultation with the cardiologist on the use of additional medications, or in relation to social issues, including recommending communication with the patient association or social worker.

Additional supervision was ensured by the analysis of the completed patient *diaries*. In cases an electronic diary form was used, monitoring and analysis was done online. In cases a paper form was used, the participant had to take a photo of the completed form and send as image to the physiotherapist by phone or email, respectively. Therefore, the physiotherapist was able to analyse the data to monitor the safety of the programme performance and provide feedback on the dynamics of the individual monitored data, both within one day and in a weekly perspective, as well as seeing progress after four weeks or more, which could further serve as a basis for increasing the intensity of physical exercise.

The patients were provided an opportunity to communicate with the physiotherapist in an online diary or in the form of phone text messages between scheduled phone conversations, if necessary.

The total duration of FIZIO-I was 12 weeks, it was entirely home-based with elements of telehealth, such as, phone conversations and analysis of diaries, and included three individual on-site consultations with the physiotherapist at a clinic – the first was conducted at the beginning with the aim of individually adapting the programme, preparation, and training to use equipment, explaining and teaching the elements of FIZIO-I. A second on-site consultation was conducted four weeks after starting the programme with the aim of adjusting the programme, to maximize clinical safety and qualitative performance. The third consultation was held at the end of 12 weeks with the aim of providing an individualized plan of further recommendations on secondary prevention and promotion of health behaviours and continuation of the use of acquired self-control and self-management skills.

1.4 Assessment Methods

1.4.1 Primary outcome

The perceived opportunity to participate in activities of daily life in the context of one's health condition was set as the primary outcome of this study on the interdisciplinary treatment approach adding FIZIO-I to MED-TH, allowing to describe the unique individual perspective of quality of life in patients with PAH.

Several validated questionnaires are available to assess subjective participation experience (Martin Ginis et al., 2017), one of these instruments is the Impact on Participation and Autonomy Questionnaire (IPA), which was chosen and used in this study. IPA was created in the Netherlands and includes the concept of decisional autonomy as an integral component of participation,

describing the perceived opportunity to live life as one wants in the context of one's health condition or disability (Cardol et al., 1999; Cardol et al., 2002). With permission from the authors of the original Dutch version, the English version of the IPA questionnaire in Latvian was translated following the guidelines for cross-cultural adaptation of self-report measures (Beaton et al., 2000). The initial translation version was reviewed by two patients with PH fluent in both Latvian and English, and minor adjustments were made to the wording of the individual statements. In the pilot study in a sample of patients with cardiopulmonary disease, high internal consistency was approved for all IPA subscales with Cronbach's alpha ranging from 0.85 to 0.94: excellent ($\alpha \geq 0.9$) internal consistency was reported in the subscales: AO (0.92) and WE (0.94), but good ($0.9 > \alpha \geq 0.8$) on other subscales: AI (0.85), FR (0.86), and SL (0.85).

The 32 items assess perceived participation on five subscales:

- *Autonomy indoors* (AI) includes the chances of taking care of yourself, the way one wants (washing, dressing, eating, etc.), getting around the house when and where one wants.
- *Family role* (FR) includes the role, tasks and responsibilities within the family, performing tasks around the house and the garden, using money.
- *Autonomy outdoors* (AO) includes items about frequency of social contacts, possibilities to spend leisure time and get around outdoors when and where one wants, leading the life one wants.
- *Social life and relationships* (SL) include quality of social life, relationships, communication, respect, intimacy, helping and supporting other people.
- *Work and education* (WE) include items about paid and voluntary work, education and training.

All items have five possible answers (very good, good, fair, poor, and very poor), indicating chance of participating when and how one wants. Nine additional items assess perceived problems caused by limitations in participation and are intended to facilitate clinical decision-making, and therefore were not included in the analysis. The IPA results were calculated and incorporated into the analysis in two ways. The median score for each subscale was calculated, based on the IPA manual to the English version (Kersten, 2007). Based on the manual mentioned, the subscale score can be calculated if at least 75 % of the statements are answered. To identify and analyse the perceived chance to participate in each particular activity represented in the individual statement, the total raw score was calculated and converted to the transform score (expressed in percentage) (i. e., converting the sum of absolute points into percentages, taking into account the maximum value and the total range of the row of interval numbers), where a higher score presents less chance to participate in everyday life due to health problems.

1.4.2 Secondary outcomes

Exercise capacity

To assess exercise capacity, a six-minute walk test (6MWT) was performed. The six-minute walk test (6MWT) is a submaximal exercise test, widely used to assess exercise capacity in patients with heart failure and pulmonary hypertension and is also recommended for risk stratification and follow-up evaluations (Demir & Küçükoğlu, 2015; Waller et al., 2020; Zelniker et al., 2018). 6MWT was performed according to the guidelines of the *American Thoracic Society* (ATS, 2002), with SpO_2, heart rate, and blood pressure monitoring. The distance (m) covered during the test was recorded and included in the data analysis. As minimal clinically significant difference (> 33m) was determined based on previous studies in patients with PAH (Mathai et al., 2012;

Seo et al., 2021). Additionally, data on SpO2 (%), that is, score at rest and minimum score during the test, were recorded and maximal reduction during the test was detected in relation to resting SpO2 (%) (desaturation) and included in the analysis. Clinically significant desaturation was determined during 6MWT based on the threshold level of decrease of 3 or more SpO_2 % from baseline (resting) level or to 88 % (Agarwala & Salzman, 2020; Gupta, Ruppel, & Espiritu, 2020).

Inspiratory muscles strength

To assess strength of inspiratory muscles, a submaximal static inspiratory mouth pressure ($IP_{submax)}$ test was used. Measurement of maximum static inspiratory mouth pressure assesses global respiratory muscle strength and is widely used in a clinical setting and studies on the effectiveness of respiratory training, is closely related to exertional dyspnoea, and is responsive to assess changes within subjects (Laveneziana et al., 2019). IP_{submax} was performed using a PHILIPS Threshold IMT device (see details above Chapter1.3.1) The patient sits upright, puts a special nose clip on, covers the mouthpiece of the device with his mouth, and is asked to perform an uninterrupted maximal deep inhalation through the mouth. Three attempts were made, and the best result of the pressure reached (cmH_2O) was recorded. Inspiratory pressure was measured at the lung volume in which the patients breathe tidally, so it was treated as submaximal inspiration pressure. The device used had an upper limit of 41 cmH_2O; nevertheless, it was optimal, as all participants had relatively low scores at the beginning of the study and only part of the TG participants reached the upper limit in repeated assessments.

Self-Efficacy

To assess perceived self-efficacy, the General Self-Efficacy Scale (GSE) was used, which is a self-reported questionnaire aimed at evaluating coping with daily problems and adaptation after experiencing all kinds of stressful life events. GSE was created on perceived self-efficacy as an operational construct related to subsequent behaviour and, therefore, is relevant for clinical practice and behaviour change (Schwarzer & Jerusalem, 1995). GSE is one of the three most commonly used measures of overall self-efficacy in clinical trials (Whitehall et al., 2021). Latvian translation (Buliņa, 2009) was used; its reliability was tested in the pilot study in a sample of patients with cardiopulmonary disease and high internal consistency (Cronbach's alpha 0.93) and the test-retest correlation (R = 0.94) was approved. The GSE includes 10 statements with responses on a four-point scale. The total score was calculated and converted to the transform score (%) (like above mentioned in the IPA), where a higher score presents a higher sense of self-efficacy.

Daily physical activity

To evaluate daily physical activity, the accelerometry measurement was chosen, which is gaining ever wider popularity in both research and clinical work, developing an opportunity to objectively assess physical activity in the daily lives of people (Bashshur et al., 2014; Migueles et al., 2017; Sehgal, Small & Highland, 2019) and to evaluate prevention and health promotion goals in different target populations, accelerometry is increasingly being used as an outcome measure (Halliday et al., 2018; Mesquita et al., 2017; Rockette-Wagner et al., 2022). In this study 3D accelerometer (motion sensor) MOX (*model MMOXX1.01, Maastricht Instruments BV, The Netherlands*) was used created by the University of Maastricht. The MOX unit includes a three-axis accelerometer sensor (*ADXL362; Analog Devices, Norwood, MA, USA*), and allows continuous

measurement and data storage for a period of up to seven days (Maastricht Instruments, 2022). For sensor configuration and data downloading and processing, the *MOX1 IDEEQ* software was used. MOX, as well as its predecessors CAM and DAAFB, have been approved and tested (Migueles et al., 2017; van der Weegen et al., 2015) and used as an outcome measure in different patient groups (Kenkhuis et al., 2021; Mesquita et al., 2017). The sensor was applied and worn on the thigh, with the recording frequency 25-30 Hz (Migueles et al., 2017). It was worn for seven consecutive days, including during sleep, bathing, or showering. Participants were encouraged to participate in their routine activities while completing the assessment. At completion, the data were downloaded and the daily time in each of the physical activity levels (sedentary, standing, low intensity, moderate intensity, and high intensity activities) was calculated by software considering the registered time unit of acceleration measurement, filter, and sensor position based on validated algorithms (Maastricht Instruments, 2022; Migueles et al., 2017). The absolute time spent at each level of physical activity was expressed as a percentage of the total time spent awake.

Perceived quality of sleep

To assess perceived quality of sleep, the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989) was used, which is a self-reported questionnaire with appropriate psychometric properties, allowing one to assess the quality of sleep and its disorders over the past month, as well as their dynamics (Bush et al., 2012, Chu et al., 2020; Riemann et al., 2017). The Latvian translation of *Mapi Research Trust* was used; its reliability was tested in the pilot study in a sample of patients with cardiopulmonary disease and high internal consistency (Cronbach's alpha 0.8) and the test-retest correlation (R = 0.99) was approved. The PSQI consists of 19 statements. A total score is calculated in the range

of 0 to 21 points, where a higher score indicates a worse quality of sleep. The total score was recorded; a score of more than five points was interpreted as poor sleep quality (Spiesshoefer et al., 2019; Tan et al., 2020).

1.4.3 Secondary outcomes

For the general characteristics of the sample, sociodemographic and clinical data (i. e., PAH aetiology, time since diagnosis confirmation and treatment, co-morbidities) were collected. To describe the cardiopulmonary hemodynamic data of the last right heart catheterization and echocardiography, and current spirometry were compiled. To describe the current emotional state, a screening for anxiety and depressive symptoms was performed. After 12 weeks and at follow-up assessment the data on events since the previous assessment were collected for all participants: change of PAH medical therapy; adverse events, thus as, exacerbation of PAH with or without hospitalization, episode of syncope, death, significant increase in BNP; substantial changes in daily life, i. e., change of place of residence, notable changes in family circumstances (e.g., loss of a loved one, divorce), beginning of new daily activities; other health-related events (e.g., injuries, acute infections, exacerbation of co-morbidity, elective therapeutic interventions). To evaluate adherence in participants from TG after 12 weeks data from diaries and phone conversations about performance of intended elements of the programme were summarized.

1.5 Data analysis

Data were analysed with mathematical statistics methods, which were chosen stepwise, based on recommendations for small groups (Morgan, 2017). In data analysis, the intention-to-treat principle was applied (McCoy, 2017). Data analysis was performed using IBM SPSS Statistics (v. 23.0). For outcome measure scores whose data were continuous (i. e., IPA transform score,

percentage; 6MWT distance, m; $IP_{submax,}$ cmH_2O; accelerometry results, percentage of awake time spent at each level of physical activity; GSE transform score, percentage) at first the normality assumption was verified by probability plots (i. e., analysis of *Quantil-Quantil plots)* recommended for use in small sample sizes (Morgan, 2017; Van Belle et al., 2004). In all measures the normality assumption was justified, with the exception for percentage of time spent in high-intensity activities, and thus for this accelerometry score, nonparametric analysis was chosen (see below). For other measures in the next step, the assumption of equal variance was evaluated by the ratio of the largest and smallest variances. The common recommendation is to assume that the group variances are equal if the ratio of the largest to the smallest variance is ≤ 3, but as in the study the sample sizes were unbalanced, lower cut-off value was chosen, that is, 1.5. Based on this rule of thumb, we concluded that the equal variance assumption is reasonable for 6MWT results, thus the two-sample *t*-test was used to compare the means between TG and CG at all assessments. In turn, the assumption of equal variance was not reasonable for the rest of the data, that is, IP_{submax}, accelerometery, IPA total, GSE results, therefore Welch's extensions to the *t*-test were performed assuming unequal variances (heteroscedastic), respectively (Morgan, 2017). To analyse changes in means within each group between baseline, after 12 weeks and follow-up assessments a paired two-sample *t*-test was performed. Since the IPA median scores for the subscales and the total PSQI score were categorical data, a non-parametric analysis was performed using the Mann-Whitney U test to examine the difference between the groups and the Wilcoxon sign rang test to evaluate changes within the group between assessments. A similar non-parametric analysis was performed for the percentage of high-intensity activities from accelerometry scores. α level 0.05 was chosen; therefore, the results as statistically significant were determined if $p < 0.05$. For repeated measures, the significance values were adjusted using the

Bonferroni correction and set α level 0.025. To measure the effect size for the results of *t*-test, Cohen's d (d) was calculated, and its thresholds were interpreted as a small (0.2), medium (0.5) and large (0.8) effect (Serdar et al., 2021). While to measure the effect size for the results of the Wilcoxon or Mann-Whitney U test, the rank biserial coefficient (rc) the Glass rank biserial coefficient (rg) was performed and its thresholds were interpreted as a small (<0.3), medium (0.3–0.5) and large (> 0.5) effect (> 0.5) (Kerby, 2014). For statistically significant results ($p < 0.05$) *post hoc* statistical power was calculated using the G-Power software, according to the values, and a power of at least 80 % ($1-\beta \geq 0.8$) was assumed as appropriate to control β error (Serdar et al., 2021).

2 Results

2.1 Study population and descriptive characteristics

Twenty-one (21) patients diagnosed with PAH were included and randomly assigned to TG or CG (see Figure 2.1). There were no significant differences in the baseline demographic and clinical characteristics between the groups. Detailed participant characteristics are shown in Table 2.1 (see Annex).

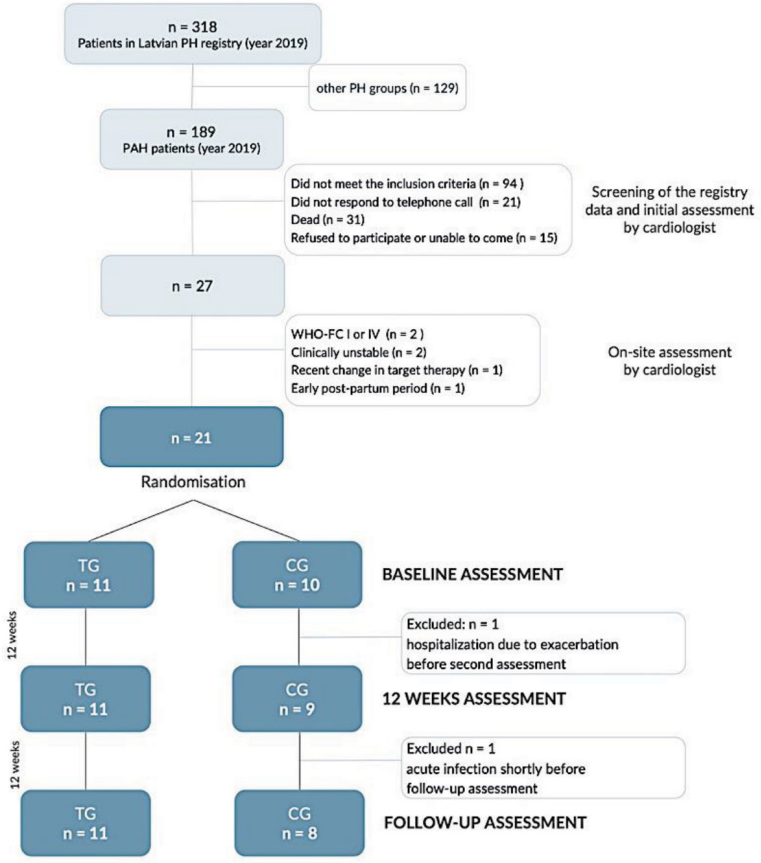

Figure 2.1 **The study participants flow chart**

Abbreviations: TG, training group; CG, control group, PH, pulmonary hypertension; PAH, pulmonary arterial hypertension; WHO-FC; World Health Organization functional class

No predefined adverse events were observed in TG during the 24-week study period. In the CG, a participant had exacerbation of PAH and needed hospitalization.

The MED-TH pathogenetic therapy group was not changed in any of the study participants, however, in four participants: one TG, three CG between evaluation after 12 weeks and follow-up, the dose of the pathogenetic drug used was increased. In most of the participants in both groups, the dose of MED-TH diuretic medication was adjusted as needed during the study period.

All patients in the training group *showed high adherence* throughout the programme, achieving satisfactory performance. Analysis of diary data confirmed that none of the participants had completely interrupted the programme in any of the weeks, but some participants had not fulfilled some elements of the programme (muscle strength or aerobic exercise) on certain days (less than 10 % of the total scheduled days), and the most common reasons were planned outdoor activities (e.g., doctor's appointment) or an exacerbation of comorbidities (e.g., lumbago).

2.2 Primary outcome: participation in everyday life

2.2.1 Results of IPA median scores for each subscale

The IPA median scores were summarized in four of the five IPA subscales. A total of 12 participants (5 from TG, 7 from CG) did not respond to the statements on the WE subscale; therefore, this subscale was excluded from further analysis. The results for each subscale are shown in Figure 2.2 (see Annex). A statistically significant difference between the groups was found in the follow-up assessment in three of the four IPA subscales analysed: AO ($p = 0.01$, $rg = 0.66$, $1\text{-}\beta = 0.95$), FR ($p = 0.04$, $rg = 0.55$, $1\text{-}\beta = 0.8$), and AI ($p = 0.04$, $rg = 0.51$, $1\text{-}\beta = 0.68$) based on median scores, indicating the perceived lower chance of participating in activities of each subscale for

participants in CG compared to participants in TG 24 weeks after the start of the study. In *post hoc* analysis, results of AO and FR approved appropriate statistical power. At the same time, a significant difference between the assessments within the group was approved only for the AO results in CG between the baseline and the follow-up median score ($p = 0.04$, $rc = 0.51$, $1\text{-}\beta = 0.87$).

2.2.2 Results of IPA total transform score

A statistically significant decrease in the total IPA score was approved in TG: from baseline to 12 weeks ($p = 0.005$, $d = 1.1$, $1\text{-}\beta = 0.96$), from baseline to follow-up ($p = 0.004$, $d = 1.1$, $1\text{-}\beta = 0.97$) pointing to improved participation of patients in their everyday life in the context of their health condition. For the indicated changes in *post hoc* analysis, appropriate statistical power was approved. No significant changes in CG were observed. Detailed results see in Figure 2.3 and Table 2.2.

Table 2.2

The IPA total score at baseline, after 12 weeks and follow-up in each group

IPA total score (transform %)	**Baseline M ± SD**	**After 12 weeks M ± SD**	**Change within group p (d)**	**Follow-Up M ± SD**	**Change within group p (d)**
TG	24.4 ± 13.0	20.0 ± 10.7	**0.005 (1.1)***	18.6 ± 10.2	**0.004 (1.1)***
CG	25.6 ± 16.1	30.6 ± 18.0	0.092 (0.6)	31.3 ± 20.2	0.068 (0.8)
Difference between groups p (d)	0.981 (0)	0.148 (0.7)		0.135 (0.8)	

Levels of statistical significance (p values) are shown for between-group difference, based on t-tests result for independent samples performed with Welsch extension, and for change within group, based on paired sample t-tests accordingly. Cohen's d represents effect size of results.

The bold numbers represent $p < 0.05$ or < 0.025 (for repeated measures adjusted with Bonferroni correction)

* Indicates the results for which $p < 0.05$ (0.025) and $1\text{-}\beta \geq 0.8$.

Abbreviations: TG, training group; CG, control group; IPA, Impact on Participation and Autonomy; M, mean; SD, standard deviation.

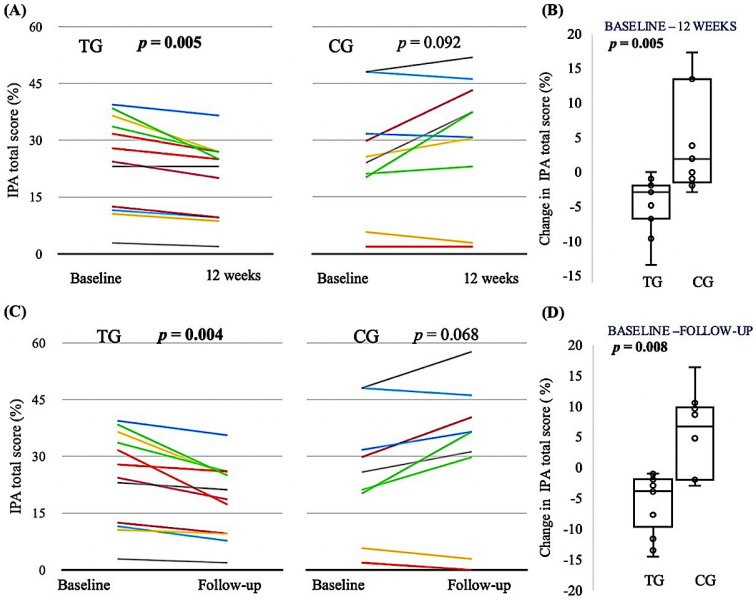

Figure 2.3 **Changes in the IPA total scores between assessments within each group and the difference between groups***

* Charts (A and C) present paired profiles of the IPA total score (transform percentage) in each participant and a statistical significance level (p values) of change between assessments within the group based on paired sample t-test results. Charts (B and D) present box plots for change in each group and a statistical significance level (p values) for difference between groups, based on Mann-Whitney U tests results.
The bold numbers present the results for which $p < 0.05$.
Abbreviations: TG, training group; CG, control group; IPA, Impact on Participation and Autonomy

2.3 Secondary outcomes

2.3.1 Physical functions

Exercise capacity

Only in TG was a statistically significant ($p < 0.001$) increase in the distance of 6MWT confirmed: from baseline to 12 weeks the mean change of 51.8 m (CI: 25.7 to 77.9 m; Cohen's d = 1.7), and from baseline to follow-up the mean change of 75.5 m (CI: 46.1 to 104.8 m; Cohen's d = 2.1). Both mean changes are also rated clinically significant. For the indicated changes in *post hoc* analysis, appropriate statistical power was approved. In contrast, no significant improvements were observed in CG. See Table 2.3 in Annex.

At baseline, 16 (76.2 %) of all participants: 8 TG and 5 CG, showed clinically important desaturation during 6MWT: mean 7.1 ± 2.4 (median 7) TG and 6.2 ± 6.1 (median 3) CG. After 12 weeks, only two participants in TG had desaturation and in both was less severe, and none of the participants demonstrated desaturation at the follow-up evaluation. In the CG, no uniform trend was found for the dynamics of the desaturation characteristics, as for two participants who initially did not demonstrate desaturation, it was shown in the evaluations after 12 weeks and follow-up, while for three participants with initially small desaturation, it was no longer found in the repeated evaluations.

Inspiratory muscle strength

Only in TG was a statistically significant ($p < 0.001$) increase in the IP_{submax} confirmed: from baseline to 12 weeks the mean change of 9.8 cm H_2O (CI: 6.9 to 12.7 cmH_2O; Cohen's d = 2.2), and from baseline to follow-up the mean change of 10.5 cmH_2O (CI: 7.6 to 13.5 cmH_2O; Cohen's d = 2.4), and in *post hoc* analysis, appropriate statistical power was approved for both. On the contrary, a statistically significant decrease from baseline to follow-up

assessment was observed in CG ($p = 0.01$; $d = 0.8$), however this result did not reach the appropriate statistical power ($1-\beta = 0.48$). See Table 2.3 (see Annex).

2.3.2 Self-efficacy

Only in TG was a statistically significant ($p = 0.004$) increase in the GSE score confirmed from baseline to 12 weeks: the mean change of 9.4 % (CI: 3.7 to 15.0 %; Cohen's $d = 1.04$), and in *post hoc* analysis, the appropriate statistical power was approved. No improvement was observed in CG. Both after 12 weeks and at follow-up, statistically significant differences between the groups were observed, although the results did not reach the appropriate statistical power: $1-\beta = 0.72$ and $1-\beta = 0.59$, respectively. Detailed results see in Table 2.3 (see Annex).

2.3.3 Daily physical activity: accelerometry results

Detailed accelerometry results are shown in Table 2.4 (see Annex).

A statistically significant decrease in *sedentary time* was observed in both groups: from baseline to 12 weeks the mean change in TG was 6.7 % (CI: 2.2 to 11.1 %; Cohen's $d = 0.9$) and in CG 12.4 % (CI: 2.3 to 22.6 %; Cohen's $d = 1.4$) accordingly, and for both results in *post hoc* analysis, appropriate statistical power was approved; while from baseline to follow-up the mean change in TG was 9.4 % (CI: 3.6 to 15.1 %; Cohen's $d = 1.0$) and in CG 13.1 % (CI: 1.9 to 24.3 %; Cohen's $d = 0.9$) respectively, but in *post hoc* analysis, only for results in TG appropriate statistical power was detected: accordingly TG: $1-\beta = 0.85$ un CG: $1-\beta = 0.59$. There were no significant differences between the groups in either assessment in daily sedentary time. Furthermore, the results on *sedentary time* revealed that at baseline *less than 8 hours per day sedentary spent* only $n = 1$ (4.8 %) of the sample who was from TG. Furthermore, after 12 weeks, 5 (25 %) participants: 4 (36.4 %) TG and 1 (11.1 %) CG, but at follow-up

4 (21.1 %): 3 (27.3 %) TG and 1 (12.5 %) CG, respectively. On the other hand, 81 % of all participants studied at baseline spent *10 or more* hours per day *sedentary:* 7 (63.6 %) TG and all participants in CG. After 12 weeks, this proportion decreased to 45 % of the whole sample: 3 (27.3 %) TG and 6 (66.7 %) CG participants; at follow-up 52.6 % of all participants: 4 (36.4 %) TG and 6 (75 %) CG showed 10 or more sedentary hours per day.

Only in TG was a statistically significant increase in daily time in *low or moderate intensity activities*: in low intensity activities significant change within group was detected with large effect size both between baseline and 12 weeks, and follow-up (Cohen's d = 1.5 and 1.2 respectively); for moderate intensity activities only between baseline to follow-up significant increase was observed with large effect size ($p = 0.002$; Cohen's d = 1.3). In *post hoc* analysis, only for changes between baseline and follow-up, appropriate statistical power was reached. The daily time in *high intensity* activity accounted for the smallest proportion: the baseline TG median value 1.06 % (IQR 0.67–1.45); CG 0.11 % (IQR 0.05–0.41) respectively; a statistically significant difference between the groups was confirmed, based on the Mann-Whitney test result ($p = 0.009$, $rg = 0.75$). No changes were observed between assessments in either of the groups; at the same time, the statistically significant difference between the groups remained after 12 weeks and at follow-up.

2.3.4 Perceived quality of sleep

At baseline in 74 % of all participants poor sleep quality was observed according to the PSQI score, equal in both groups. Only in TG after 12 weeks and at follow-up, the number of participants with poor sleep quality had decreased, along with the decrease in the median PSQI value: a statistically significant change between baseline and 12 weeks was approved ($p = 0.013$, $rc = 0.76$). In *post hoc* analysis, the appropriate statistical power was approved

(1-β = 0.91). Unlike in CG the number of participants with poor sleep quality did not change significantly, the median value of the group showed a tendency (*rc* = 0.42), to increase from baseline to follow-up, without statistical significance.

3 Discussion

Pulmonary arterial hypertension as a rare, progressive, and life-threatening disease is a dual challenge, as it requires balancing a deep and specific pathogenetic understanding with the unique needs of the patient as a person living with a long-term health disorder. In the treatment of patients with PAH, it is necessary to combine specialized healthcare services and long-term interventions aimed at improving the ability to manage chronic disease and dynamic adaptation. Along with the goals of risk stratification and mitigation, the patient treatment outcome should include the fulfilment of the patient's needs to improve and maximise the opportunity to live life as one wants it, thus living a meaningful life.

This is the first study in Latvia on an interdisciplinary approach in the treatment of patients with PAH, combining targeted drug therapy with a comprehensive home-based and remotely supervised physiotherapy programme. Furthermore, it was its first study to highlight the analysis of participation by assessing the perceived ability to decide how to live your own life in the context of the health condition of patients with PH, providing a new way of looking at treatment outcomes by incorporating notions of autonomy and participation in a conceptual understanding of health-related quality of life (HRQoL). Such a way allows more to reflect the experience of patients about one's life with a rare, life-threatening, and chronic disease. The use of such an approach, both for the patient and for health care professionals, allows shifting the focus from the limitations caused by the disease to the opportunities to participate in activities that are important to the patient, thus creating a comprehensive treatment model. It resonates with *Hedman et al.* (2015) study that disclosed perspective of older people living with chronic illness describing ability or disability of less importance than the meaning of everyday life. Furthermore, the characteristics of limitations in everyday life do not reflect older

people's, with long-term illness, views on autonomy and participation, instead of 'the ability to act' describing different abilities for meaningful activities of the individual (Hedman et al., 2015). Similarly, Howard, Ferrari & Mehta (2014) raised the need to understand and respect the needs of the patient with PAH and his expectations from treatment, which often differ from the view of the medical professional, especially with the appearance of targeted medical therapy along with the focus on reducing symptoms, improving exercise capacity, as well as slowing down the disease progression and improving life expectancy. At the same time, patients with PAH may have more pressing needs based on current daily life, related to the ability to perform certain daily tasks and improve quality of life, as well as to obtain social and emotional support from both medical professionals and patient organisations (Howard, Ferrari & Mehta, 2014).

In addition, considering the broader range of patient concerns in interpreting treatment outcomes in both research and clinical care resonates with the idea presented by McGoon et al. (2019) stating that symptomatology, exercise capacity, hemodynamic indices, as well as various aspects of the diagnostic process represent only the 'tip of the iceberg' of the overall adverse impact caused by PH on the patient's life during treatment, including overall quality of life, employment, education, loneliness, need for information, need to ask for help, financial impact and access to care. This, in turn, justifies the importance of the patient perspective, which the authors divide into two interrelated prisms – the perspective of each individual in the given situation, and the overall perspective of the 'cohort' of PH patients, including the most common aspects. Thus, pointing to both an individualised approach in the treatment of each patient, as well as the promotion of patient organisations and their involvement in the planning of care decisions (McGoon et al., 2019).

In general, the results of the doctoral thesis study confirm that the interdisciplinary treatment approach aimed at patients with PAH delays the reduction of participation in everyday life activities and creates a resource so that the patient can improve his opportunities to participate in daily life in the way he wants, despite the PAH and the long-term effects of its treatment.

As mentioned above, the concept of participation has not been analysed in the studies published so far in patients with PH; however, its interpretation in terms of quality of life allows us to analyse the results of our study in the context of studies, in which outcome measurements included other health-related quality of life instruments for patients with PAH. Patient-reported HRQoL is recognized as an important and relevant outcome in PAH clinical trials, and it is recommended to integrate such tools into daily clinical practice for patients with PAH (Humbert & Lau, 2021). Most studies on physical activity interventions use one of several generic or disease-specific self-reported HRQoL measurement tools, the most widely used instrument being the SF-36 questionnaire, which describes the limitations of daily activities caused by health disorders (Grünig et al., 2019; Zeng et al., 2020). Zeng et al. (2020) in the systematic review of the effectiveness and safety of exercise training and rehabilitation in PH, included five studies with SF-36 as an outcome measure in the meta-analysis and demonstrated a statistically significant improvement in HRQoL measurements in all domains of the questionnaire, including physical and psychoemotional aspects. Unfortunately, the commonly applied conceptional sense of HRQoL as a treatment outcome and, accordingly, selected measurement tools substantially reduce the fundamental multidimensional concept of QoL (WHO, 2012), and mainly exclude the reference points of a particular patient in his own everyday life, and do not disclose either the ‘abilities to act’ or possible opportunities, such as internal and external resources. At the same time, persons with functional limitations describe the concept of participation as a set of values that includes

active and meaningful participation, choice and control, accessibility and opportunities, while highlighting the need to define and describe one's participation freely and based on patient perspective, rather than reaching predetermined societal norms (Hammel et al., 2008). Defining health as "the dynamic balance of physical, mental, social, and existential well-being in adapting to the conditions of life and the environment", while keeping in mind the changing needs of patients with PH and the need to adapt at different disease stages and treatment phases, the key issue for an individual to experience good health and enjoy the related quality of life is finding ways to adapt to their situations (Krahn et al., 2021; Rawlings et al., 2020). In general, this allows healthcare professionals in cooperation with the patient and his family to plan and implement targeted and relevant treatment for the patient.

There is reason to believe that the benefits of the intervention used in the study in the context of participation were made possible exactly by the individual adjustment of FIZIO-I to the individual's unique needs and contextual factors, as well as the combination and implementation of the various therapeutic components within the framework of interdisciplinary treatment, stimulating the patient to use internal and external resources and creating optimal adaptation.

Participation in everyday life in context of health condition

The results of the doctoral thesis study confirmed that the investigated comprehensive, home based and remotely supervised physiotherapy programme within interdisciplinary treatment approach prevents the deterioration of participation in everyday life for patients with PAH in the longer term on such IPA subscales as AO, FR, and AI, including activities such as walking both at home and outdoors when and where one wants, tasks and responsibilities within the family, frequency of social contacts, possibilities to spend leisure time, etc. There are very few studies found in academic sources to date about the target

population that analyse long-term outcomes at follow-up. In a study of a six-month home-based intervention, Wojciuk et al. (2021) analysed health-related quality of life using the SF-36 questionnaire and confirmed improvements in self-reported performance of various activities such as climbing stairs, walking longer distances, shopping relocation, house cleaning, immediately after the intervention, but no maintenance of the obtained improvement was observed at the follow-up after 12 months, however, the researchers were not able to survey the control group, so no conclusions can be drawn from comparing the two groups. However, the IPA results are only partially comparable to those reflected by the SF-36 because the ability to adapt to perform activities in a modified way with permanent functional limitations, which is an important goal of treatment in chronic diseases, does not appear. This is also brought up in the context of PH in a recent study by Martinez Menaca et al. (2021), repeatedly emphasising the teaching of self-management skills as a key element of treatment. It should be stressed that the patients perceived the greatest limitations in the activities of the subscales of AO and FR. Also, in the subscale AO, CG participants were found to have a statistically significant deterioration at the follow-up. One important aspect that emerged from the analysis is that TG participants through comments written on IPA questionnaires described that their improvement in perceived *chance to participate in a variety of outdoor activities* (AO) was related to their ability to plan everything, consideration of feeling both physical and emotional as well as actual weather conditions, adherence to medication routine, and other important aspects of optimal adaptation. These results mirror data from studies on the perspective of patients with PH that described the need to organise and plan daily life, pay attention to physical and emotional well-being and follow a routine of sleep and diet (Ferrari & Skåra, 2019; Goddard et al., 2017). In addition, Rawling et al. (2020) in the synthesis of qualitative studies on the experience of adult patients living with PH described four main topics, one of

which emphasised the transitional nature of PH. Coming to the stage with the aim of stabilising the disease, maintaining a good quality of life and survival, the person faces the challenge of finding a balance between restrictions, a sense of loss, and an attempt to live a previous life despite the exacerbation of symptoms and possible worsening, while forming a new identity and life (Rawling et al., 2020). Furthermore, looking at PAH as a chronic disease, it is necessary to highlight the possibility of the investigated intervention to maintain the opportunity to *participate in activities related to frequency of social contacts*. At the same time, in our study, no substantial deterioration or differences between groups were found in the IPA subscale SL that mainly describes the quality of social relationships, which can be explained by the relatively older age of the participants, and it is highly possible that other issues arise in younger patients, as current evidence from qualitative research suggests that quality concerns of social life would be more relevant in younger patients with PAH as well as in patients with less time after confirmation of diagnosis (Rawling et al., 2020). Recognising that social participation, for example, meeting friends, volunteer work, club activities, and quality of social relationships, described as sense of belonging, respect, inclusion, are important predictors of well-being in persons living with long-term health problems, interventions to support participation are highlighted as a relevant part of the interdisciplinary treatment approach (Maguire, Hanly, & Maguire, 2021). Furthermore, note that studies of the patient's perspective agree that patients with PAH often describe feeling insecure, isolated, and living with an invisible disease (Ferrari & Skåra, 2019; Rawling et al., 2020), therefore, to fully eliminate the impact of PAH on a patient's life, complex interventions in addition to medical treatment of the underlying disease are important, and therefore our treatment approach has the potential to support an individual living with PAH to cope with disease. The observed benefits of the investigated programme to improve the perceived

participation related to frequency of social contacts might be due to the change in the perception about their health condition and the improved sense of self-control abilities, as are approved relevant correlations between these factors in other studies (Meulenkamp et al., 2019).

Returning to the initial **idea of the dual challenge**, developing treatment approaches for patients with PAH, which, at the same time as shifting the focus from functional limitations to opportunities, adaptation and meaningful life, requires to provide a base for safe activities, seeing as prerequisites both the safety control implemented by the physiotherapist and the patient's self-control skills, knowledge of action, and the realisation of self-management. One of the underlying principles of the investigated FIZIO-I intervention is the precondition that it can be initiated and safely performed if the patient with PAH receives an optimized MED-TH and during it, active cooperation between the treating cardiologist, physiotherapist and the patient is ensured. At the same time, safety supervision by a physiotherapist was purposefully included, monitoring the patients' self-control indicators, biomarkers in blood serum (BNP, CRO), as well as use of predefined limits and its indicators with recommendations on appropriate action in daily life, to facilitate the interpretation of self-control indices and induce appropriate self-management strategies. The obtained results regarding the absence of adverse events and the possibility of successful intervention progression, as well as the inclusion of biomarkers within the reference limits, indicated the safety of FIZIO-I in the studied sample. These results add to the evidence for the safety of remotely supervised, home-based physiotherapy programmes in the target population subject to the above-mentioned preconditions (Brown et al., 2018; Wojciuk et al., 2021).

In the doctoral thesis, based on the initial hypothesis about the benefits of adding the developed FIZIO-I to a stable target medical therapy, an analysis of several secondary outcomes was included, which were justified by confirming

the effectiveness of the studied intervention in improving physical functions, perceived self-efficacy, daily physical activity, and sleep quality.

Exercise capacity

This study provides further evidence on complex exercise programmes to improve exercise capacity in patients with PAH who receive stable target medical therapy, confirming a significant improvement in the 6MWT results in TG participants. The Waller et al. (2020) review on the effectiveness of various exercise programmes in patients with PAH revealed an increase in the mean distance of 6MWT of 40–69 m in 12-week programmes (n = 5), of which only one was home-based and revealed a 40 m improvement in the distance of 6MWT, thus our results after 12 weeks demonstrate a quite similar improvement (51.8 m), but in follow-up (75.5 m) confirm superiority. Similar results were obtained in the recent pilot study by Wojciuk et al. (2021) that confirmed the long-term efficacy of a 6-month home-based programme in improving exercise capacity (mean 71.38 ± 83.4 m) one year after the initial evaluation. On the other hand, in a recently published European multi-centre study, which used an average 25-day inpatient exercise programme that was continued at home for another 11–12 weeks, the mean improvement in 6MWT walking distance of 30.7 m (CI 15.4–45.9) was confirmed. The authors explain the obtained significant, but relatively smaller improvement compared to other studies with the possible variation of the training protocol between the centres, as well as the initially high 6MWT scores (Grünig et al., 2021).

The results obtained in our study indicate that the investigated interdisciplinary treatment approach, combining FIZIO-I with MED-TH, is not only safe, but also has the additional benefit thanks to its individual adaptation, complex nature and integration into daily life, thus creating improvement of long-term exercise capacity. Also, despite the fact that the participants in both

groups showed heterogeneity in the 6MWT walking distance, the possibility of individual adaptation of the intervention ensured a significant improvement both in participants with low initial and relatively high 6MWT scores. For example, after 12 weeks, the participant with the shortest initial distance walked (140 m) demonstrated an improvement by 80 m, while the participant with the longest initial distance walked (480 m) also demonstrated a significant improvement (120 m) (Butane et al., 2019; Butane et al., 2021). There is reason to believe that the combination of the physical exercise programme with other elements of the studied intervention also contributed to the equivalent improvement in exercise capacity, despite the use of lower exercise intensity compared to the previously studied, inpatient exercise programmes (Waller et al., 2020), especially when thinking of relaxation, developing self-control and self-management skills.

At the same time, results on decrease in desaturation during 6MWT should be highlighted. At baseline, 76.2% of participants equally from both groups experienced significant desaturation during the 6MWT, which is consistent with literature data for patients with PH (Gupta, Ruppel, & Espiritu, 2020). Intervention studies using the 6MWT as an outcome measure typically analyse distance and, in some studies, the chronotropic response, while SpO_2 is monitored and used as a criterion for exercise cessation, we could not find studies that included it in the outcome description. At the same time, the occurrence of desaturation during physical exertion has been shown to be a significant prognostic indicator for increased mortality in PH and other chronic cardiopulmonary diseases (Agarwala & Salzman, 2019; Gupta, Ruppel, & Espiritu, 2020; Misu et al., 2019). Thus, the obtained study results on the effectiveness of the used intervention to reduce desaturation for TG participants can be considered a clinically significant benefit. Yoshimura et al. (2020) in his analysis of patients with heart failure during the 6MWT confirmed that the cardiopulmonary response differs depending on the distance covered during the

6MWT, i.e., patients with heart failure who had a lower exercise capacity (distance covered less than 300 m) showed a less efficient respiratory stereotype that was characterised by a higher respiratory frequency in combination with a lower tidal volume, and slower oxygen consumption and respiratory minute volume under the influence of exercise, which in patients with heart failure is explained by both inadequate peripheral mechanisms and reduced cardiac output. Considering the above, there is a reason to believe that the reduction of desaturation observed in our study during 6MWT in TG participants could be related to the benefit of inspiratory muscle training and techniques included in relaxation, including conscious control of breathing and conscious modification of breathing stereotype.

Inspiratory muscle strength

The results of the thesis study added to the evidence of the effectiveness of physical exercise programmes that include specific inspiratory training to improve inspiratory muscle function, and also provided new insights into the possibility of maintaining the benefit in the long term in TG participants, thereby preventing the potential deterioration of inspiratory muscle function observed in CG participants. It should be mentioned right away that the measurement of the submaximal strength of the inspiratory muscles was used in the doctoral thesis study compared to the measurement of the maximum inspiratory muscle strength most often described in the literature, however, the submaximal test used in the study is considered appropriate, allowing the determination of the dysfunction of the inspiratory muscles and its reduction after the intervention in the studied sample. In recent studies analysing specific inspiratory muscle strength training in patients with PAH, the mean observed improvement in maximal inspiratory muscle strength measures was from 17.8 to 30.8 cmH_2O after an eight-week programmes (Aslan et al., 2020; Tran et al., 2021), which is a relatively greater

improvement than our results after 12-weeks (mean improvement 9.8 (CI: 6.9–12.7) cmH_2O accordingly). This could be explained by the intensity of the inhalation exercise (lower in our study) and the mean baseline values, which in our study were lower (29 cmH_2O) compared to the above studies with (55.7 to 78.2 cmH_2O). At the same time, the obtained long-term result should be highlighted, especially considering that there was significant deterioration in the CG, which acquires special significance in connection with the presence of co-morbidities in most of the participants, as well as the high proportion of elderly participants.

Weakness of inspiratory muscles and its prevention are stressed in the latest systematic reviews and clinical work recommendations, especially in patients with cardiovascular diseases (including heart failure, after myocardial infarction, after cardio-surgical interventions, cerebrovascular events and peripheral artery diseases), reaching the conclusion that a targeted inspiratory muscle assessment and training programme should be applied to every patient as part of cardiac rehabilitation (Azambuja, de Oliveira, & Sbruzzi, 2020; Neto et al., 2016; Smith & Taylor, 2022). Considering that there is evidence of the correlation of inspiratory muscle dysfunction with the provocation of dyspnoea during physical exertion in both cardiovascular and lung diseases, the correlation of inspiratory muscle training with the improvement of total exercise capacity is only logical (Langer et al., 2018; Neto et al., 2016; Smith & Taylor, 2022).

Perceived self-efficacy

The results of the dissertation study showed a statistically significant improvement in perceived general self-efficacy immediately after the FIZIO-I, indicating better coping with daily problems and better adaptation. However, it should be noted that this improvement was no longer statistically significant in the follow-up assessment, suggesting the need for regular long-term

collaboration with healthcare professionals. This is also discussed in the literature data on patients with PH perspective (Ferrari & Skåra, 2019; McGoon et al., 2019). Furthermore, in CG at follow-up a trend in the decrease in the GSE score (Cohen's d = 0.5) was observed. The results agree with the study by Fors et al. (2018) that approved the effectiveness of a person-centred telephone support intervention to mitigate worsening self-efficacy in patients with chronic obstructive pulmonary disease (COPD) and / or chronic heart failure after 6 months. To expand on the study, the subsequent study by Ali et al. (2021), in which person-centred telephone support was combined with a digital platform, adds that the same intervention was effective to improve task-specific self-efficacy in patients with chronic obstructive pulmonary disease and / or chronic heart failure. In FIZO-I we used a similar approach for the weekly telephone conversation with each participant to provide support and encouragement. Therefore, such or similar intervention could be applied as an optimal solution to provide long-term healthcare service to ensure the sustainability of the results and prevent deterioration of perceived self-efficacy. Ali et al. (2021) similarly concludes from their data that person-centred care by telephone could be a successful way to help patients with a chronic disease handle their illness.

The obtained results on the effectiveness of FIZIO-I in improving perceived self-efficacy in TG participants can be seen as a significant result of treatment, as patients who have successfully learned this and engage in self-management of the disease have better quality of life indicators, fewer episodes of hospitalisation and higher life expectancy (Riegel et al., 2021). In the intervention studies published so far, self-efficacy or specific self-management abilities have not been included in the evaluation of the treatment outcome for patients with PH, however, in a recent publication, the targeted improvement of self-management abilities and the evaluation of the achievement of this goal are also brought up in the target group of patients with PAH (Martinez Menaca

et al., 2021). However, publications on the perspective of patients with PH have always promoted a complex treatment approach, including active involvement of the patient and promotion of self-management abilities (Graarup, Ferrari, & Howard, 2016; Rawlings et al., 2020).

The potential of FIZIO-I to improve perceived self-efficacy is related to both the targeted development of self-control and self-management skills and the exposure to educational elements. Therefore, in physiotherapy interventions for patients with PAH, along with physical exercises, equally important attention should be paid to education, support and encouragement, creating patient-centred communication. This finding matches with the need to be heard and receive information relevant to the current situation and the patient's unique needs highlighted in other studies of the patient perspective (Brewer et al., 2021; Graarup, Ferrari & Howard, 2016; Rawlings et al., 2020). Equally important is the development of self-control skills by providing appropriate equipment (pulse oximeter) and training in self-monitoring and data interpretation. At the same time, optimal self-control abilities allow for the implementation of a secure remotely supervised physiotherapy intervention, thus encouraging the search for remote monitoring options as well as organizing a preparatory stage in outpatient or day-patient settings (Butane et al., 2019; Riegel et al., 2021). Within the scope of the study, we came to the notion that in clinical work, in addition to the general perceived self-efficacy questionnaire used in the study, it would be meaningful to specifically evaluate the improvement of self-control and self-management skills, which would indicate the achievement of the set goal. This agrees with the study findings of Martinez Menaca et al. (2021), in which the authors recommend considering an instrument that captures patient satisfaction / experience with treatment as an outcome measure for patients with PAH, highlighting aspects such as effective communication between healthcare providers and the patient;

new models of interaction, including via internet or other peers; the patient's self-management ability.

Daily physical activity

In addition, the results of this study reveal an increase in the level of low-moderate daily physical activity at the follow-up by TG participants, pointing to the expected benefit of the investigated comprehensive, home-based and remotely supervised physiotherapy programme in changing behaviour and thus promoting the change of daily habits, in addition to highlighting the need for time to change behaviours. This again encourages thinking about long-term collaboration with health professionals to support and motivate a patient in this journey and resonates with the patient perspective in meeting the challenges of the adaptation and change of daily habits during PAH treatment (Rawlings et al., 2020). Instead, such increase in daily physical activities was not found for the CG. These results are in line with findings from the Chia et al. (2020) international survey of exercise experience for people living with PH indicating that supervised exercise programmes, psychological support, and specific education are factors that promote activity in the target group, along with uncertainty about the safety and benefits of physical activity, the perceived limitations of symptoms, fear, and anxiety as potential barriers.

Furthermore, the results of our study indicated that initially, on average, 67.2% (TG) and 75.6% (CG), respectively, spent their time awake sedentary. The obtained data were equivalent to the high proportion of sedentary time spent per day reported in other studies. In the sample of patients with PAH studied by Matura et al. (2016) they represented 85%, while the study of Pugh et al. (2012) found as much as 92.1% of sedentary time in a sample of patients with PAH. Also, a recently published study of patients with chronic thromboembolic PH reported an average of 60% of daily sedentary time (Schmidt et al., 2022). This finding is relevant in the context of the existence of extensive evidence of the

correlation of sedentary time with an increase in the risk of cardiovascular diseases, higher total hospitalisation and mortality rates both in the PH target group, in patients with other cardiological diseases, and in healthy individuals (Bellettiere et al., 2019; Biswas et al., 2015; Ekelund et al., 2019; Mainguy et al., 2011; Pugh et al., 2012; Saunders et al., 2020). Analysing the changes in sedentary time, a statistically significant decrease was found for both groups from baseline to 12 week and follow-up assessments. This finding can be explained by seasonality: the initial assessment was done at the end of winter, after 12 weeks spring had started, and the follow-up was carried out in the summer. This assumption is based on the results of a comprehensive review in the field, which indicates a decrease in sedentary time in spring and summer compared to winter and autumn in different age groups and regardless of place of residence (Garriga et al., 2021; Hoaas et al., 2019; Turris et al., 2021). For patients with PAH, the negative effects of hot and humid weather are highlighted separately (Jehn et al., 2014), which is not applicable in our study, because Latvia has moderately warm and dry weather in spring and early summer. The influence of the season encourages, in future, when studying similar interventions that are integrated into the daily life of patients, to extend the study period to cover different times of the year, which is especially important in the context of Latvia, since the majority of the studied sample lived outside urban areas and their hobbies were related to gardening, picking berries and mushrooms in the forest.

Returning to the above-mentioned results on the increase of time spent by TG patients in low-moderate physical activities, unfortunately it was currently not possible to perform a comparative analysis in the target population, while the current systematic review on the effectiveness of various interventions in promoting physical activity in patients with chronic obstructive pulmonary disease concludes that the existing evidence does not support improvements in daily physical activity after no single intervention, and there is insufficient

evidence for long-term efficacy (Burge et al., 2020). Also, in a review of various interventions for patients with congenital heart disease, the authors conclude that the studies are mostly of low quality and show little possible improvement in the level of daily physical activity (Wadey et al., 2021). Awick et al. (2017) analysed the level of physical activity of elderly people before and after engaging in different physical activities for a period of 6 months (dancing, walking and exercise programmes) and found a small effect (d = 0.23) on the increase in time spent in medium and high intensity activities. On the other hand, the results of a randomised control trial by de Roos et al. (2018) of a 10-week supervised outpatient physiotherapy group session and a self-paced home walking programme in patients with chronic obstructive pulmonary disease showed a medium effect (d = 0.51) for an increase in time spent in low-intensity physical activity, but no data were collected about the stability of the result in the long term. Compared to the above-mentioned studies, the results of the doctoral thesis study indicate a greater effect of the increase in the time spent in low-moderate physical activities at the follow-up (d = 1.2 and d = 1.3, respectively), confirming a statistically significant difference between groups and the results reaching adequate statistical power (more than 80%).

The obtained increase in the time spent in low-moderate physical activities for TG participants can be highlighted as a clinically relevant achievement in the context of the evidence obtained in other studies about the correlation between higher involvement in physical activities and better indicators in the 6MWT distance, self-reported quality of life, as well as better right ventricle systolic function in patients with PAH (Cascino et al., 2019; Minhas, 2022; Panagiotou et al., 2019; Sehgal, Chowdhury, et al., 2019). In the studies mentioned above, the authors conclude that an objective assessment of daily physical activity should be included as a treatment outcome measure in patients with PAH, while reemphasizing the reciprocal nature of the correlation.

At the same time, the increase obtained in our study in the time spent in physical activities of low-moderate intensity is clinically important in the context of the characteristics of the study sample: the high proportion of elderly participants, mostly women, the frequent presence of various co-morbidities (mainly other cardiological as well as metabolic diseases), as well as elevated BMI for half of the sample. Other studies have demonstrated the beneficial effects of daily low to moderate/high intensity physical activity to reduce cardiometabolic risk factors specifically in seniors, especially middle-aged and elderly women (LaMonte et al., 2017), while changing daily physical activity habits in the senior population is a major challenge, e.g., Zhang et al. (2022) came to the conclusion in their qualitative study that the interventions need to promote self-efficacy, motivation, social support and involvement of seniors.

Sleep quality

The study found evidence of the effectiveness of FIZIO-I for a statistically significant improvement in perceived sleep quality after 12 weeks , which should be highlighted in relation to baseline indicators of poor sleep quality in the majority of the study sample as a whole (71.4%), as other studies have reported the essential role of sleep quality in the context of cardiology in general, although the researchers indicate that there is much unknown, and at the same time, sleep quality is put forward as a potential influence factor that has not yet been fully evaluated (Fan et al., 2021; Li et al., 2021; Spiesshoefer et al., 2019; Yan et al., 2021). The study results of Matura et al. (2015) in a sample of patients with PAH confirmed the correlation of poorer sleep quality with more pronounced PAH symptoms, emotional distress and lower self-reported quality of life, while pointing to the potential possibilities of targeted interventions. There is reason to believe that the improvement of sleep quality in TG participants was related to the modification of sleep mode and daily habits and planning of daily regimen

(period while the person is awake), as well as exposure to relaxation techniques and the already mentioned improvement of inspiratory muscle functions. Compared to the Matura et al. (2017) biofeedback study results on the controlled slow-paced breathing exercises, in which a small effect on sleep quality was observed after eight weeks (d = 0.11, with a group median decrease of 3 points), our results as regards to improvement in sleep quality can be interpreted as superior, showing a large effect (rc = 0.76). This could be explained by a longer intervention time, but mainly by the complexity of FIZIO-I, as other studies have provided evidence for the beneficial effects of both physical exercise (Banno et al., 2018; Xie et al., 2021), the direct and indirect effects of relaxation methods (reducing the activity of the sympathetic nervous system and manifestations of anxiety, improving the ability to manage stress) (Edinger et al., 2021; Li et al., 2015; Liu et al., 2020; Murawski et al., 2018; Sun et al., 2013) and the importance of targeted promotion of sleep hygiene (including the promotion of healthy daily physical activity habits, respecting one's own well-being, planning rest) (Davidson, Dickson, & Han, 2019; Edinger et al., 2021).

The results obtained in the doctoral thesis on the increase in daily physical activity and the improvement of sleep quality after FIZIO-I in the studied sample of patients with PAH indicate the potential of the analysed interdisciplinary treatment approach to promote the formation of healthy daily habits. Behavioural change and the promotion of healthy habits/lifestyle are topical for achieving optimal treatment outcomes in patients with chronic diseases, but especially in patients with cardiac diseases, which pose a challenge to health care providers (Guerreiro et al., 2021; Heron et al., 2016; McAuliffe et al., 2021; Heron et al., 2016). The publications of recent years emphasize the paradigm shift in cardiac rehabilitation, bringing secondary prevention and effective long-term management of multiple chronic comorbidities as a key element (Buckley, 2021; Shapiro & Fazio, 2020; Vilela et al., 2021). In the interdisciplinary treatment

approach, even for patients with PAH, an increasing emphasis is placed on the purposeful formation of healthy daily habits, thus promoting optimal adaptation to daily life with PAH, and at the same time helping to achieve an improvement in the clinical condition with less frequent hospitalizations and better survival rates (Martinez Menaca et al., 2021; Minhas, 2022; Pugh et al., 2012).

Limitations and strengths of the study

Some limitations of the study should be considered in the interpretation of the results obtained from the doctoral thesis and in the process of drawing conclusions. First, the small sample size. However, it should be considered that PH is a rare disease, in the study only an isolated group (Group 1) was included, and this was a study based on the national PH register. Furthermore, two participants in CG had to be excluded, which was already noted in the results (one participant had a PAH exacerbation followed by hospitalisation that precluded his assessment at 12 weeks, and the other had an acute infection just before the follow-up assessment). While being aware of the small sample size, appropriate data processing methods were purposefully selected. Through the careful selection of appropriate statistical tests through the stepwise checking of statistical assumptions along with performed post hoc analysis to detect achieved statistical power, thus control beta error, meaningful conclusions may be drawn. Furthermore, the main results in the post hoc analysis confirmed sufficient statistical power. Second, the current study was unable to describe and analyse perceived participation in work and education activities (IPA subscale WE), due to the small number of answers provided to the relevant statements and that could be explained by the retirement or preretirement age in a large part of the participants along with general labour market trends in Latvia and with weak traditions of volunteering. In addition, the current study was limited to ensure

“blinding” of participants that could bring bias through patients self-reported results.

The onset of the COVID-19 pandemic during the implementation of the practical part of the study was a big challenge for all involved – both researchers and participants. However, since the programme was remotely supervised, its implementation was not interrupted, which indirectly confirmed the availability of the analysed intervention in conditions of limited face-to-face health care services. At the same time, the pandemic and the emergency situation could have affected the results, as the participants felt additional stress, insecurity, and changed their daily habits. However, the obtained positive results allow us to think about the possibilities of the intervention used in the study to provide support and encouragement, and to refer to the actual needs of the patient.

The objective evaluation of daily physical activity with accelerometry as one of the secondary outcome measurements was a reasonable choice and a further novelty of the doctoral thesis. This method has not yet been widely used either in the target population or in other patient groups, to purposefully analyse the results of interventions. The study of motion sensors and their application in research has developed rapidly in recent years, which is also evidenced by the improvement of product offers and the volume of published approval studies in the Maastricht University accelerometry research group, with which cooperation took place for the purposes of the study of the doctoral thesis. Objective monitoring and evaluation of daily physical activity opens opportunities not only in research, but also in the clinical work of physiotherapists to promote the formation of healthy daily physical activity habits.

Unfortunately, it was not possible to realize one of the initial ideas of the research about the creation of a specific mobile application, however, taking into account the trends of both research and healthcare organization, digital solutions would be among the directions of further development, which could also be

implemented within the framework of interdisciplinary treatment. But we also made sure during the study that the use of technology in elderly patients was often limited due to both lacking skills and equipment, therefore preference was given to the conventional forms of communication (telephone conversation), as well as the use of paper diaries and handouts. Therefore, along with the development of digital solutions, we must think of the users, who might not be able to use them and provide them with an alternative. An advantage of the study was the evaluation of the results not only immediately after the end of the intervention, but also after a longer period, which allowed us to draw conclusions of the sustainability of the achieved results, as well as the possibilities of maintaining the existing opportunity to participate in daily activities, delaying the potential deterioration, which is an essential aspect when analysing patients with PAH – a chronic, progressive and life-threatening disease.

At the same time, the possible adaptation of the developed and investigated physiotherapy programme to the needs and contextual factors of each patient is highlighted as an advantage, which indicates its potential for its application to patients with other PH groups and for further improvement to develop subsequent interdisciplinary treatment services for patients with PH in Latvia.

Conclusions

The results obtained in this study allow us to draw the following conclusions:

1. The methodology of the comprehensive home-based and remotely supervised physiotherapy programme developed (FIZIO-I) is appropriate for implementation within an interdisciplinary treatment approach in patients with PAH (PH).
2. FIZIO-I added to MED-TH prevents the possible deterioration of the perceived participation of patients in activities of their everyday life in the context of one's health condition and is a resource to encourage the improvement of the perceived opportunity to live life as one wants, despite the long-term impact of PAH and its treatment.
3. FIZIO-I added to MED-TH approves a significant increase in 6MWT distance and a decrease in desaturation, as well as an improvement in inspiratory muscle functions, which in general points to a significant improvement in physical functions in patients with PAH.
4. FIZIO-I added to MED-TH provides a significant improvement in perceived self-efficacy, highlighting better perceived control over everyday problems and better adaptation abilities in patients with PAH, however, the improvement does not maintain in the long term.
5. FIZIO-I added to MED-TH approves a significant increase in the time spent in low-moderate intensity physical activities in the long term, indicating the formation of healthy daily habits in patients with PAH, while highlighting the importance of sufficient time for behaviour change to occur.
6. FIZIO-I added to MED-TH provides a significant improvement in perceived sleep quality, highlighting better relaxation and rest abilities in everyday life in patients with PAH, however, the improvement is not maintained in the long term.

Proposals

1. The comprehensive home-based and remotely supervised physiotherapy programme developed can be implemented in the clinical setting of Paula Stradins Clinical University Hospital (PSKUS) in collaboration with the Rare Disease Unit in PSKUS, Latvian Cardiology Centre, and with the Pulmonary Hypertension Society. The developed programme has the potential to be adapted in patients with other PH groups.
2. The participation aspect must be included in the patient's self-reported health-related quality of life evaluation (for example, with the IPA questionnaire translated and adapted in the study), to reveal and understand the experience of patients about their life with PAH, thus creating a comprehensive treatment model that is focused on patient's needs.
3. The created physiotherapy programme appears as a starting point for the development of an interdisciplinary treatment model for patients with PH in Latvia. The results of the thesis and the previous close collaboration with the patients' representatives from the Latvian Pulmonary Hypertension Association (PHB) allow us to outline the following paths of development:
    a. According to study results that indicated the need for long-term health care services to maintain the improvements achieved and prevent possible deterioration in patients with PAH (as well as other PH groups), long-term support, motivation, and encouragement could be achieved through regular phone or online communications, face-to-face follow-up visits at the clinic (coordinating with a cardiologist visit), in the future create a specific mobile application.
    b. Seeing self-control abilities as a basic element for both safe implementation of home-based and remotely supervised interventions and optimal adaptation as the goal of treatment for patients with chronic diseases, we recommend introducing specific but simple tools

for assessing self-control abilities in clinical work (e.g. within a larger assessment of patient satisfaction/experience related to treatment, adapting Martinez Menaca et al. (2021) tool idea that could serve as an outcome measure and treatment quality indicator).

c. Considering the prerequisites for the safe implementation of the developed comprehensive home-based and remotely supervised physiotherapy programme (including stable target medical therapy for at least three months), it will not be possible to include patients immediately after confirming the diagnosis and beginning therapy, during adjustment to target therapy, as well as clinically unstable patients or with expressed functional impairment. Therefore, early face-to-face consultations with a physiotherapist and individual recommendations could be planned for first-time diagnosed patients with PAH and other groups of PH.

d. In planning the implementation of physiotherapy services to provide both the developed programme and additional long-term and early interventions, a cost calculation is necessary to carry out, including costs for self-monitoring and training devices, as well as intending appropriate physiotherapist's workload for ensuring telehealth interventions and developing individual recommendations and handouts. Furthermore, quality indicators, that are especially relevant in the context of PAH as a rare disease, need to be defined. Given that targeted and structured cooperation with the patient's association, including peer support, is also envisaged, a broader discussion on the financial resources of such an intervention would be necessary.

e. Knowing that clinical symptoms and functional impairments are only a visible part of 'the iceberg', intersectoral cooperation with the integration of healthcare and social services, seeing the organization

of patients as a 'bridge', should be planned promptly. Furthermore, it is important to pay attention to the perspective of the patient's family and their involvement in the treatment process.

4. The home-based and remotely supervised form of implementation of the developed physiotherapy programme significantly improves its accessibility for patients from different regions of Latvia, which has been justified and proven itself in the conditions of limited access to face-to-face healthcare services (for example, due to restrictions caused by the pandemic). Furthermore, the effectiveness of the developed physiotherapy programme and high patient adherence encourage the wider use of this form of physiotherapy, including patients with other cardiological and pulmonological diseases. Such a therapeutic approach with a home-based and remotely supervised form of implementation should be considered for secondary prevention and chronic disease management goals to promote healthy daily habits.

Publications

Scientific publications in editions included in international databases (*Web of Science* un *SCOPUS*):

1. **Butāne, L.**, Spilva-Ekerte, L., Šablinskis M., Skride A., Šmite, D. 2022. Individually tailored home-based physiotherapy programme makes sustainable improvement in exercise capacity and daily physical activity in patients with pulmonary arterial hypertension. *Therapeutic Advances in Respiratory Disease*. 16, 1–16.

2. **Butāne, L.**, Spilva-Ekerte, L., Skride, A., Šmite, D. 2022. Individually Tailored Remote Physiotherapy Programme Improves Participation and Autonomy in Activities of Everyday Life along with Exercise Capacity, Self-Efficacy, and Low-Moderate Physical Activity in Patients with Pulmonary Arterial Hypertension: A Randomized Controlled Study. *Medicina (Kaunas, Lithuania)*, 58(5), 662.

3. **Butāne, L.**, Šablinskis, M., Skride, A., Šmite, D. 2021. Individually tailored 12-week home-based exercise programme improves both physical capacity and sleep quality in patients with pulmonary arterial hypertension. *Cor et Vasa*, 63(3), 325–332.

4. **Butāne, L.**, Šmite, D., Šablinskis, M., Skride, A. 2019. Individualized home-based exercise programme for idiopathic pulmonary arterial hypertension patients: A preliminary study. *Cor et Vasa*, 61(4), 403–410.

Presentations at scientific conferences

1. **Butane, L**., Šmite, D., Skride A. 2018. Individualized home-based exercise programme for the idiopathic pulmonary arterial hypertension patients: feasibility study. *21st European Congress of Physical and Rehabilitation Medicine*. Viļņa, Lietuva, 01.05.–06.05.2018.

2. **Butane, L.,** Šmite, D., Skride, A. 2018. Home-based exercise programme for the idiopathic pulmonary arterial hypertension patients: multiple case study. *6th World Symposium on Pulmonary Hypertension*. Nica, Francija, 27.02.–01.03.2018.

3. **Butāne, L**., Šmite, D., Skride, A. 2019. Analysis of daily physical activities by combination accelerometer and diary monitoring data: feasibility study in two different populations. *Journal of Rehabilitation Medicine* Vol.51. *Baltic and North Sea Congress of PRM*. Oslo, Norvēģija, 09.–10.10.2019.

4. **Butāne, L**., Šmite, D., Skride, A. 2019. Study protocol for a randomized controlled trial of individualized home-based exercise programme in pulmonary arterial hypertension. *RSU International Research Conference* "*Knowledge for use in practice".* Rīga, Latvija, 01.–03.04.2019.

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Annex

Annex 1

Tables and figures of results

Table 2.1

Characteristics of participants

Variables		TG (n = 11)	CG (n = 10)	p
Age (years)		68 (57–73)	66 (65–75)	
(n)	< 45	2	1	
	45–55	–	-	0.78
	55–65	2	2	
	65–75	5	5	
	75	2	2	
Gender (n)				
	Women / Men	10/1	9/1	–
BMI (kg/m^2)		25.7 (23.5–30.2)	26.7 (22.4–35.3)	
(n)	18.5–24.99	6	5	0.41
	25–29.99	2	1	
	> 30	3	4	
PAH aetiology (n)				
	Idiopathic	6	4	–
	Connective tissue disease	2	3	
	Congenital heart disease	2	2	
PAH medical therapy (n)				
	PDE5 inhibitor	11	10	
	ERA	4	5	–
	Ventavis	1	–	
	Spironolactonum	11	9	
	Oxygen therapy	–	2	
Co-morbidities (n)				
	Hypertension	6	5	
	Dislipidemia	5	7	–
	CHF	9	7	
	AF	7	5	
Time since diagnosis (years)		1.8 (1–2.2)	1.9 (1.6–2.8)	0.60

Table 2.1 continued

Variables	TG (n = 11)	CG (n = 10)	p
Cardiac catheterization data			
mPAP (mmHg)	46 (30.5–58)	54.5 (38.3–58.8)	0.31
PVR (WU)	6.8 (4.9–11.2)	7.8 (5.3–12.9)	0.57
PAWP (mmHg)	11 (9.5–14)	11.5 (10.3–14.5)	0.72
(n) ≤ 12	7	6	
15–13	2	2	
> 15	2	2	
Cpc-PH *	2	2	
Echocardiographic data			
TAPSE (mm)	18 (14–18)	18 (14–19)	0.93
LVEF (%)	50 (46–57.5)	50 (50–52)	0.97
Spirometry			
FVC (% pred)	72 (65–86.5)	71 (64–90)	0.54
FEV_1 (% pred)	74 (70.5–78)	76 (53–79)	0.88
FEV_1/FVC (% pred)**	90.6 (79.6–90)	87 (76.7–90)	0.24

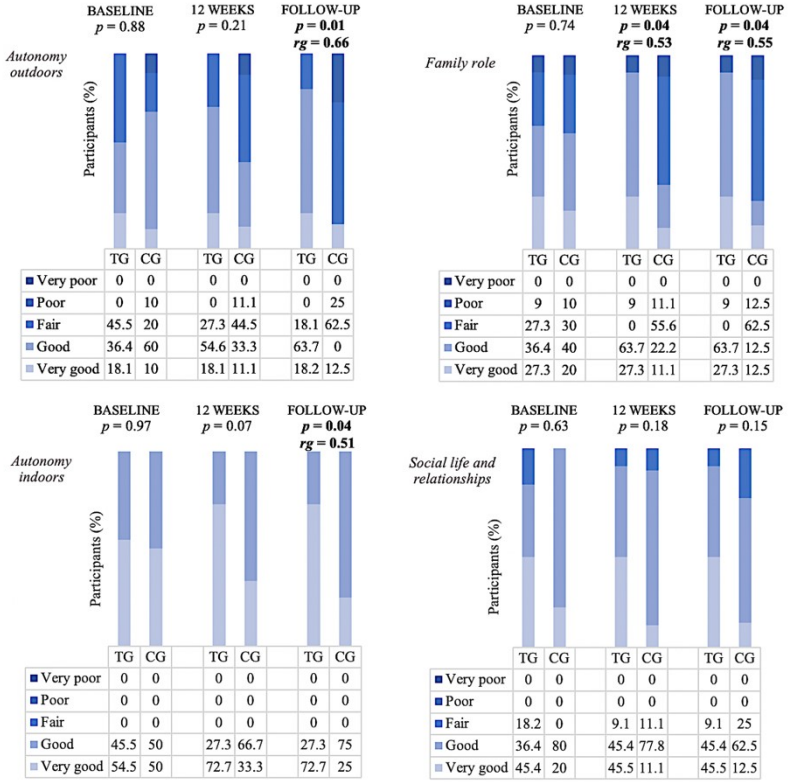
Data are presented as the number of participants (n) or medians (interquartile range, showing Q1 (25 % percentile) and Q3 (75 % percentile).

Levels of statistical significance (p values) are shown for between-group difference, based on Mann Whitney U test.

*Cpc-PH: PAWP > 15 mmHg and DPG ≥ 7 mmHg and / or PVR > 3 WU; three participants with Cpc-PH had congenital heart disease (two from TG, one from CG), but one a connective tissue disease (systemic sclerosis) (from CG).

** Ratio FEV_1/FVC less than 65 % were observed in two CG participants along with FEV1 < 80 %

Abbreviations: BMI, body mass index; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PDE, phosphodiesterase; ERA, endothelin receptor antagonist; CHF, chronic heart failure; AF, atrial fibrillation; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; Cpc-PH, combined postcapillary and precapillary pulmonary hypertension; TAPSE, tricuspid annular plane systolic excursion; LVEF, left ventricular ejection fraction; FVC, forced vital capacity; FEV_1, forced expiratory volume in one second.



	TG	CG	TG	CG	TG	CG
Very poor	0	0	0	0	0	0
Poor	0	10	0	11.1	0	25
Fair	45.5	20	27.3	44.5	18.1	62.5
Good	36.4	60	54.6	33.3	63.7	0
Very good	18.1	10	18.1	11.1	18.2	12.5

	TG	CG	TG	CG	TG	CG
Very poor	0	0	0	0	0	0
Poor	9	10	9	11.1	9	12.5
Fair	27.3	30	0	55.6	0	62.5
Good	36.4	40	63.7	22.2	63.7	12.5
Very good	27.3	20	27.3	11.1	27.3	12.5

	TG	CG	TG	CG	TG	CG
Very poor	0	0	0	0	0	0
Poor	0	0	0	0	0	0
Fair	0	0	0	0	0	0
Good	45.5	50	27.3	66.7	27.3	75
Very good	54.5	50	72.7	33.3	72.7	25

	TG	CG	TG	CG	TG	CG
Very poor	0	0	0	0	0	0
Poor	0	0	0	0	0	0
Fair	18.2	0	9.1	11.1	9.1	25
Good	36.4	80	45.4	77.8	45.4	62.5
Very good	45.4	20	45.5	11.1	45.5	12.5

Figure 2.2 **The IPA median scores in each of analyses subscales at baseline, after 12 weeks, and follow-up in TG and CG***

* In charts the proportion of members in each group by the median score in the subscale in all three assessments are presented. Levels of statistical significance (p values) are shown for between-group difference, based on Mann-Whitney U tests results. Glass rank biserial coefficients *(rg* values) represent effect size accordingly.Bolded numbers present the results for which $p < 0,05$ and $1-\beta \geq 0,8$.
Abbreviations: TG, training group; CG; control group

Table 2.3

6MWT, IP_{submax} and GSE results

Characteristics		Baseline M ± SD	After 12 weeks M ± SD	Change within Group p (d)	Follow-Up M ± SD	Change within Group p (d)
6MWT (m)	TG	378.3 ± 124.3	450.0 ± 114.0	**0.001 (1.7)***	473.6 ± 118.8	**< 0.001 (2.1)***
	CG	296.1 ± 110.1	290.6 ± 112.2	0.840 (0.2)	302.5 ± 139.7	0.127 (0.2)
Difference between groups p (d)		0.115 (0.7)	**0.006 (1.4)***		**0.014 (1.3)***	
IP_{submax} (cmH_2O)	TG	28.3 ± 5.2	38.1 ± 2.9	**< 0.001 (2.2)***	38.8 ± 2.8	**< 0.001 (2.4)***
	CG	26.8 ± 6.2	26.1 ± 6.5	0.262 (0.4)	25.9 ± 6.9	**0.014 (0.8)**
Difference between groups p (d)		0.454 (0.3)	**< 0.001(2.4)***		**< 0.001 (2.4)***	
GSE (%)	TG	64.9 ± 2.7	74.2 ± 17.5	**0.004 (1.04)***	69.4 ± 16.5	0.218 (0.34)
	CG	55.2 ± 25.0	50.7 ± 20.1	0.373 (0.28)	46.3 ± 25.0	0.246 (0.51)
Difference between groups p (d)		0.62 (0.24)	**0.014 (1.21)**		**0.043 (1.08)**	

Levels of statistical significance (p values) are shown for between-group difference, based on t-tests result for independent samples performed with Welsch extension, and for change within group, based on paired sample t-tests accordingly. Cohen's d represents effect size of results.
The bold numbers represent $p < 0.05$ or < 0.025 (for repeated measures adjusted with Bonferroni correction)
* Indicate the results for which $p < 0.05$ (0,025) and $1\text{-}\beta \geq 0{,}8$.
GSE results are presented as total score in transform percentage, where a higher score presents a higher sense of self-efficacy.
Abbreviations: TG, training group; CG, control group; 6MWT, six-minute walk test; IP_{submax}, submaximal inspiratory pressure test; GSE, General Self-Efficacy questionnaire; *M, mean; SD, standard deviation.*

Table 2.4

Accelerometry results

Level of physical activity (% from total awake time)		Baseline M ± SD	After 12 weeks M ± SD	Change within Group p (d)	Follow-Up M ± SD	Change within Group p (d)
SEDENTARY	TG	67.2 ± 8.8	60.7 ± 10.1	**0.008 (0.9)***	58.1 ± 0.1	**0.005 (1.0)***
	CG	75.6 ± 3.6	63.4 ± 9.1	**0.003 (1.4)***	65.2 ± 11.2	0.038 (0.9)
Difference between groups p (d)		0.20 (0.9)	0.55 (0.2)		0.17 (0.6)	
STANDING	TG	25.4 ± 6.4	28.7 ± 8.8	0.031 (0.8)	28.8 ± 8.9	0.055 (0.7)
	CG	21.6 ± 5.7	29.8 ± 7.7	0.028 (0.9)	28.8 ± 9.7	0.032 (0.7)
Difference between groups p (d)		0.18 (0.6)	0.702 (0.1)		0.9 (0)	
LOW INTENSITY	TG	1.3 ± 0.4	1.6±0.5	**< 0.001 (1.5)***	1.8 ± 0.7	**0.002 (1.2)***
	CG	1.0 ± 0.6	1.1 ± 0.4	0.77 (0.3)	0.9 ± 0.4	0.595 (0.2)
Difference between groups p (d)		0.23 (0.6)	**0.036 (1.1)**		**0.005 (1.6)***	
MODERATE INTENSITY	TG	7.1 ± 3.4	8.0 ± 2.4	0.209 (0.4)	9.5 ± 3.5	**0.002 (1.3)***
	CG	4.9 ± 2.8	5.4 ± 2.0	0.668 (0.20)	4.8 ± 1.8	0.192 (0.0)
Difference between groups p (d)		0.12 (0.7)	**0.017 (1.2)**		**0.002 (1.7)***	

Accelerometry results are presented as percentage from total awake time, during seven evaluated days, spent in each level of physical activity. The results on high intensity physical activity are not included in the table, as they were described and analyzed by methods of nonparametric statistics (see describtion in the text). Levels of statistical significance (p values) are shown for between-group difference, based on t-tests result for independent samples performed with Welsch extension, and for change within group, based on paired sample t-tests accordingly. Cohen's d represents effect size of results.

The bold numbers represent $p < 0.05$ or < 0.025 (Bonferroni correction)

* Indicate the results for which $p < 0.05$ (0,025) and $1\text{-}\beta \geq 0{,}8$.

Abbreviations: TG, training group; CG; M, mean; SD, standard deviation