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The Pulmonary Hypertension And Home-Based (PHAHB) Exercise Intervention: Protocol for a Feasibility Trial

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PHAHB Intervention Protocol

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4 1 **The Pulmonary Hypertension And Home-Based (PHAHB) Exercise Intervention:**
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6 2 **Protocol for a Feasibility Trial**
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9 3
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ABSTRACT

Introduction: Novel therapies for pulmonary hypertension (PH) have improved survival and slowed disease progression. However, patients still present with symptoms of exertional dyspnoea and fatigue, which impacts their ability to perform activities of daily living, reduces exercise tolerance and impairs their quality of life (QoL). Exercise training has shown to be safe and effective at enhancing QoL and physical function in PH patients, yet it remains an under-utilized adjunct therapy. Most exercise training for PH patients has been offered through hospital-based programmes. Home-based exercise programmes provide an alternative model that has the potential to increase the availability and accessibility of exercise training as an adjunct therapy in PH. The purpose of this study is to investigate the feasibility, acceptability, utility and safety of a novel remotely supervised home-based PH exercise programme.

Methods: Single arm intervention with a pre/post comparisons design and a follow up maintenance phase will be employed. Eligible participants (n= 25) will be recruited from the Mater Misericordiae University Hospital PH Unit. Participants will undergo a 10-week remote home-based exercise program, with induction training, support materials, telecommunication support and health coaching sessions. The primary outcome measures are feasibility, acceptability, utility and safety of the intervention. Secondary outcomes will include the impact of the intervention on exercise capacity, physical activity levels, strength, health-related quality of life and exercise self-efficacy, assessed at baseline, 10 weeks (post intervention) and 20 weeks (follow up).

Ethics and dissemination: Ethics approval has been obtained from the Mater Misericordiae Institutional Review Board REF:1/378/2032 and Dublin City University Research Ethics DCUREC/2018/246. A manuscript of the results will be submitted to a peer-reviewed journal and results will be presented at conferences, community and consumer forums and hospital

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3 50 research conferences. Trial Registration: ISRCTN Registry: ISRCTN83783446. Protocol
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5 51 version. 2.0.
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10 52 **Keywords:** Pulmonary Hypertension, exercise rehabilitation, physical activity, home-based,
11
12 53 remote delivery, wearable technology, health coaching.
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16

17 54 **Strengths and limitations of this study**

- 18
19
20 55 • This is the first study to assess the feasibility, utility and acceptability of a novel
21
22 56 distance-based exercise intervention for PH patients
23
24 57 • The intervention is pragmatic and scalable and could be integrated into existing
25
26 58 healthcare pathways.
27
28 59 • As PH is a rare disease with a small population size within Ireland, there is a lack of a
29
30 60 usual care control group which is a limitation of the study.
31
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35

36 62 **INTRODUCTION**

37
38 63 Despite earlier diagnosis and improved pharmaceutical therapies, many PH participants
39
40 64 continue to experience exertional symptoms of dyspnoea and fatigue, which leads to a
41
42 65 reduction in functional capacity and in turn, quality of life (QoL). Consequently, there is greater
43
44 66 recognition for a more holistic approach to PH treatment beyond pharmacological therapies[1].
45
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50 67 Exercise rehabilitation and physical activity (PA) interventions have continuously
51
52 68 demonstrated effectiveness as adjuvant therapies for improving exercise capacity and QoL in
53
54 69 a spectrum of cardio-pulmonary disorders[2-4]. Although research investigating exercise in
55
56 70 PH is an emerging field of study, the body of evidence continues to grow. Recent systematic
57
58 71 reviews and meta-analyses have reported improvements in exercise capacity and QoL in PH[6-
59
60

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1
2
3 72 11], which has prompted a renewed focus on exercise training and pulmonary rehabilitation
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5 73 for PH patients.
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9

10 74 In 2015, the European Society of Cardiology /European Respiratory Society published
11
12 75 the first guidelines, stating that exercise training should be implemented by specialist PH
13
14 76 centres as an adjunct to medical therapy for stable PH participants[12]. Currently, the optimal
15
16 77 mode, intensity, and duration of the training and the characteristics of participants most likely
17
18 78 to benefit from exercise training remains unknown[13]. To date, the Hiedelberg program in
19
20 79 Germany remains the gold standard exercise program in PH. It involves an intensive 3-week
21
22 80 in-patient induction phase, with a continued multimodality, monitored outpatient period[14].
23
24 81 Despite the proven beneficial outcomes of this program, it is deemed resource intensive to
25
26 82 operate and roll out.
27
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31
32

33 83 An alternative and pragmatic approach, found to be as effective as a supervised exercise
34
35 84 programme in cardiac rehabilitation, is a home-based model[15]. Home-based interventions
36
37 85 provide solutions to common barriers to participation in centre-based programs such as access
38
39 86 and transport issues, and are less expensive[16]. Further, older adults and patient populations
40
41 87 express a preference for unsupervised, self-paced, low-moderate intensity PA, specifically
42
43 88 walking[17-18]. Home-based interventions have not been studied extensively in PH. Through
44
45 89 the use of telehealth, distance-based programmes could potentially offer an alternative mode
46
47 90 of delivery for exercise training to increase adherence, availability and affordability for PH
48
49 91 patients.
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56 92 Previous exercise interventions in PH have not included strategies to maximise
57
58 93 adherence. An evidence-based approach to implement lifestyle changes requires the
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2
3 94 implementation of health behaviour change strategies grounded in health behaviour change
4
5 95 theory[19]. Evidence-based behaviour change techniques (BCT's) can be used to improve
6
7 96 intervention effectiveness[20]. For example, the combination of the following BCT's: self-
8
9 97 monitoring; goal setting; providing feedback on performance; and, review of behaviour goals,
10
11 98 is associated with increased intervention effectiveness in PA interventions[21]. Interventions
12
13 99 that meet the support needs and offer opportunities for self-monitoring have been found to be
14
15 100 effective for improving PA in other chronic disease groups[22]. Wearable technology holds
16
17 101 great potential as an easy to use, low cost self-monitoring tool with feedback[23] and are
18
19 102 perceived as acceptable and useful for individuals with chronic diseases[24]. Furthermore,
20
21 103 telecommunication allows for real-time verbal and visual interaction between patients and
22
23 104 clinicians.
24
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31 105 The primary aim of this study is to assess the feasibility, acceptability, utility and safety
32
33 106 of a novel home-based exercise training programme for PH patients. BCT's will be integrated
34
35 107 in the intervention through wearable technology devices, the use of print and electronic
36
37 108 materials and health coaching and support calls. The secondary aim is to examine the impact
38
39 109 of the intervention on exercise capacity, physical activity levels, strength, health-related QoL
40
41 110 and exercise self-efficacy.
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111 METHODS AND ANALYSIS

112 Study Design

113 The study will employ a single group pre-post-intervention design with a follow up
114 maintenance phase. The purpose of the maintenance phase is to assess if the intervention
115 facilitates the adoption of independent exercise in participants when support is removed. The
116 study will adhere to the Standard Protocol Items: Recommendations for Interventional Trials

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3 117 Reporting Template (SPIRIT)[25]. Participants will complete assessments at baseline (T1),
4
5 118 after the 10- week intervention (T2) and at 20-weeks follow up (T3).
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119

120 **Eligibility Criteria**

121 Inclusion criteria are male or female > 18 years, with a diagnosis of PH by right
122 heart catheterisation showing baseline mean pulmonary arterial pressure ≥ 25 mm Hg,
123 pulmonary vascular resistance ≥ 240 dyn s cm⁻⁵, pulmonary capillary wedge pressure ≤ 15
124 mmHg and receiving optimized conventional PH therapy. Participants must be clinically stable
125 with no medication changes in the 2 months prior to enrolment.

126 Exclusion criteria include PH of any cause other than outlined in the inclusion criteria such as
127 PH from left heart disease or lung disease/hypoxia, pregnancy, signs of right heart
128 decompensation, acute infection and pyrexia, change in disease-targeted therapy within the last
129 2 months, scheduled to receive an investigational drug during the course of the study,
130 FEV1/FVC <0.5, total lung capacity <70% of the normal value, active liver disease, porphyria,
131 elevations of serum transaminases >3 x upper limit of normal (ULN), bilirubin >1.5 x ULN,
132 haemoglobin concentration <75% of the lower limit of normal, systolic blood pressure <85
133 mmHg, active myocarditis, unstable angina pectoris, exercise induced ventricular arrhythmias,
134 decompensated heart failure, hypertrophic obstructive cardiomyopathy or impaired left
135 ventricular function.

136

137 **Participant Recruitment**

138 Participants will be recruited from the Pulmonary Hypertension Unit at the Mater
139 Misericordiae University Hospital, Dublin, Ireland. Eligible participants will be invited to
140 participate during their routine 3-6-month clinic visit. They will be given a verbal explanation

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2
3 141 of the study and provided with a participation information sheet by their PH Specialist
4
5 142 (SG/BMC) or a member of their team. After receiving the information, potential participants
6
7 143 will have the option to speak on the day to a member of the research team or to receive a follow-
8
9 144 up phone call within 1-2 days. Participants will have the opportunity to ask questions and will
10
11 145 have time to consider their participation. Written consent will be obtained by mail.
12
13
14

15 146

147 **Sample Size**

148 A key objective of this feasibility study is to collate primary outcome measures to
149 help inform sample size calculations for future outcome trials. Pilot study sample size typically
150 ranges from 24 to 50[26-28]. We estimate a target sample size of 25 to be sufficient for this
151 feasibility study[27].
152

153 **Procedure**

154 Participants will complete all assessments, induction training and exercise training
155 in their own home and will maintain contact with researchers via telecommunication
156 technologies (phone, videoconferencing and email). Following consent, a baseline assessment
157 will be conducted (see Table 1) and participants will be provided with an accelerometer to
158 record their activity for the following week, along with a prepaid postage envelope to return
159 device. The assessment procedure will be repeated at T2 (10-weeks) and T3 (20-weeks).

160 Participants will be provided with a home exercise bike (NordicTrack GX 2.7U), a wearable
161 tracker watch (The Fibit Charge 3), pulse oximeter (SafeHeart SpO₂ monitor), real time single
162 lead ECG/HR/respiratory rate monitor (Frontier X), blood pressure monitor (Beurer BM44),
163 exercise manual, exercise diary and access to online videos. The exercise manual offers a
164 comprehensive, patient-friendly resource detailing; 1) general information about the trial; 2)

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1
2
3 165 useful links and contacts; 3) background information on PH; 4) education regarding exercise
4
5 166 safety and the benefits of physical activity; 5) workbook style sections on motivation, goal
6
7 167 setting, overcoming barriers and psychosocial support; 6) managing breathlessness; 7) exercise
8
9 168 intensity and limits; 8) guided home exercises with written and visual details and advice on
10
11 169 progression; and 9) advice on pacing and energy conservation. Online videos will provide a
12
13 170 visual demonstration of each exercise. Participants will be provided with an exercise diary as
14
15 171 a tool to record their activity and effort.

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18
19 172 The 10-week intervention consists of the following components: Three 60-90 min induction
20
21 173 sessions (over week 1 and 2), up to five 30-min support health coaching sessions (at week 2,
22
23 174 3, 5, 7, 9) and 3-5 weekly home-based exercise sessions. The intervention will end prior to T2
24
25 175 assessment. Participants will continue to have access to the exercise manual, bike and Fitbit
26
27 176 between T2 and T3, the maintenance phase.

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32 177

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34 178 ***Induction Training***

35
36
37 179 Induction training is a key component to ensure patients are confident to exercise at
38
39 180 home and understand the appropriate exercise intensity and how to exercise safely.1:1
40
41 181 induction sessions will take place via video conferencing. Participants will be encouraged to
42
43 182 involve a family member, friend or carer in the induction training. The sessions will focus on
44
45 183 the following topics:

46
47
48
49 184 *Session 1 - Introduction*; Education on PH and benefits of PA for PH. Familiarisation with
50
51 185 intervention materials/equipment and self-monitoring.

52
53
54 186 *Session 2 - Exercise Safety and Exercise Demonstration*; The session will focus on recognizing
55
56 187 exercise limits, warning signs, and managing exercise intensity. Visual demonstrations of
57
58 188 breathing techniques and aerobic, strength and respiratory training will be provided, with the
59
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189 opportunity for behavioural practice during the session to check technique and instil
190 confidence.

191 *Session 3 - Recap*; Exercise demonstrations and key safety points will be reviewed. Any issues
192 regarding intervention materials/equipment will be addressed and participant goals will be
193 reviewed, alongside additional tips for family/friend support and motivation.

194

195 ***Health Coaching Sessions***

196 During the intervention, participants will receive up to five 30 min formal health
197 coaching sessions via videoconferencing. These sessions will use BCTs to improve exercise
198 adherence, motivate and provide support. Over the 5 sessions the topics will include; benefits
199 of exercise, goal setting, action planning, self-monitoring, identification and management of
200 barriers to exercise, problem solving and feedback on behaviour, with the option for
201 participants to complete formal paperwork in the intervention manual. If required, additional
202 support will be available outside of scheduled sessions.

203 Participants will be asked to wear the Fitbit Charge 3 daily during the 10-weeks. The Fitbit
204 data will be used to guide individually tailored goals, assess adherence to exercise and overall
205 daily PA and as tool to provide feedback to the researcher and participants.

206

207 ***Exercise Program***

208 Participants will complete a 10-week individualised, home-based exercise
209 programme. The programme will be prescribed using the FITT principle (Frequency, Intensity,
210 Time and Type) and will employ a multimodal approach that integrates aerobic, resistance and
211 respiratory training. The goals for each component are outlined in the sections below. These
212 are aspirational goals that may not be realistic for all participants. Exercise prescription will

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1
2
3 213 be individualized based on their baseline PA levels, 6 min walk test distance (6MWD) and
4
5 214 physical capabilities. The modified Borg rating of perceived exertion (RPE) scale[29] will be
6
7
8 215 used to help prescribe exercise intensity. The RPE scale is a psychophysiological measurement
9
10 216 that translates physical stimuli to a psychological construct of perceived exertion and has been
11
12 217 validated in other clinical groups[30]. Participants will aim to achieve an RPE of 3 (moderate)
13
14 218 initially. Based on individual progress an RPE of 4 (somewhat hard) may be advised for some
15
16
17 219 participants.

18
19
20 220 All participants exercise program will include:

21
22 221 *Aerobic Training*; Participants will initially aim will be to undertake a minimum of 10 min of
23
24 222 structured aerobic exercise involving walking, cycling or a combination on ≥ 3 d/week.
25
26 223 Participants will be allowed to perform this exercise in a single bout, or accumulate it in bouts
27
28 224 of at least 5 min in duration. The duration will be progressively increased, with the goal of
29
30 225 accumulating ≥ 30 min on ≥ 5 d/week.
31
32
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35 226 *Resistance Training*; Participants will initially undertake resistance training on 2 d/week,
36
37 227 involving a single set of 6-8 repetitions of upper and lower extremity and whole body exercises.
38
39 228 Training volume will progressively increase with the goal of completing 2-3 sets of 10-12 reps
40
41 229 of 4-6 exercises on three non-consecutive days. Participants will use pursed lip breathing to
42
43 230 help airways stay open during exhalation. Bodyweight resistance will be used initially and
44
45 231 based on individual ability, tera bands, water bottles or light dumbbells will be introduced.
46
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48

49 232 *Respiratory Training*; Participants will initially perform 10 min of respiratory training at least
50
51 233 twice a week, involving a combination of stretching, breathing techniques (e.g., pursed lip,
52
53 234 diaphragmic and slow breathing), yoga, and respiratory muscle strengthening exercises.
54
55 235 Training volume will progressively increase with the goal of completing 15/20 min of
56
57 236 accumulated respiratory training on ≥ 3 d/week.
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237 Participants will wear a Frontier X device (receiver attached to a strap place around the chest)
 238 during all exercise sessions. The first 2 weeks will be monitored by researchers and then
 239 periodically monitored. This will allow access to real time ECG, heart rate (HR), respiratory
 240 rate and cadence. Oxygen saturation will be monitored and participants will be instructed to
 241 stop exercising if the SpO₂ value drops below 88%, as per guidelines[31]. Participants will
 242 document any adverse events and report to the research team immediately.

243

244 **Study Outcome Measures**

245 Outcome assessments will take place at baseline (T1), after the 10-week intervention
 246 (T2) and at 20-weeks follow up (T3). Semi-structured interviews will be conducted at T2 to
 247 assess patient's perspective on program acceptability and feasibility and at T3 to assess the
 248 follow up phase. Table 1 outline the timepoints of the outcomes.

249 Table 1: Study outcome measures and time points

Assessments	Timepoint		
	Baseline (T1)	Post-Intervention (T2)	Follow-up (T3)
Written informed consent & eligibility	X		
Demographics	X		
Medical history	X		
WHO functional class	X	X	X
Concomitant medication	X	X	X
Adverse events	X	X	X
Exercise capacity (6-MWT), Borg Dyspnea Index	X	X	X

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Muscle strength (Sit to Stand)	X	X	X
Physical activity (ActivPAL Micro)	X	X	X
Quality of life (CAMPHOR & SF-36)	X	X	X
Fear of exercise (Tampa Scale)	X	X	X
Psychological constructs	X	X	X
Intervention debrief questionnaires/ semi-structured interviews		X	X

250

251 **Primary Outcomes**

252 Primary outcome is the feasibility, acceptability, utility and safety of the intervention.

253 Feasibility of the intervention will be assessed by (i) participant recruitment (enrolment as a
 254 proportion of eligible patients) and retention (proportion that completed all assessments); (ii)
 255 engagement with the intervention measured according to attendance at induction sessions and
 256 health coaching sessions and adherence, defined as the percentage of home-based exercise
 257 sessions recorded by participants who complete the intervention assessed via log books and
 258 weekly calls) and (iii) Implementation process and fidelity of the intervention captured through
 259 observation and detailed field notes. Researchers will note the feasibility of the trial protocols
 260 including the outcome assessment and any additional information on patient interactions or
 261 response during the intervention.

262 Acceptability and utility of the intervention will be assessed through self-report
 263 questionnaires and semi-structured interview. At T2 participants will be asked to complete a
 264 self-report questionnaire, assessing perceptions of intervention appropriateness, effectiveness,
 265 quality, accessibility/usability, intrusiveness, and overall enjoyment and attitude towards the
 266 intervention.

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267 Semi-structured interviews will probe the elements outlined in the self-report
268 questionnaire and will include perceptions of intervention practicality, i.e., participants' ability
269 to undertake the prescribed activities and to accommodate the intervention within normal daily-
270 life activities. Participants will be asked to highlight barriers to participation and offer
271 suggestions for improvement and implementation. Interviews will be conducted via telephone
272 and will be audio-recorded and transcribed. Interviews at T3 will assess the 10 weeks
273 maintenance period.

274 Safety (patient reported adverse events directly related to participation in the exercise
275 intervention) will be assessed during support calls and participants will be instructed to inform
276 researchers immediately of any adverse events in the time between calls.

278 Secondary Outcomes

279 **Exercise capacity:** Assessed using the 6 min walk test (6MWT). The test will be administered
280 according to the European Respiratory Society Guidelines[32] and will be conducted at each
281 participants home using detailed step by step video and written instructions and remotely
282 supervised via phone/teleconferencing by a researcher (CMC). A family member/friend will
283 assist with conducting the test, including measuring blood pressure and SpO₂ with guidance
284 from the researcher before and after the test. Subjective symptoms (RPE and dyspnoea- Borg
285 Dyspnoea Scale 0-10) will be recorded before and after the test. The Frontier X chest worn
286 monitor will be worn during the test to provide real time feedback. The assistant will ask the
287 participant to call out their SpO₂ and HR at each min of the test. Standard encouragement will
288 be delivered by the assistant, with researcher prompting, if needed. The study participants are
289 very familiar with the 6MWT.

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3 291 **Muscular strength:** Lower body muscle strength will be assessed using the 30 sec sit-to-stand
4
5 292 test (STS) from a seat height of 40-45 cm. The STS is a commonly used field-based measure
6
7 293 of functional lower limb muscle strength, particularly in clinical and elderly populations. The
8
9 294 test will be conducted in each participant's home via teleconference. A researcher (CMC) will
10
11 295 provide a demonstration, time the test, and count the repetitions. Each participant will perform
12
13 296 two trials separated by 5 min, with the best score being recorded.
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16

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20 298 **Physical activity behaviour:** ActivPAL³ micro activity monitors (PAL Technologies Ltd.
21
22 299 Glasgow, Scotland) will be used to assess free living activity behaviour. The device samples
23
24 300 at 20Hz for 15 sec epochs and measures bodily accelerations using triaxial accelerometer. An
25
26 301 inbuilt inclinometer measures thigh inclination. Proprietary algorithms classifies activities into
27
28 302 sitting/lying time, standing time, stepping time, step count and activity counts. Participants
29
30 303 will be mailed the accelerometer together with detailed wear instruction and provided with a
31
32 304 prepaid postage envelope to return the device. They will be instructed to wear the device on
33
34 305 the anterior aspect of their right thigh continuously for 7 days, except during water immersion
35
36 306 activities (i.e., swimming and bathing). The ActivPAL is a valid and reliable measure of
37
38 307 activity and sedentary behaviour[33-34].
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44 308

309 **Psychological Outcomes and Mediators**

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49 310 **Quality of life:** The Medical Outcomes Study Short-Form 36-Item Survey (SF-36) is a well-
50
51 311 validated, generic questionnaire[35] consisting of physical functioning, physical role
52
53 312 functioning, bodily pain, and general health and the four mental subscales of vitality, social
54
55 313 functioning, emotional role functioning and mental health. The Cambridge Pulmonary
56
57 314 Hypertension Outcome Review (CAMPHOR)[36] was designed as a disease-specific health-
58
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1
2
3 315 related QoL measure for PH patients. It is widely used as a clinical and research tool in PH. It
4
5 316 is made up of 3 main dimensions which assess symptoms (25 items) functioning (15 items)
6
7 317 and quality life (25 items).

8
9
10 318 **Fatigue:** The Fatigue Severity Scale (FSS)[37] measures the patient's perception of the
11
12 319 influence of fatigue on physical and social functioning through responses to nine different
13
14 320 physical and social functioning situations. The FSS is a valid tool for assessing fatigue across
15
16 321 various health conditions[38].

17
18
19
20 322 **Self-regulatory self-efficacy for exercise:** Assessed using a modified 11-item scale[39-40],
21
22 323 which provide information on task, scheduling and recovery self-efficacy. Questions begin
23
24 324 with the stem "*How confident are you that you can...*" and include items such as "*plan exercise*
25
26 325 *sessions that will be at least moderately difficult (e.g. have you breathing a little hard, your*
27
28 326 *heart rate increases)?*". Participants rate their confidence on a Likert scale from 0 (not
29
30 327 confident at all) to 10 (very confident), with a higher score indicating greater self-efficacy for
31
32 328 exercise (Cronbach alpha, $\alpha = .951$).

33
34
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36 329 **Intentions to exercise:** Two items will measure intention to engage in moderate intensity
37
38 330 physical activity for 150 min per week in the next 10 weeks, based on previously established
39
40 331 measures[41].

41
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43
44 332 **Outcome expectations:** Ten-items will assess outcome expectations. Five-items are derived
45
46 333 from the validated exercise pros subscale[42] and 5-items to assess outcomes on symptoms
47
48 334 associated with PH.

49
50
51 335 **Social support:** Social support for exercise from family and friends scale[43] uses a 10-item
52
53 336 scale assessing support from family and 10 items reflecting support from friends. Responses
54
55 337 will be recorded on a Likert scale of 1-5, with higher scores representing greater social support.
56
57 338 (Cronbach alpha, family $\alpha = .926$, friends $\alpha = .921$).

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339

340 Data Management

341 The trial will be overseen by the trial management group, consisting the principal
342 investigator, the trial-coordinator and health coach. They will meet every 4 weeks and will
343 oversee all aspects of the conduct of the trial including performing safety oversight activities.
344 Individual data will be de-identified, coded and entered. Each participant, after providing
345 consent, will be assigned a personal identification code (PIC), which will be used on all case
346 report forms and in all electronic databases. Quantitative data will be double data entered, and
347 data validation will take place according to the procedures set out in the data management plan
348 and data validation plan. Prior to any statistical analysis, all variables will be checked for
349 missing, impossible and improbable values. Impossible and improbable values will be defined
350 by clinical opinion and will include values that are outside three standard deviations of the
351 mean value.

353 Statistical Analysis

354 Statistical analysis of quantitative data will be performed using SPSS Version 24. Prior
355 to statistical analysis, the Shapiro-Wilks test will be applied to check for normality. Continuous
356 variables will be reported as mean (range), mean (standard deviation) or median and inter-
357 quartile range, depending on distribution, and categorical variables as frequency (%).
358 Descriptive analyses will be undertaken to summarise participant characteristics and the
359 quantitative data of the intervention feasibility, acceptability and utility. Qualitative data from
360 post trial interviews and researcher field notes will be analyzed using inductive thematic
361 analysis to identity common themes[44]. A one-way ANOVA with repeated measures will be

PHAHB Intervention Protocol

362 used to compare the mean differences in secondary outcome variables between baseline(T1),
363 10 weeks(T2) and 20 weeks (T3).

364

365 **Patient and Public Involvement**

366 Formative qualitative research took place with PH patients during intervention
367 development stages. Semi structured 1:1 phone interviews (N=20) were conducted providing
368 insight into patient barriers and motivators to PA, current PA levels, past experience and
369 personal preferences on components of an exercise programme. The findings fed into the
370 design of the intervention along with PH clinician input. A patient representative provided
371 opinions on the study protocol, patient-facing documentation (e.g. Participants Information
372 Sheet) and intervention material (e.g. exercise manual) to ensure it was patient friendly.

373 **Discussion**

374 The promise of exercise training in the treatment and management of PH has gained
375 significant interest over the past two decades. The observed positive effects of exercise
376 programs on patients' exercise capacity, functional capacity and QoL[44] make a strong
377 argument for the inclusion of exercise as an adjunctive therapy for stable PH patients[46].
378 Considering that structured and resource-intensive hospital-based exercise programs are
379 unlikely to be scalable, it is an opportune time to assess the efficacy, safety and impact of
380 home-based programs as an alternative mode of delivery for PH patients.

381 A home-based exercise program may eliminate many of the barriers associated with
382 in-patients or out-patients setting such as transportation issues, location, long wait periods for
383 availability and further accessibility for patients. A recent review of exercise interventions in
384 PH by Ozemek and colleagues[46] highlighted the need for inclusion of home exercise
385 programs to allow patients achieve the optimal 5 to 6 days of structured exercise.

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3 386 This study will utilise a remote delivery for exercise training with the use of telehealth methods,
4
5 387 wearable technology, performance feedback and behavioural support to deliver and monitor
6
7 388 the intervention. The aim is to eliminate the burden on patients to attend several times per
8
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10 389 week to an outpatient clinic, accommodate resource availability, make the program achievable
11
12 390 in a 'real world' setting and improve the reach beyond the traditional healthcare facilities. The
13
14 391 follow-up post intervention (T3) phase will provide insight into whether behavioural support
15
16 392 is necessary in order for PH patients to remain physically active. PH is considered a rare disease
17
18 393 and with support centralised, remote services, which include assessment of patient progress are
19
20 394 required. Remote assessment of outcomes may remove threats to external validity and
21
22 395 evaluation of the feasibility of such assessment will address the goals of implementation
23
24 396 science to close the research-to-practice gap and support implementation and scale up of
25
26 397 evidence-based interventions[47].
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30 398 To our knowledge, this will be the first study to employ the use of evidence-based
31
32 399 BCTs to examine the feasibility, utility and efficacy of a remote home-based approach to
33
34 400 exercise training for medically stable PH patients. The secondary aims of this study are to
35
36 401 evaluate whether this approach leads to improvement in selected indices of physical and
37
38 402 psychological health.
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403 Conclusion

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45 404 PH is a rare, debilitating condition with most clinics centralized and limited community
46
47 405 resources available. Telehealth holds significant potential to meet the growing support for
48
49 406 exercise training to be included as an add-on therapy by offering remote training and support,
50
51 407 which is key to long-term implementation of exercise training for the PH population. It
52
53 408 provides a service that is more accessible and may potentially offer a more affordable enhanced
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55 409 level of care. Our current understanding is limited with regards the acceptability, feasibility
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3 410 and utility of a home-program for stable PH patients. This study will help gain a valuable
4
5 411 insight into this gap in knowledge.
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413 **References**

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16 612 **Contributors:** CMC led the study conceptualisation, development of intervention content and
17 613 writing of the protocol. BK, SH, NM contributed to the study design, implementation methods
18 614 and refinement of the study protocol. All authors edited the manuscript.
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26 616 had no role in the study design and data collection, analysis and interpretation of data.
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Table 1: Study outcome measures and time points

Assessments	Timepoint		
	Baseline (T1)	Post-Intervention (T2)	Follow-up (T3)
Written informed consent & eligibility	X		
Demographics	X		
Medical history	X		
WHO functional class	X	X	X
Concomitant medication	X	X	X
Adverse events	X	X	X
Exercise capacity (6-MWT), Borg Dyspnea Index	X	X	X
Muscle strength (Sit to Stand)	X	X	X
Physical activity (ActivPAL Micro)	X	X	X
Quality of life (CAMPHOR & SF-36)	X	X	X
Fear of exercise (Tampa Scale)	X	X	X
Psychological constructs	X	X	X
Intervention debrief questionnaires/ semi-structured interviews		X	X



STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym (Page 1)
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry (Page 2)
	2b	All items from the World Health Organization Trial Registration Data Set (Page 2)
Protocol version	3	Date and version identifier (Page 2)
Funding	4	Sources and types of financial, material, and other support (Page 23)
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors (Title page and Page 23)
	5b	Name and contact information for the trial sponsor (Page 23)
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities (Page 23)
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) (Page 23)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention (Pages 3-5)
	6b	Explanation for choice of comparators (Page 7)
Objectives	7	Specific objectives or hypotheses (Page 5)

1
2 Trial design 8 Description of trial design including type of trial (eg, parallel group,
3 crossover, factorial, single group), allocation ratio, and framework (eg,
4 superiority, equivalence, noninferiority, exploratory) **(Page 5)**
5
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8 **Methods: Participants, interventions, and outcomes**
9

10 Study setting 9 Description of study settings (eg, community clinic, academic hospital)
11 (and list of countries where data will be collected. Reference to where
12 list of study sites can be obtained **(Page 7)**
13

14 Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility
15 criteria for study centres and individuals who will perform the
16 interventions (eg, surgeons, psychotherapists) **(6)**
17
18

19 Interventions 11a Interventions for each group with sufficient detail to allow replication,
20 including how and when they will be administered **(Page 7-11)**
21

22 11b Criteria for discontinuing or modifying allocated interventions for a
23 given trial participant (eg, drug dose change in response to harms,
24 participant request, or improving/worsening disease) **(N/A)**
25

26 11c Strategies to improve adherence to intervention protocols, and any
27 procedures for monitoring adherence (eg, drug tablet return,
28 laboratory tests) **(Page 8-10)**
29

30 11d Relevant concomitant care and interventions that are permitted or
31 prohibited during the trial **(Page 6)**
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33

34 Outcomes 12 Primary, secondary, and other outcomes, including the specific
35 measurement variable (eg, systolic blood pressure), analysis metric
36 (eg, change from baseline, final value, time to event), method of
37 aggregation (eg, median, proportion), and time point for each
38 outcome. Explanation of the clinical relevance of chosen efficacy and
39 harm outcomes is strongly recommended **(Page 5, & Page 11-15)**
40
41

42 Participant 13 Time schedule of enrolment, interventions (including any run-ins and
43 timeline washouts), assessments, and visits for participants. A schematic
44 diagram is highly recommended (see Figure) **(table 1)**
45

46 Sample size 14 Estimated number of participants needed to achieve study objectives
47 and how it was determined, including clinical and statistical
48 assumptions supporting any sample size calculations **(Page 7)**
49

50 Recruitment 15 Strategies for achieving adequate participant enrolment to reach
51 target sample size **(Page 6)**
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54 **Methods: Assignment of interventions (for controlled trials)**
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56 Allocation:
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1			
2	Sequence	16a	Method of generating the allocation sequence (eg, computer-
3	generation		generated random numbers), and list of any factors for stratification.
4			(To reduce predictability of a random sequence, details of any
5			planned restriction (eg, blocking) should be provided in a separate
6			document that is unavailable to those who enrol participants or assign
7			interventions (N/A)
8			
9			
10	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central
11	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
12	mechanism		describing any steps to conceal the sequence until interventions are
13			(N/A)
14			
15	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,
16			and who will assign participants to interventions (N/A)
17			
18			
19	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial
20	(masking)		participants, care providers, outcome assessors, data analysts), and
21			how (N/A)
22			
23		17b	If blinded, circumstances under which unblinding is permissible, and
24			procedure for revealing a participant's allocated intervention during
25			the trial (N/A)
26			
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Methods: Data collection, management, and analysis

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30	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other
31	methods		trial data, including any related processes to promote data quality (eg,
32			duplicate measurements, training of assessors) and a description of
33			study instruments (eg, questionnaires, laboratory tests) along with
34			their reliability and validity, if known. Reference to where data
35			collection forms can be found, if not in the protocol (Page 11-15)
36			
37			
38		18b	Plans to promote participant retention and complete follow-up,
39			including list of any outcome data to be collected for participants who
40			discontinue or deviate from intervention protocols (Page 7)
41			
42	Data	19	Plans for data entry, coding, security, and storage, including any
43	management		related processes to promote data quality (eg, double data entry;
44			range checks for data values). Reference to where details of data
45			management procedures can be found, if not in the protocol (Page
46			16)
47			
48			
49	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.
50	methods		Reference to where other details of the statistical analysis plan can be
51			found, if not in the protocol (Page 16)
52			
53		20b	Methods for any additional analyses (eg, subgroup and adjusted
54			analyses) (Page 16)
55			
56			
57		20c	Definition of analysis population relating to protocol non-adherence
58			(eg, as randomised analysis), and any statistical methods to handle
59			missing data (eg, multiple imputation) (Page 16)
60			

Methods: Monitoring

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed (Page 16)
25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct (Page 13)
	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor (Page 16)

Ethics and dissemination

26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval (Page 2)
	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) (Page 16)
	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) (Page 7)
		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable (N/A)
	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial (Page 16)
	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site (Page 23)
	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators (Page 23)
	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation (N/A)

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| Dissemination
policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions (Page 2) |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers (Page 23) |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code (Page 2) |

16 Appendices

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|-------------------------------|----|---|
| Informed consent
materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates (Appendix A) |
| Biological
specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable (N/A) |

25 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013
26 Explanation & Elaboration for important clarification on the items. Amendments to the
27 protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT
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BMJ Open

The Pulmonary Hypertension And Home-Based (PHAHB) Exercise Intervention: Protocol for a Feasibility Study

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PHAHB Intervention Protocol

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5 **1 The Pulmonary Hypertension And Home-Based (PHAHB) Exercise Intervention:**
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8 **2 Protocol for a Feasibility Study**
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PHAHB Intervention Protocol

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31 26 **ABSTRACT**
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36 27 **Introduction:** Novel therapies for pulmonary hypertension (PH) have improved survival and
37
38 28 slowed disease progression. However, patients still present with symptoms of exertional
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41 29 dyspnoea and fatigue, which impacts their ability to perform activities of daily living, reduces
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44 30 exercise tolerance and impairs their quality of life (QoL). Exercise training has shown to be
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46 31 safe and effective at enhancing QoL and physical function in PH patients, yet it remains an
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49 32 under-utilized adjunct therapy. Most exercise training for PH patients has been offered through
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51 33 hospital-based programmes. Home-based exercise programmes provide an alternative model
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54 34 that has the potential to increase the availability and accessibility of exercise training as an
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56 35 adjunct therapy in PH. The purpose of this study is to investigate the feasibility, acceptability,
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59 36 utility and safety of a novel remotely supervised home-based PH exercise programme.
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4 37 **Methods:** Single arm intervention with a pre/post comparisons design and a follow up
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6
7 38 maintenance phase will be employed. Eligible participants (n= 25) will be recruited from the
8
9 39 Mater Misericordiae University Hospital PH Unit. Participants will undergo a 10-week home-
10
11 40 based exercise program, with induction training, support materials, telecommunication support
12
13
14 41 and health coaching sessions followed by a 10-week maintenance phase. The primary
15
16 42 outcomes are feasibility, acceptability, utility and safety of the intervention. Secondary
17
18 43 outcomes will include the impact of the intervention on exercise capacity, physical activity,
19
20 44 strength, health-related quality of life and exercise self-efficacy.

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24 45 **Ethics and dissemination:** Ethics approval has been obtained from the Mater Misericordiae
25
26 46 Institutional Review Board REF:1/378/2032 and Dublin City University Research Ethics
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28 47 DCUREC/2018/246. A manuscript of the results will be submitted to a peer-reviewed journal
29
30 48 and results will be presented at conferences, community and consumer forums and hospital
31
32 49 research conferences. Trial Registration: ISRCTN Registry: ISRCTN83783446. Protocol
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34 50 version. 2.0.

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41 51 **Keywords:** Pulmonary Hypertension, exercise rehabilitation, physical activity, exercise
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43 52 training, home-based, remote delivery, wearable technology, health coaching.

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49 53 **Strengths and limitations of this study**

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52 54 • This is the first study to assess the feasibility, utility, safety and acceptability of a novel
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54 55 distance-based exercise intervention for PH patients

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- 56 • The intervention is pragmatic and scalable and could be integrated into existing
57 healthcare pathways.
- 58 • As PH is a rare disease with a small population size within Ireland, there is a lack of a
59 usual care control group which is a limitation of the study.

60

For peer review only

PHAHB Intervention Protocol

61 **INTRODUCTION**

62 Despite earlier diagnosis and improved pharmaceutical therapies, many PH participants
63 continue to experience exertional symptoms of dyspnoea and fatigue, which leads to a
64 reduction in functional capacity and in turn, quality of life (QoL). Consequently, there is greater
65 recognition for a more holistic approach to PH treatment beyond pharmacological therapies[1].

66 Exercise rehabilitation and physical activity (PA) interventions have continuously
67 demonstrated effectiveness as adjuvant therapies for improving exercise capacity and QoL in
68 a spectrum of cardio-pulmonary disorders[2-5]. Although research investigating exercise in PH
69 is an emerging field of study, the body of evidence regarding its efficacy continues to grow.
70 Recent systematic reviews and meta-analyses have reported improvements in exercise capacity
71 and QoL in PH [6-11], which has prompted a renewed focus on exercise training and
72 pulmonary rehabilitation for PH patients.

73 In the 2015, the European Society of Cardiology /European Respiratory Society
74 published guidelines for the diagnosis and treatment of pulmonary hypertension, it was
75 recommended that exercise training should be implemented by specialist PH centres as an
76 adjunct to medical therapy for stable PH participants [12]. Currently, the optimal mode,
77 intensity, and duration of exercise training, and the characteristics of participants most likely
78 to benefit from exercise training are poorly understood [13]. To date, the centre-based
79 Hiedelberg rehabilitation program remains the gold standard exercise program in PH. It
80 involves an intensive 3-week in-patient induction phase, with a continued multimodality,

PHAHB Intervention Protocol

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4 81 monitored outpatient period [14]. Despite improvements in exercise capacity, muscle function,
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7 82 QoL and pulmonary haemodynamics, the initial in-patient phase is resource intensive to
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10 83 operate and roll out [15].
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14 84 An alternative and pragmatic approach, found to be as effective as a supervised exercise
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16 85 programme in cardiac rehabilitation, is a home-based model of delivery [16]. Home-based
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19 86 interventions also provide solutions to common barriers to participation in centre-based
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22 87 programs such as access and transport issues, and are less expensive [17]. Further, patient
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25 88 populations express a preference for unsupervised, self-paced, low-moderate intensity PA,
26
27 89 specifically walking [18-19]. Through the use of telehealth, distance-based programmes could
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30 90 potentially offer an alternative mode of delivery for exercise training to increase adherence,
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32 91 availability and affordability for PH patients.
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36 92 Although the few studies examining the beneficial effects of home-based exercise
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39 93 training in PH are promising [20-21] none included strategies to maximise adherence. An
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42 94 evidence-based approach to implement lifestyle changes requires the implementation of health
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45 95 behaviour change strategies grounded in behaviour change theory [22]. Evidence-based
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47 96 behaviour change techniques (BCT's) can be used to improve intervention effectiveness [23].
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49 97 For example, the combination of the following BCT's: self-monitoring; goal setting; providing
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52 98 feedback on performance; and, review of behaviour goals, is associated with increased
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55 99 intervention effectiveness in PA interventions [24]. Interventions that meet the support needs
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57 100 and offer opportunities for self-monitoring have been found to be effective for improving PA
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59 101 in other chronic disease groups[25]. Wearable technology holds great potential as an easy to
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PHAHB Intervention Protocol

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4 102 use, low cost self-monitoring tool with continuous feedback [26] and are perceived as
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7 103 acceptable and useful for individuals with chronic diseases [27]. Through the use of telehealth,
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10 104 distance-based programmes could potentially offer an alternative mode of delivery for exercise
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12 105 training to increase adherence, availability and affordability for PH patients. The aim of this
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14 106 study is to assess the feasibility, acceptability, utility and safety of a novel home-based exercise
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17 107 training programme for PH patients.

108 **METHODS AND ANALYSIS**

109 **Study Design**

110 The study will employ a single group pre-post-intervention design with a follow up
111 maintenance phase. The purpose of the maintenance phase is to assess if the intervention
112 facilitates the adoption of independent exercise in participants when formal support is removed.
113 The study will adhere to the Standard Protocol Items: Recommendations for Interventional
114 Trials Reporting Template (SPIRIT)[28]. Participants will complete assessments at baseline
115 (T1), after the 10-week intervention (T2) and at 20-weeks follow up (T3).

117 **Eligibility Criteria**

118 Inclusion criteria are male or female > 18 years, with a diagnosis of PH (WHO Groups
119 I and IV) by right heart catheterisation showing baseline mean pulmonary arterial pressure ≥ 25
120 mm Hg, pulmonary vascular resistance ≥ 240 dyne s cm⁻⁵, pulmonary capillary wedge pressure
121 ≤ 15 mmHg and receiving optimized conventional PH therapy. Participants must be clinically
122 stable with no medication changes in the 2 months prior to enrolment.

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4 123 Exclusion criteria include PH of any cause other than outlined in the inclusion criteria such as
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6 124 PH from left heart disease or lung disease/hypoxia (WHO Groups II and III) , pregnancy, signs
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9 125 of right heart decompensation, acute infection and pyrexia, change in disease-targeted therapy
10
11 126 within the last 2-months, scheduled to receive an investigational drug during the course of the
12
13 127 study, FEV1/FVC <0.5, total lung capacity <70% of the normal value, active liver disease,
14
15 128 porphyria, elevations of serum transaminases >3 x upper limit of normal (ULN), bilirubin >1.5
16
17 129 x ULN, haemoglobin concentration <75% of the lower limit of normal, systolic blood pressure
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19 130 <85 mmHg, active myocarditis, unstable angina pectoris, exercise induced ventricular
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21 131 arrhythmias, decompensated heart failure, hypertrophic obstructive cardiomyopathy or
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23 132 impaired left ventricular function.
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134 **Participant Recruitment**

35 135 Participants will be recruited from the Pulmonary Hypertension Unit at the Mater
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37 136 Misericordiae University Hospital, Dublin, Ireland. Eligible participants will be invited to
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39 137 participate during their routine 3-6 month clinic visit. They will be given a verbal explanation
40
41 138 of the study and provided with an information sheet by their PH Specialist (SG/BMC) or a
42
43 139 member of their clinical team. After receiving the information, potential participants will have
44
45 140 the option to speak on the day to a member of the research team or to receive a follow-up phone
46
47 141 call within 1-2 days. Participants will have the opportunity to ask questions and will have time
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49 142 to consider their participation. Written consent will be obtained by mail.
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PHAHB Intervention Protocol

144 **Sample Size**

145 Pilot study sample size typically ranges from 24 to 50[29-31]. We estimate a target
146 sample size of 25 to be sufficient for this feasibility study [30].

147 **Primary Outcomes**

148 **Feasibility:** Assessed by participant recruitment (enrolment as a proportion of eligible
149 participants) and retention (proportion that completed all assessments); (ii) engagement with
150 the intervention measured according to attendance at induction sessions and health coaching
151 sessions and adherence, defined as the percentage of home-based exercise sessions recorded
152 by participants who complete the intervention assessed via log books and weekly calls) and
153 (iii) by examining delivery as intended (as per protocol) and health coach perceptions
154 concerning how patients' received the intervention components. This will be captured
155 immediately after each session in order to keep a record of how delivery was received in
156 relation to the planned delivery (e.g., if a participants required extra time or further support
157 following the induction training session).

158 **Acceptability and utility:** Assessed through self-report questionnaires completed at T2 and
159 interviews. The questionnaire will assess participant perceptions of intervention
160 appropriateness, effectiveness, quality, accessibility/usability, intrusiveness, and overall
161 enjoyment and attitude towards the intervention. Semi-structured interviews with a sub-set of
162 participants (~ n=12) will be conducted within 2-weeks of completing the T2 assessment. The
163 interviews will further explore acceptability and utility of the intervention including
164 perceptions concerning exercise prescription, adherence to different components of the
165 intervention, in addition to the facilitating and hindering factors to participation. Participants

PHAHB Intervention Protocol

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4 166 will also be asked to offer suggestions for improvement and implementation. Interviews will
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7 167 be conducted via telephone or online platforms (i.e., Zoom) and will be audio-recorded and
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9 168 transcribed.

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12 169 **Safety:** Participants will be instructed to inform researchers immediately of any adverse
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14 170 advent. In addition, participants will be questioned about adverse events directly related to
15
16 171 participation in the exercise intervention during a bi-weekly support call.
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23 173 **Secondary Outcomes**

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26 174 **Exercise capacity:** Assessed using the 6-min walk test (6MWT). The test will be administered
27
28 175 according to the European Respiratory Society Guidelines [32] and will be conducted at home
29
30 176 using detailed step-by-step video and written instructions and remotely supervised via
31
32 177 phone/teleconferencing by a researcher (CMC). A family member/friend will assist with
33
34 178 conducting the test, including measuring blood pressure and SpO₂ with guidance from the
35
36 179 researcher before and after the test. Subjective symptoms (RPE and dyspnoea- Borg Dyspnoea
37
38 180 Scale 0-10) will be recorded before and after the test. The Frontier X chest worn monitor will
39
40 181 be worn during the test to provide real-time feedback. The assistant will ask the participant to
41
42 182 call out their SpO₂ and HR at each minute of the test. Standard encouragement will be delivered
43
44 183 by the assistant, with researcher prompting, if needed.
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54 185 **Muscular strength:** Lower body muscle strength will be assessed using the 30-sec sit-to-stand
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56 186 test (STS) from a seat height of 40-45 cm. The STS is a commonly used field-based measure
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PHAHB Intervention Protocol

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4 187 of functional lower limb muscle strength, particularly in clinical and elderly populations. The
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7 188 test will be conducted in each participant's home via teleconference. A researcher (CMC) will
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10 189 provide a demonstration, time the test, and count the repetitions. Each participant will perform
11
12 190 two trials separated by 5-min, with the best score being recorded.
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18 192 **Physical activity behaviour:** ActivPAL³ micro activity monitors (PAL Technologies Ltd.
19
20 193 Glasgow, Scotland) will be used to assess free living activity behaviour. The device samples
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23 194 at 20Hz for 15-sec epochs and measures bodily accelerations using triaxial accelerometer. An
24
25 195 inbuilt inclinometer measures thigh inclination. Proprietary algorithms classifies activities into
26
27
28 196 sitting/lying time, standing time, stepping time, step count and activity counts. Participants will
29
30 197 be mailed the accelerometer together with detailed wear instruction and provided with a
31
32
33 198 prepaid postage envelope to return the device. They will be instructed to wear the device on
34
35 199 the anterior aspect of their right thigh continuously for 7-days, except during water immersion
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37
38 200 activities (i.e., swimming and bathing). The ActivPAL is a valid and reliable measure of
39
40 201 activity and sedentary behaviour [33-34].
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203 **Psychological Outcomes and Mediators**

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49 204 **Quality of life:** The Medical Outcomes Study Short-Form 36-Item Survey (SF-36) is a well-
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52 205 validated, generic questionnaire [35] consisting of physical functioning, physical role
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54 206 functioning, bodily pain, and general health and the four mental subscales of vitality, social
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57 207 functioning, emotional role functioning and mental health. The Cambridge Pulmonary
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59 208 Hypertension Outcome Review (CAMPHOR)[36] was designed as a disease-specific health-
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209 related QoL measure for PH patients. It is widely used as a clinical and research tool in PH. It
210 is made up of three dimensions which assess symptoms (25 items) functioning (15 items) and
211 quality life (25 items).

212 **Fatigue:** The Fatigue Severity Scale (FSS)[37] measures the patient's perception of the
213 influence of fatigue on physical and social functioning through responses to nine different
214 physical and social functioning situations. The FSS is a valid tool for assessing fatigue across
215 various health conditions[38].

216 **Self-regulatory self-efficacy for exercise:** Assessed using a modified 11-item scale[39-40],
217 which provide information on task, scheduling and recovery self-efficacy. Questions begin
218 with the stem "*How confident are you that you can...*" and include items such as "*plan exercise*
219 *sessions that will be at least moderately difficult (e.g. have you breathing a little hard, your*
220 *heart rate increases)?"*. Participants rate their confidence on a 0-10 Likert scale, with a higher
221 score indicating greater self-efficacy for exercise (Cronbach alpha, $\alpha = .951$).

222 **Intentions to exercise:** Two items will measure intention to engage in moderate-intensity
223 physical activity for 150-min/week in the next 10-weeks, based on previously established
224 measures[41].

225 **Outcome expectations:** Ten-items will assess outcome expectations. Five-items are derived
226 from the validated exercise pros subscale [42] and 5-items to assess outcomes related to
227 common symptoms reported in PH, 'such as breathlessness' [43].

228 **Social support:** Social support for exercise from family and friends scale[44] uses a 20-item
229 scale to assess support from family and friends respectively. Responses will be recorded on a

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230 Likert scale of 1-5, with higher scores representing greater social support. (Cronbach alpha,
231 family $\alpha = .926$, friends $\alpha = .921$).

232

233 Outcome assessments will take place at baseline (T1), after the 10-week intervention (T2) and
234 at 20-weeks follow up (T3). Semi-structured interviews will be conducted at T2 to assess
235 patient's perspective on program acceptability and feasibility and at T3 to assess the follow up
236 phase. Table 1 outlines the timeline of the assessments.

237 Procedure

238 Participants will complete all assessments, induction training and exercise training in
239 their own home and will maintain in contact with researchers via telecommunication
240 technologies (phone, videoconferencing and email). Following consent, a baseline assessment
241 will be conducted (see Table 1) and participants will be provided with an accelerometer to
242 record their activity for the following week, along with a prepaid postage envelope to return
243 device. The assessment procedure will be repeated at T2 (10-weeks) and T3 (20-weeks).

244 Participants will be provided with a home exercise bike (NordicTrack GX 2.7U), a wearable
245 tracker watch (The Fitbit Charge 3), pulse oximeter (SafeHeart SpO₂ monitor), real time single
246 lead ECG/HR/respiratory rate monitor (Frontier X), blood pressure monitor (Beurer BM44), a
247 TheraBand, exercise manual, exercise diary and access to online videos. The exercise manual
248 was partly based on the design of previous PA intervention in chronic disease - PPARCS [26]
249 and WATTAP [45] trials and also our formative research with PH patients. The formative
250 research highlighted the lack of understanding of the benefits of exercise, the importance of
251 self-regulation strategies to support motivation and exercise engagement and the desire for

PHAHB Intervention Protocol

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4 252 visual picture and instruction of exercise. Concerns of breathlessness and energy management
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7 253 were also evident in interviews with PH patients and integrated into the exercise manual. The
8
9 254 manual offers a comprehensive, patient-friendly resource detailing; 1) general information
10
11 255 about the study; 2) useful links and contacts; 3) background information on PH; 4) education
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14 256 regarding exercise safety and the benefits of physical activity; 5) workbook style sections on
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17 257 motivation, goal setting, overcoming barriers and psychosocial support; 6) managing
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19 258 breathlessness; 7) exercise intensity and limits; 8) guided home exercises with written and
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22 259 visual details and advice on progression; and 9) advice on pacing and energy conservation.
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24 260 Participants will receive video clips of a qualified exercise specialist performing the exercises.
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27 261 Participants will be encouraged to refer to the video to ensure adherence to correct technique.
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29 262 Online videos will provide a visual demonstration of each exercise. Participants will be
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32 263 provided with an exercise diary as a tool to record their activity and effort. BCTs will be
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35 264 integrated in the intervention through wearable technology devices, the use of print and visual
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37 265 materials and health coaching and support calls.
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40 266 The 10-week intervention consists of the following components: Three 60-90 min induction
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42 267 sessions (week 0 and 1), up to five 30-min support health coaching sessions (at week 2, 3, 5,
43
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45 268 7, 9) and 3-5 weekly home-based exercise sessions. The intervention will end prior to T2
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47 269 assessment. Participants will continue to have access to the exercise manual, bike and Fitbit
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50 270 during the maintenance phase.

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56 272 ***Induction Training***
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273 Induction training (1:1), via video conferencing, is a key component to ensure
274 patients are confident to exercise at home and understand the appropriate exercise intensity and
275 how to exercise safely. Participants will be encouraged to involve a family member, friend or
276 carer in the induction training. The sessions will focus on the following topics:

277 *Session 1 - Introduction*; Education on PH and benefits of PA for PH. Familiarisation with
278 intervention materials/equipment and self-monitoring.

279 *Session 2 - Exercise Safety and Exercise Demonstration*; The session will focus on recognizing
280 exercise limits, warning signs, and managing exercise intensity. Visual demonstrations of
281 breathing techniques and aerobic, strength, and respiratory training will be provided, with the
282 opportunity for behavioural practice during the session to check technique and instil
283 confidence.

284 *Session 3 - Recap*; Exercise demonstrations and key safety points will be reviewed. Any issues
285 regarding intervention materials/equipment will be addressed and participant goals will be
286 reviewed, alongside additional tips for family/friend support and motivation.

288 ***Health Coaching Sessions***

289 The health coaching sessions (via videoconferencing) will use BCTs to foster exercise
290 adherence, motivate and provide support. Over the 5 sessions the topics will include; benefits
291 of exercise, goal setting, action planning, self-monitoring, identification and management of
292 barriers to exercise, problem solving and feedback on behaviour, with the option for

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293 participants to complete formal paperwork in the intervention manual. If required, additional
294 support will be available outside of scheduled sessions.

295 Participants will be encouraged to wear the Fitbit Charge 3 daily during the intervention. The
296 Fitbit data will be used to guide individually tailored goals, assess adherence to exercise and
297 overall daily PA and as tool to provide feedback to the researcher and participants.

298

299 ***Exercise Program***

300 Participants will complete a 10-week individualised, home-based exercise programme.

301 The programme will be prescribed using the FITT principle (Frequency, Intensity, Time and
302 Type) and will employ a multimodal approach that integrates aerobic, resistance and
303 respiratory training. The goals for each component are outlined in the sections below. These
304 are aspirational goals that may not be realistic for all participants. Exercise prescription will
305 be individualized based on their baseline PA levels, 6-min walk test distance (6MWD) and
306 physical capabilities. The modified Borg rating of perceived exertion (RPE) scale[46] will be
307 used to help prescribe exercise intensity. The RPE scale is a psychophysiological measurement
308 that translates physical stimuli to a psychological construct of perceived exertion and has been
309 validated in other clinical groups[47]. Participants will aim to achieve an RPE of 3 (moderate)
310 initially. Based on individual progress an RPE of 4 (somewhat hard) may be advised for some
311 participants. The exercise program will include:

312 *Aerobic Training*; Participants will initially aim will be to undertake a minimum of 10-min of
313 structured aerobic exercise involving walking, cycling or a combination on ≥ 3 d/week.

314 Participants will be allowed to perform this exercise in a single bout, or accumulate it in bouts

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4 315 of at least 5-min in duration. The duration will be progressively increased, with the goal of
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6 316 accumulating ≥ 30 min on ≥ 5 d/week.

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9 317 *Resistance Training;* Participants will initially undertake resistance training on 2 d/week,
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11 318 involving a single set of 6-8 repetitions of upper and lower extremity and whole body exercises.
12
13 319 Training volume will progressively increase with the goal of completing 2-3 sets of 10-12 reps
14
15 320 of 4-6 exercises on three non-consecutive days. Participants will use pursed lip breathing to
16
17 321 help airways stay open during exhalation. Bodyweight resistance will be used initially and
18
19 322 based on individual ability, TheraBand's, water bottles or light dumbbells will be introduced.

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21 323 *Respiratory Training;* Participants will initially perform 10-min of respiratory training at least
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23 324 twice a week, involving a combination of stretching, breathing techniques (e.g., pursed lip,
24
25 325 diaphragmic and slow breathing), and respiratory muscle strengthening exercises. Training
26
27 326 volume will progressively increase with the goal of completing 15/20 min of accumulated
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29 327 respiratory training on ≥ 3 d/week. Participants can progress to use a TheraBand to complete
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31 328 respiratory training.

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33 329 Participants will wear a Frontier X device (receiver attached to a strap place around the chest)
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35 330 during exercise sessions. The first 2-weeks will be monitored by researchers and then
36
37 331 periodically monitored. This will allow access to real time ECG, heart rate (HR), respiratory
38
39 332 rate and cadence. Oxygen saturation will be monitored and participants will be instructed to
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41 333 stop exercising if the SpO₂ value drops below 88%, as per guidelines[48]. Participants will
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43 334 document any adverse events and report to the research team immediately.

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336 Data Management

337 The trial will be overseen by the trial management group, consisting the principal
338 investigator, the trial-coordinator and health coach. They will meet every 4-weeks and will
339 oversee all aspects of the conduct of the trial including performing safety oversight activities.
340 Individual data will be de-identified, coded and entered. Each participant will be assigned a
341 personal identification code (PIC), which will be used on all case report forms and in all
342 electronic databases. Prior to any statistical analysis, all variables will be checked for missing,
343 impossible and improbable values. Impossible and improbable values will be defined by
344 clinical opinion and will include values that are outside three standard deviations of the mean
345 value.

347 Statistical Analysis

348 Statistical analysis of quantitative data will be performed using SPSS Version 24. Prior
349 to statistical analysis, the Shapiro-Wilks test will be applied to check for normality. Continuous
350 variables will be reported as mean (range), mean (standard deviation) or median and inter-
351 quartile range, depending on distribution, and categorical variables as frequency (%).
352 Descriptive analyses will be undertaken to summarise participant characteristics and the
353 quantitative data of the intervention feasibility, acceptability and utility. Qualitative data from
354 post-trial interviews and researcher field notes will be analyzed using inductive thematic
355 analysis to identity common themes[49]. A linear mixed model analysis (MMA) will be used
356 to examine the impact of time in this study . A MMA is a suitable approach to modelling time
357 series data which contains repeated measures [50]. The MMA does not require complete data

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358 sets and does not exclude participants with missing data [51]. Furthermore, MMA has less
359 stringent assumptions than other repeated measures models (such as analysis of variance) and
360 also exhibits increased power to detect treatment effects. The data will adjust for confounding
361 variables, such as age, baseline line fitness, gender and PH group.

362 **Patient and Public Involvement**

363 Formative qualitative research took place with PH patients during intervention
364 development stages. Semi-structured phone interviews (N=19) were conducted providing
365 insight into patient barriers and motivators to PA, and exercise preferences. The findings fed
366 into the design of the intervention along with PH clinician input. A patient representative
367 provided opinions on the study protocol, patient-facing documentation (e.g., Participants
368 Information Sheet) and intervention material (e.g., exercise manual) to ensure it was patient
369 friendly.

370 **Discussion**

371 The promise of exercise training in the treatment and management of PH has gained
372 significant interest over the past two decades. The observed positive effects of exercise
373 programs on patients' exercise capacity, functional capacity and QoL[52] make a strong
374 argument for the inclusion of exercise as an adjunctive therapy for stable PH patients[53].
375 Considering that structured and resource-intensive hospital-based exercise programs are
376 unlikely to be scalable, it is an opportune time to assess the efficacy, safety and impact of
377 home-based programs as an alternative mode of delivery for PH patients.

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4 378 A home-based exercise program may eliminate many of the barriers associated with in-
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7 379 patients or out-patients setting such as transportation issues, location, long wait periods for
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9 380 availability and accessibility for patients. A recent review of exercise interventions in PH by
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12 381 Ozemek and colleagues [53] highlighted the need for inclusion of home exercise programs to
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14 382 allow patients achieve the optimal 5 to 6 days of structured exercise.

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17 383 This study will utilise a remote delivery for exercise training with the use of telehealth
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20 384 methods, wearable technology, performance feedback and behavioural support to deliver and
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23 385 monitor the intervention. The aim is to eliminate the burden on patients to attend several times
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26 386 per week to an outpatient clinic, accommodate resource availability, make the program
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28 387 achievable in a 'real world' setting and improve the reach beyond the traditional healthcare
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30 388 facilities. The follow-up post intervention (T3) phase will provide insight into whether
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33 389 behavioural support is necessary in order for PH patients to remain physically active.
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36 390 Furthermore, it will allow us to assess resource needs in future home-based exercise
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38 391 programmes such as the provision of specific exercise equipment and the use of ubiquitous,
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40 392 low cost devices to monitor activity and safety (e.g. bike, wearable activity tracker). PH is
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43 393 considered a rare disease and with support centralised, remote services, which include
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46 394 assessment of patient progress are required. Remote assessment of outcomes may remove
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48 395 threats to external validity and evaluation of the feasibility of such assessment will address the
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50 396 goals of implementation science to close the research-to-practice gap and support
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53 397 implementation and scale up of evidence-based interventions[54].

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56 398 To our knowledge, this will be the first study to employ the use of evidence-based BCTs
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59 399 to examine the feasibility, utility and efficacy of a remote home-based approach to exercise
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4 400 training for medically stable PH patients. The secondary aims of this study are to evaluate
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6 401 whether this approach leads to improvement in selected indices of physical and psychological
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12 403 PH is a rare, debilitating condition with most clinics centralized and limited community
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14 404 resources available. Telehealth holds significant potential to meet the growing support for
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16 405 exercise training to be included as an adjunct therapy by offering remote training and support,
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18 406 which is key to long-term implementation of exercise training for the PH population. It
19
20 407 provides a service that is more accessible and may potentially offer a more affordable enhanced
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22 408 level of care. Our current understanding is limited concerning the acceptability, feasibility and
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24 409 utility of a home-program for stable PH patients. This study will help gain a valuable insight
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26 410 into this gap in knowledge.
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37 412 **Ethics and dissemination:** Ethics approval has been obtained from the Mater Misericordiae
38
39 413 Institutional Review Board REF:1/378/2032 and Dublin City University Research Ethics
40
41 414 DCUREC/2018/246. A manuscript of the results will be submitted to a peer-reviewed journal
42
43 415 and results will be presented at conferences, community and consumer forums and hospital
44
45 416 research conferences. Trial Registration: ISRCTN Registry: ISRCTN83783446. Protocol
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598 **Contributors:** CMC, BK, SJH, NMC, SG, BMC, and NM were involved in study
599 conceptualisation, development of intervention content and writing of the protocol. AMC
600 provided guidance on the statistical analysis. CMC led the writing of the manuscript and all
601 authors edited and reviewed the manuscript.

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603 role in the study design and data collection, analysis and interpretation of data.

604 **Competing interest statement:** None declared.

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612 Table 1: Study outcome measures and time points

Assessments	Time		
	Baseline (T1)	Post- Intervention (T2)	Follow-up (T3)
Written informed consent & eligibility	X		
Demographics	X		
Medical history	X		
WHO functional class	X	X	X
Concomitant medication	X	X	X
Adverse events	X	X	X
Exercise capacity (6-MWT), Borg Dyspnea Index	X	X	X
Muscle strength (Sit to Stand)	X	X	X
Physical activity (ActivPAL Micro)	X	X	X
Quality of life (CAMPHOR & SF-36)	X	X	X

PHAHB Intervention Protocol

Psychological constructs	X	X	X
Intervention debrief questionnaires/ semi-structured interviews		X	X

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STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym (Page 1)
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry (Page 3)
	2b	All items from the World Health Organization Trial Registration Data Set (Page 3)
Protocol version	3	Date and version identifier (Page 3)
Funding	4	Sources and types of financial, material, and other support (Page 29)
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors (Title page and Page 29)
	5b	Name and contact information for the trial sponsor (Page 29)
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities (Page 29)
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) (Page 29)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention (Pages 5-7)
	6b	Explanation for choice of comparators (Page 9)
Objectives	7	Specific objectives or hypotheses (Page 7)

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Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) (Page 7)
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Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) (and list of countries where data will be collected. Reference to where list of study sites can be obtained (Page 8)
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Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) (7)
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Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered (Page 13-17)
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	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) (N/A)
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	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) (Page 13-17)
--	-----	---

	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial (Page 8)
--	-----	---

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended (Page 7 & 9-13)
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Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) (table 1)
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Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations (Page 9)
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Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size (Page 8)
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Methods: Assignment of interventions (for controlled trials)

Allocation:

1			
2	Sequence	16a	Method of generating the allocation sequence (eg, computer-
3	generation		generated random numbers), and list of any factors for stratification.
4			(To reduce predictability of a random sequence, details of any
5			planned restriction (eg, blocking) should be provided in a separate
6			document that is unavailable to those who enrol participants or assign
7			interventions (N/A)
8			
9			
10	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central
11	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
12	mechanism		describing any steps to conceal the sequence until interventions are
13			(N/A)
14			
15	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,
16			and who will assign participants to interventions (N/A)
17			
18			
19	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial
20	(masking)		participants, care providers, outcome assessors, data analysts), and
21			how (N/A)
22			
23		17b	If blinded, circumstances under which unblinding is permissible, and
24			procedure for revealing a participant's allocated intervention during
25			the trial (N/A)
26			
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Methods: Data collection, management, and analysis

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29			
30	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other
31	methods		trial data, including any related processes to promote data quality (eg,
32			duplicate measurements, training of assessors) and a description of
33			study instruments (eg, questionnaires, laboratory tests) along with
34			their reliability and validity, if known. Reference to where data
35			collection forms can be found, if not in the protocol (Page9-13)
36			
37			
38		18b	Plans to promote participant retention and complete follow-up,
39			including list of any outcome data to be collected for participants who
40			discontinue or deviate from intervention protocols (Page 13)
41			
42	Data	19	Plans for data entry, coding, security, and storage, including any
43	management		related processes to promote data quality (eg, double data entry;
44			range checks for data values). Reference to where details of data
45			management procedures can be found, if not in the protocol (Page
46			18)
47			
48			
49	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.
50	methods		Reference to where other details of the statistical analysis plan can be
51			found, if not in the protocol (Page 18)
52			
53			
54		20b	Methods for any additional analyses (eg, subgroup and adjusted
55			analyses) (Page 18)
56			
57		20c	Definition of analysis population relating to protocol non-adherence
58			(eg, as randomised analysis), and any statistical methods to handle
59			missing data (eg, multiple imputation) (Page 18)
60			

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed (Page 18)
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial (N/A)
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct (Page 10)
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor (Page 18)

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval (Page 3)
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) (Page 18)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) (Page 8)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable (N/A)
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial (Page 18)
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site (Page 29)
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators (Page 18)
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation (N/A)

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| Dissemination
policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions (Page 3) |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers (Page 29) |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code (Page 3) |

15 Appendices

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|-------------------------------|----|---|
| Informed consent
materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates (Appendix A) |
| Biological
specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable (N/A) |

25 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013
26 Explanation & Elaboration for important clarification on the items. Amendments to the
27 protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT
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BMJ Open

The Pulmonary Hypertension And Home-Based (PHAHB) Exercise Intervention: Protocol for a Feasibility Study

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PHAHB Intervention Feasibility Study Protocol

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5 **1 The Pulmonary Hypertension and Home-Based (PHAHB) Exercise Intervention:**
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8 **2 Protocol for a Feasibility Study**
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14 4 *Ciara McCormack^{a*}, Brona Kehoe^b, Sarah J. Hardcastle^{a,c}, Noel McCaffrey^d, Andrew*
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- 20 *Word Count: 4016*

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21

22 **ABSTRACT**

23 **Introduction:** Novel therapies for pulmonary hypertension (PH) have improved survival and
24 slowed disease progression. However, patients still present with symptoms of exertional
25 dyspnoea and fatigue, which impacts their ability to perform activities of daily living, reduces
26 exercise tolerance and impairs their quality of life (QoL). Exercise training has shown to be
27 safe and effective at enhancing QoL and physical function in PH patients, yet it remains an
28 under-utilized adjunct therapy. Most exercise training for PH patients has been offered through
29 hospital-based programmes. Home-based exercise programmes provide an alternative model
30 that has the potential to increase the availability and accessibility of exercise training as an
31 adjunct therapy in PH. The purpose of this study is to investigate the feasibility, acceptability,
32 utility and safety of a novel remotely supervised home-based PH exercise programme.

33 **Methods:** Single arm intervention with a pre/post comparisons design and a follow up
34 maintenance phase will be employed. Eligible participants (n= 25) will be recruited from the
35 Mater Misericordiae University Hospital PH Unit. Participants will undergo a 10-week home-
36 based exercise programme, with induction training, support materials, telecommunication
37 support and health coaching sessions followed by a 10-week maintenance phase. The primary
38 outcomes are feasibility, acceptability, utility and safety of the intervention. Secondary
39 outcomes will include the impact of the intervention on exercise capacity, physical activity,
40 strength, health-related quality of life and exercise self-efficacy.

41 **Ethics and dissemination:** Ethics approval has been obtained from the Mater Misericordiae

PHAHB Intervention Feasibility Study Protocol

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4 42 Institutional Review Board REF:1/378/2032 and Dublin City University Research Ethics
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6 43 DCUREC/2018/246. A manuscript of the results will be submitted to a peer-reviewed journal
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9 44 and results will be presented at conferences, community and consumer forums and hospital
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12 45 research conferences. Trial Registration: ISRCTN Registry: ISRCTN83783446. Protocol
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14 46 version. 2.0.

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19 47 **Keywords:** Pulmonary Hypertension, exercise rehabilitation, physical activity, exercise
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22 48 training, home-based, remote delivery, wearable technology, health coaching.

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26 49 **Strengths and limitations of this study**

- 27
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30 50 • This is the first study to assess the feasibility, utility, safety and acceptability of a novel
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32 51 distance-based exercise intervention for PH patients
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35 52 • The intervention is pragmatic and scalable and could be integrated into existing
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37 53 healthcare pathways
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40 54 • As PH is a rare disease with a small population size within Ireland, there is a lack of a
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42 55 usual care control group which is a limitation of the study
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PHAHB Intervention Feasibility Study Protocol

57 INTRODUCTION

58 Despite earlier diagnosis and improved pharmaceutical therapies, many PH participants
59 continue to experience exertional symptoms of dyspnoea and fatigue, which leads to a
60 reduction in functional capacity and in turn, QoL. Consequently, there is greater recognition
61 for a more holistic approach to PH treatment beyond pharmacological therapies[1].

62 Exercise rehabilitation and physical activity (PA) interventions have continuously
63 demonstrated effectiveness as adjuvant therapies for improving exercise capacity and QoL in
64 a spectrum of cardio-pulmonary disorders[2-5]. Although research investigating exercise in PH
65 is an emerging field of study, the body of evidence regarding its efficacy continues to grow.
66 Recent systematic reviews and meta-analyses have reported improvements in exercise capacity
67 and QoL in PH [6-11], which has prompted a renewed focus on exercise training and
68 pulmonary rehabilitation for PH patients.

69 In the 2015, the European Society of Cardiology /European Respiratory Society
70 recommended that exercise training should be implemented by specialist PH centres as an
71 adjunct to medical therapy for stable PH participants [12]. Currently, the optimal mode,
72 intensity, and duration of exercise training, and the characteristics of participants most likely
73 to benefit from exercise training are poorly understood [13]. To date, the centre-based
74 Heidelberg rehabilitation programme remains the gold standard exercise programme in PH. It
75 involves an intensive 3-week in-patient induction phase, with a continued multimodality,
76 monitored outpatient period [14]. Despite improvements in exercise capacity, muscle function,

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4 77 QoL and pulmonary haemodynamics, the initial in-patient phase is resource intensive to
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7 78 operate and roll out [15].
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11 79 An alternative and pragmatic approach, found to be as effective as a supervised exercise
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14 80 programme in cardiac rehabilitation, is a home-based model of delivery [16]. Home-based
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17 81 interventions also provide solutions to common barriers to participation in centre-based
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20 82 programmes such as access and transport issues, and are less expensive [17]. Further, patient
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23 83 populations, including PH [18] express a preference for unsupervised, self-paced, low-
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26 84 moderate intensity PA, specifically walking [19-20]. Through the use of telehealth, distance-
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29 85 based programmes could potentially offer an alternative mode of delivery for exercise training
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32 86 to increase adherence, availability and affordability for PH patients.
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34 87 Although the few studies examining the beneficial effects of home-based exercise
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37 88 training in PH are promising [21-22] none included strategies to maximise adherence. An
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40 89 evidence-based approach to implement lifestyle changes requires the implementation of health
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43 90 behaviour change strategies grounded in behaviour change theory [23]. Evidence-based
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46 91 behaviour change techniques (BCT's) can be used to improve intervention effectiveness [24].
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49 92 For example, the combination of the following BCT's: self-monitoring; goal setting; providing
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52 93 feedback on performance; and, review of behaviour goals, is associated with increased
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55 94 intervention effectiveness in PA interventions [25]. Interventions that meet the support needs
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58 95 and offer opportunities for self-monitoring have been found to be effective for improving PA
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60 96 in other chronic disease groups [26]. Wearable technology holds great potential as an easy to
97 use, low cost self-monitoring tool with continuous feedback [27] and are perceived as

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4 98 acceptable and useful for individuals with chronic diseases [28]. Through the use of telehealth,
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7 99 distance-based programmes could potentially offer an alternative mode of delivery for exercise
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10 100 training to increase adherence, availability and affordability for PH patients. The aim of this
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12 101 study is to assess the feasibility, acceptability, utility and safety of a novel home-based exercise
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14 102 training programme for PH patients.

19 103 **METHODS AND ANALYSIS**22 104 **Study Design**

25 105 The study will employ a single group pre-post-intervention design with a follow-up
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27 106 maintenance phase. The purpose of the maintenance phase is to assess if the intervention
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30 107 facilitates the adoption of independent exercise in participants when formal support is removed.
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33 108 The study will adhere to the Standard Protocol Items: Recommendations for Interventional
34
35 109 Trials Reporting Template (SPIRIT)[29]. Participants will complete assessments at baseline
36
37 110 (T1), after the 10-week intervention (T2) and at 20-weeks follow up (T3).

43 112 **Eligibility Criteria**

46 113 Inclusion criteria are male or female > 18 years, with a diagnosis of PH (WHO Groups
47
48 114 I and IV) by right heart catheterisation showing baseline mean pulmonary arterial pressure ≥ 25
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51 115 mm Hg, pulmonary vascular resistance ≥ 240 dyne s cm⁻⁵, pulmonary capillary wedge pressure
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54 116 ≤ 15 mmHg and receiving optimized conventional PH therapy. Participants must be clinically
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56 117 stable with no medication changes in the 2 months prior to enrolment.

PHAHB Intervention Feasibility Study Protocol

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4 118 Exclusion criteria include PH of any cause other than outlined in the inclusion criteria such as
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7 119 PH from left heart disease or lung disease/hypoxia (WHO Groups II and III), pregnancy, signs
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9 120 of right heart decompensation, acute infection and pyrexia, change in disease-targeted therapy
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11 121 within the last 2-months, scheduled to receive an investigational drug during the course of the
12
13 122 study, FEV1/FVC <0.5, total lung capacity <70% of the normal value, active liver disease,
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15 123 porphyria, elevations of serum transaminases >3 x upper limit of normal (ULN), bilirubin >1.5
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17 124 x ULN, haemoglobin concentration <75% of the lower limit of normal, systolic blood pressure
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19 125 <85 mmHg, active myocarditis, unstable angina pectoris, exercise induced ventricular
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21 126 arrhythmias, decompensated heart failure, hypertrophic obstructive cardiomyopathy or
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23 127 impaired left ventricular function.
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129 Participant Recruitment

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35 130 Participants will be recruited from the Pulmonary Hypertension Unit at the Mater
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37 131 Misericordiae University Hospital, Dublin, Ireland. Eligible participants will be invited to
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39 132 participate during their routine 3-6-month clinic visit. They will be given a verbal explanation
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41 133 of the study and provided with an information sheet by their PH Specialist (SG/BMC) or a
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43 134 member of their clinical team. After receiving the information, potential participants will have
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45 135 the option to speak on the day to a member of the research team or to receive a follow-up phone
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47 136 call within 1-2 days. Participants will have the opportunity to ask questions and will have time
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49 137 to consider their participation. Written consent will be obtained by mail.
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PHAHB Intervention Feasibility Study Protocol

139 **Sample Size**

140 Pilot study sample size typically ranges from 24 to 50 [30-32]. We estimate a target
141 sample size of 25 to be sufficient for this feasibility study [31].

142 **Primary Outcomes**

143 **Feasibility:** Assessed by participant recruitment (enrolment as a proportion of eligible
144 participants) and retention (proportion that completed all assessments); (ii) engagement with
145 the intervention measured according to attendance at induction sessions and health coaching
146 sessions and adherence, defined as the percentage of home-based exercise sessions recorded
147 by participants who complete the intervention assessed via log books and weekly calls) and
148 (iii) by examining delivery as intended (as per protocol) and health coach perceptions
149 concerning how patients' received the intervention components. This will be captured
150 immediately after each session in order to keep a record of how delivery was received in
151 relation to the planned delivery (e.g., if a participants required extra time or further support
152 following the induction training session).

153 **Acceptability and utility:** Assessed through self-report questionnaires completed at T2 and
154 interviews. The questionnaire will assess participant perceptions of intervention
155 appropriateness, effectiveness, quality, accessibility/usability, intrusiveness, and overall
156 enjoyment and attitude towards the intervention. Semi-structured interviews with a sub-set of
157 participants (~ n=12) will be conducted within 2-weeks of completing the T2 assessment. The
158 interviews will further explore acceptability and utility of the intervention including
159 perceptions concerning exercise prescription, adherence to different components of the
160 intervention, in addition to the facilitating and hindering factors to participation. Participants

PHAHB Intervention Feasibility Study Protocol

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4 161 will also be asked to offer suggestions for improvement and implementation. Interviews will
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7 162 be conducted via telephone or online platforms (i.e., Zoom) and will be audio-recorded and
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9 163 transcribed.

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12 164 **Safety:** Participants will be instructed to inform researchers immediately of any adverse
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14 165 advent. In addition, participants will be questioned about adverse events directly related to
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16 166 participation in the exercise intervention during a bi-weekly support call.
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24 168 **Secondary Outcomes**

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26 169 **Exercise capacity:** Assessed using the 6-min walk test (6MWT). The test will be administered
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28 170 according to the European Respiratory Society/ American Thoracic Society technical standard
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30 171 Guidelines [33] and will be conducted at home using detailed step-by-step video and written
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32 172 instructions and remotely supervised via phone/teleconferencing by a researcher (CMC). A
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34 173 family member/friend will assist with conducting the test, including measuring blood pressure
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36 174 and SpO₂ with guidance from the researcher before and after the test. The Frontier X heart rate
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38 175 monitor will be worn during the test to provide real-time feedback. The assistant will ask the
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40 176 participant to call out their SpO₂ and HR at each minute of the test. Subjective symptoms of
41
42 177 dyspnoea and fatigue will be recorded using the Modified Borg Scale (0-10) [34] before and
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44 178 after the test. Standard encouragement will be delivered by the assistant, with researcher
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46 179 prompting, if needed.
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4 181 **Muscular strength:** Lower body muscle strength will be assessed using the 30-sec sit-to-stand
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7 182 test (STS) from a seat height of 40-45 cm. The STS is a commonly used field-based measure
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10 183 of functional lower limb muscle strength, particularly in clinical and elderly populations. The
11
12 184 test will be conducted in each participant's home via teleconference. A researcher (CMC) will
13
14 185 provide a demonstration, time the test, and count the repetitions. Each participant will perform
15
16
17 186 two trials separated by 5-min, with the best score being recorded.
18
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20 187

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22
23 188 **Physical activity behaviour:** ActivPAL³ micro activity monitors (PAL Technologies Ltd.
24
25 189 Glasgow, Scotland) will be used to assess free living activity behaviour. The device samples
26
27
28 190 at 20Hz for 15-sec epochs and measures bodily accelerations using triaxial accelerometer. An
29
30 191 inbuilt inclinometer measures thigh inclination. Proprietary algorithms classifies activities into
31
32 192 sitting/lying time, standing time, stepping time, step count and activity counts. Participants will
33
34
35 193 be mailed the accelerometer together with detailed wear instruction and provided with a
36
37
38 194 prepaid postage envelope to return the device. They will be instructed to wear the device on
39
40 195 the anterior aspect of their right thigh continuously for 7-days, except during water immersion
41
42
43 196 activities (i.e., swimming and bathing). The ActivPAL is a valid and reliable measure of
44
45 197 activity and sedentary behaviour [35-36].
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199 **Psychological Outcomes and Mediators**

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54 200 **Quality of life:** The Medical Outcomes Study Short-Form 36-Item Survey (SF-36) is a well-
55
56
57 201 validated, generic questionnaire [37] consisting of physical functioning, physical role
58
59 202 functioning, bodily pain, and general health and the four mental subscales of vitality, social
60

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4 203 functioning, emotional role functioning and mental health. The Cambridge Pulmonary
5
6 204 Hypertension Outcome Review (CAMPHOR)[38] was designed as a disease-specific health-
7
8
9 205 related QoL measure for PH patients. It is widely used as a clinical and research tool in PH and
10
11 206 assess symptoms (25 items) functioning (15 items) and quality life (25 items).

12
13
14 207 **Fatigue:** The Fatigue Severity Scale (FSS)[39] measures the patient's perception of the
15
16 208 influence of fatigue on physical and social functioning through responses to nine different
17
18 209 physical and social functioning situations. The FSS is a valid tool for assessing fatigue across
19
20 210 various health conditions[40].

21
22 211 **Self-regulatory self-efficacy for exercise:** Assessed using a modified 11-item scale [41-42],
23
24 212 which provide information on task, scheduling and recovery self-efficacy. Questions begin
25
26 213 with the stem "*How confident are you that you can...*" and include items such as "*plan exercise*
27
28 214 *sessions that will be at least moderately difficult (e.g. have you breathing a little hard, your*
29
30 215 *heart rate increases)?*". Participants rate their confidence on a 0-10 Likert scale, with a higher
31
32 216 score indicating greater self-efficacy for exercise (Cronbach alpha, $\alpha = .951$).

33
34 217 **Intentions to exercise:** Two items will measure intention to engage in moderate-intensity
35
36 218 physical activity for 150-min/week in the next 10-weeks, based on previously established
37
38 219 measures[43].

39
40 220 **Outcome expectations:** Ten-items will assess outcome expectations. Five-items are derived
41
42 221 from the validated exercise pros subscale [44] and 5-items to assess outcomes related to
43
44 222 common symptoms reported in PH, 'such as breathlessness' [45].

45
46 223 **Social support:** Social support for exercise from family and friends scale [46] uses a 20-item
47
48 224 scale to assess support from family and friends respectively. Responses will be recorded on a

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225 Likert scale of 1-5, with higher scores representing greater social support. (Cronbach alpha,
226 family $\alpha = .926$, friends $\alpha = .921$).

227

228 Outcome assessments will take place at baseline (T1), after the 10-week intervention (T2) and
229 at 20-weeks follow up (T3). Semi-structured interviews will be conducted at T2 to assess
230 patient's perspective on programme acceptability and feasibility and at T3 to assess the follow
231 up phase. Table 1 outlines the timeline of the assessments.

232 Procedure

233 Participants will complete all assessments, induction training and exercise training in
234 their own home and will maintain in contact with researchers via telecommunication
235 technologies (phone, videoconferencing and email). Following consent, a baseline assessment
236 will be conducted (see Table 1) and participants will be provided with an accelerometer to
237 record their activity for the following week. The assessment procedure will be repeated at T2
238 (10-weeks) and T3 (20-weeks).

239 Participants will be provided with a home exercise bike (NordicTrack GX 2.7U), a wearable
240 tracker watch (The Fitbit Charge 3), pulse oximeter (SafeHeart SpO₂ monitor), real time single
241 lead ECG/HR/respiratory rate monitor (Frontier X), blood pressure monitor (Beurer BM44), a
242 TheraBand, exercise manual, exercise diary and access to online videos. The exercise manual
243 was partly based on the design of previous PA intervention in chronic disease - PPARCS [27]
244 and WATTAP [47] trials and also our formative research with PH patients. The formative
245 research highlighted the lack of understanding of the benefits of exercise, the importance of
246 self-regulation strategies to support motivation and exercise engagement and the desire for

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4 247 visual picture and instruction of exercise. Concerns of breathlessness and energy management
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6
7 248 were also evident in interviews with PH patients and integrated into the exercise manual. The
8
9 249 manual offers a comprehensive, patient-friendly resource detailing; 1) general information
10
11 250 about the study; 2) useful links and contacts; 3) background information on PH; 4) education
12
13
14 251 regarding exercise safety and the benefits of physical activity; 5) workbook style sections on
15
16 252 motivation, goal setting, overcoming barriers and psychosocial support; 6) managing
17
18 253 breathlessness; 7) exercise intensity and limits; 8) guided home exercises with written and
19
20 254 visual details and advice on progression; and 9) advice on pacing and energy conservation.
21
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23
24 255 Participants will receive video clips of a qualified exercise specialist performing the exercises.
25
26 256 Participants will be encouraged to refer to the video to ensure adherence to correct technique.
27
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29 257 Online videos will provide a visual demonstration of each exercise. Participants will be
30
31 258 provided with an exercise diary as a tool to record their activity and effort perception. BCTs
32
33 259 will be integrated in the intervention through wearable technology devices, the use of print and
34
35 260 visual materials and health coaching and support calls.
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38
39 261 The 10-week intervention consists of the following components: Three 60-90 min induction
40
41 262 sessions (week 0 and 1), up to five 30-min support health coaching sessions (at week 2, 3, 5,
42
43 263 7, 9) and 3-5 weekly home-based exercise sessions. The intervention will end prior to T2
44
45 264 assessment. Participants will continue to have access to the exercise manual, bike and Fitbit
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47
48 265 during the maintenance phase.
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269 ***Induction Training***

270 Induction training (1:1), via video conferencing, is a key component to ensure patients
271 are confident to exercise at home and understand the appropriate exercise intensity and how to
272 exercise safely. Participants will be encouraged to involve a family member, friend or carer in
273 the induction training. The sessions will focus on the following topics:

274 *Session 1 - Introduction*; Education on PH and benefits of PA for PH. Familiarisation with
275 intervention materials/equipment and self-monitoring.

276 *Session 2 - Exercise Safety and Exercise Demonstration*; The session will focus on recognizing
277 exercise limits, warning signs, and managing exercise intensity. Visual demonstrations of
278 breathing techniques and aerobic, strength, and respiratory training will be provided, with the
279 opportunity for behavioural practice during the session to check technique and instil
280 confidence.

281 *Session 3 - Recap*; Exercise demonstrations and key safety points will be reviewed. Any issues
282 regarding intervention materials/equipment will be addressed and participant goals will be
283 reviewed, alongside additional tips for family/friend support and motivation.

284

285 ***Health Coaching Sessions***

286 The health coaching sessions (via videoconferencing) will use BCTs to foster exercise
287 adherence, motivate and provide support. Over the 5 sessions the topics will include; benefits
288 of exercise, goal setting, action planning, self-monitoring, identification and management of
289 barriers to exercise, problem solving and feedback on behaviour, with the option for

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290 participants to complete formal paperwork in the intervention manual. If required, additional
291 support will be available outside of scheduled sessions.

292 Participants will be encouraged to wear the Fitbit Charge 3 daily during the intervention. The
293 Fitbit data will be used to guide individually tailored goals, assess adherence to exercise and
294 overall daily PA and as tool to provide feedback to the researcher and participants.

295

296 ***Exercise Programme***

297 Participants will complete a 10-week individualised, home-based exercise programme.

298 The programme will be prescribed using the FITT principle (Frequency, Intensity, Time and

299 Type) and will employ a multimodal approach that integrates aerobic, resistance and

300 respiratory training. The goals for each component are outlined in the sections below. These

301 are aspirational goals that may not be realistic for all participants. Exercise prescription will

302 be individualized based on their baseline PA levels, 6-min walk test distance (6MWD) and

303 physical capabilities. The modified Borg rating of perceived exertion (RPE) scale [48] will be

304 used to help prescribe exercise intensity. The RPE scale is a psychophysiological measurement

305 that translates physical stimuli to a psychological construct of perceived exertion and has been

306 validated in other clinical groups [49]. Participants will aim to achieve an RPE of 3 (moderate)

307 initially. Based on individual progress an RPE of 4 (somewhat hard) may be advised for some

308 participants. The exercise programme will include:

309 *Aerobic Training*; Participants will initially aim to undertake a minimum of 10-min of

310 structured aerobic exercise involving walking, cycling or a combination on ≥ 3 d/week.

311 Participants will be allowed to perform this exercise in a single bout, or accumulate it in bouts

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of at least 5-min in duration. The duration will be progressively increased, with the goal of accumulating ≥ 30 min on ≥ 5 d/week.

Resistance Training; Participants will initially undertake resistance training on 2 d/week, involving a single set of 6-8 repetitions of upper and lower extremity and whole body exercises. Training volume will progressively increase with the goal of completing 2-3 sets of 10-12 reps of 4-6 exercises on three non-consecutive days. Participants will use pursed lip breathing to help airways stay open during exhalation. Bodyweight resistance will be used initially and based on individual ability, TheraBands, water bottles or light dumbbells will be introduced.

Respiratory Training; Participants will initially perform 10-min of respiratory training at least twice a week, which will follow the protocol established by the Heidelberg PH research group [50]. This involves a combination breathing techniques (e.g., pursed lip, diaphragmic and slow breathing) emphasising control over their rate of inspiration to expiration and to strengthen the diaphragm, stretching of the chest and thoracic muscles (e.g., cat-to-cow) and respiratory muscle strengthening exercises. Training volume will progressively increase with the goal of completing 15/20 min of accumulated respiratory training on ≥ 3 d/week. The intensity of the respiratory muscle strengthening exercises can be progressed using a TheraBand.

Participants will wear a Frontier X device (receiver attached to a strap placed around the chest) during exercise sessions. The first 2-weeks will be monitored by researchers and then periodically monitored. This will allow access to real time ECG, heart rate (HR), respiratory rate and cadence. Oxygen saturation will be monitored and participants will be instructed to stop exercising if the SpO₂ value drops below 88%, as per guidelines[51]. Participants will document any adverse events and report to the research team immediately.

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335 Data Management and Timeline

336 The trial will be overseen by the trial management group, consisting the principal
337 investigator, the trial-coordinator and health coach. They will meet every 4-weeks and will
338 oversee all aspects of the conduct of the trial including performing safety oversight activities.
339 Individual data will be de-identified, coded and entered. Each participant will be assigned a
340 personal identification code (PIC), which will be used on all case report forms and in all
341 electronic databases. Prior to any statistical analysis, all variables will be checked for missing,
342 impossible and improbable values. Impossible and improbable values will be defined by
343 clinical opinion and will include values that are outside three standard deviations of the mean
344 value. Study recruitment began at the end of September 2020 and the study is expected to be
345 completed in July 2021.

346

347 Statistical Analysis

348 Statistical analysis of quantitative data will be performed using SPSS Version 24. Prior
349 to statistical analysis, the Shapiro-Wilks test will be applied to check for normality. Continuous
350 variables will be reported as mean (range), mean (standard deviation) or median and inter-
351 quartile range, depending on distribution, and categorical variables as frequency (%).
352 Descriptive analyses will be undertaken to summarise participant characteristics and the
353 quantitative data of the intervention feasibility, acceptability and utility. Qualitative data from
354 post-trial interviews and researcher field notes will be analyzed using inductive thematic
355 analysis to identify common themes[52]. A linear mixed model analysis (MMA) will be used

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4 356 to examine the impact of time in this study . A MMA is a suitable approach to modelling time
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6 357 series data which contains repeated measures [53]. The MMA does not require complete data
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9 358 sets and does not exclude participants with missing data [54]. Furthermore, MMA has less
10
11 359 stringent assumptions than other repeated measures models (such as analysis of variance) and
12
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14 360 also exhibits increased power to detect treatment effects. The data will adjust for confounding
15
16
17 361 variables, such as age, baseline line fitness, gender and PH group.

362 Patient and Public Involvement

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23 363 Formative qualitative research took place with PH patients during the intervention
24
25 364 development stages. Semi-structured phone interviews (N=19) were conducted providing
26
27
28 365 insight into patient barriers and motivators to PA, and exercise preferences. The findings fed
29
30 366 into the design of the intervention along with PH clinician input. A patient representative
31
32
33 367 provided opinions on the study protocol, patient-facing documentation (e.g., participants
34
35 368 information sheet) and intervention material (e.g., exercise manual) to ensure it was patient
36
37
38 369 friendly.

370 Discussion

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45 371 The promise of exercise training in the treatment and management of PH has gained
46
47 372 significant interest over the past two decades. The observed positive effects of exercise
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50 373 programmes on patients' exercise capacity, functional capacity and QoL[55] make a strong
51
52 374 argument for the inclusion of exercise as an adjunctive therapy for stable PH patients[56].
53
54
55 375 Considering that structured and resource-intensive hospital-based exercise programmes are
56
57 376 unlikely to be scalable, it is an opportune time to assess the efficacy, safety and impact of
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60 377 home-based programmes as an alternative mode of delivery for PH patients.

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4 378 A home-based exercise programme may eliminate many of the barriers associated with
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7 379 in-patients or out-patients setting such as transportation issues, location, long wait periods for
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9 380 availability and accessibility for patients. A recent review of exercise interventions in PH by
10
11
12 381 Ozemek and colleagues [56] highlighted the need for inclusion of home exercise programmes
13
14 382 to allow patients achieve the optimal 5 to 6 days of structured exercise.

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18 383 This study will utilise a remote delivery for exercise training with the use of telehealth
19
20 384 methods, wearable technology, performance feedback and behavioural support to deliver and
21
22
23 385 monitor the intervention. The aim is to eliminate the burden on patients to attend several times
24
25 386 per week to an outpatient clinic, accommodate resource availability, make the programme
26
27
28 387 achievable in a 'real world' setting and improve the reach beyond the traditional healthcare
29
30 388 facilities. The follow-up post intervention (T3) phase will provide insight into whether
31
32
33 389 behavioural support is necessary in order for PH patients to remain physically active.
34
35 390 Furthermore, it will allow us to assess resource needs in future home-based exercise
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38 391 programmes such as the provision of specific exercise equipment and the use of ubiquitous,
39
40 392 low cost devices to monitor activity and safety (e.g. bike, wearable activity tracker). Remote
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43 393 assessment of outcomes may remove threats to external validity and evaluation of the
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45 394 feasibility of such assessment will address the goals of implementation science to close the
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48 395 research-to-practice gap and support implementation and scale up of evidence-based
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50 396 interventions[57].

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54 397 To our knowledge, this will be the first study to employ the use of evidence-based BCTs
55
56 398 to examine the feasibility, utility and efficacy of a remote home-based approach to exercise
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59 399 training for medically stable PH patients. The secondary aims of this study are to evaluate
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4 400 whether this approach leads to improvement in selected indices of physical and psychological
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7 401 health.

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10 402 PH is a rare, debilitating condition with most clinics centralized and limited community
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12 403 resources available. Telehealth holds significant potential to meet the growing support for
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15 404 exercise training to be included as an adjunct therapy by offering remote training and support,
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18 405 which is key to long-term implementation of exercise training for the PH population. It
19
20 406 provides a service that is more accessible and may potentially offer a more affordable enhanced
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22
23 407 level of care. Our current understanding is limited concerning the acceptability, feasibility and
24
25 408 utility of a home-based programme for stable PH patients. This study will help gain a valuable
26
27
28 409 insight into this gap in knowledge.

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35 411 **Ethics and dissemination:** Ethics approval has been obtained from the Mater Misericordiae
36
37 412 Institutional Review Board REF:1/378/2032 and Dublin City University Research Ethics
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40 413 DCUREC/2018/246. A manuscript of the results will be submitted to a peer-reviewed journal
41
42 414 and results will be presented at conferences, community and consumer forums and hospital
43
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45 415 research conferences. Trial Registration: ISRCTN Registry: ISRCTN83783446. Protocol
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47 416 version. 2.0

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44 607 **Contributors:** CMC, BK, SJH, NMC, SG, BMC, and NM were involved in study
45
46 608 conceptualisation, development of intervention content and writing of the protocol. AMC
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48 609 provided guidance on the statistical analysis. CMC led the writing of the manuscript and all
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50 610 authors edited and reviewed the manuscript.
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57 612 role in the study design and data collection, analysis and interpretation of data.
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4 613 **Competing interest statement:** None declared.
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32 621 Table 1: Study outcome measures and time points
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Assessments	Time		
	Baseline (T1)	Post- Intervention (T2)	Follow-up (T3)
Written informed consent & eligibility	X		
Demographics	X		
Medical history	X		
WHO functional class	X	X	X

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Concomitant medication	X	X	X
Adverse events	X	X	X
Exercise capacity (6-MWT)	X	X	X
Muscle strength (Sit to Stand)	X	X	X
Physical activity (ActivPAL Micro)	X	X	X
Quality of life (CAMPHOR & SF-36)	X	X	X
Psychological constructs	X	X	X
Intervention debrief questionnaires/ semi-structured interviews		X	X

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STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym (Page 1)
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry (Page 3)
	2b	All items from the World Health Organization Trial Registration Data Set (Page 3)
Protocol version	3	Date and version identifier (Page 3)
Funding	4	Sources and types of financial, material, and other support (Page 29)
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors (Title page and Page 29)
	5b	Name and contact information for the trial sponsor (Page 29)
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities (Page 29)
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) (Page 29)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention (Pages 5-7)
	6b	Explanation for choice of comparators (Page 9)
Objectives	7	Specific objectives or hypotheses (Page 7)

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Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) (Page 7)
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Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) (and list of countries where data will be collected. Reference to where list of study sites can be obtained (Page 8)
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Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) (7)
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Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered (Page 13-17)
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	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) (N/A)
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	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) (Page 13-17)
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	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial (Page 8)
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Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended (Page 7 & 9-13)
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Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) (table 1)
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Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations (Page 9)
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Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size (Page 8)
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Methods: Assignment of interventions (for controlled trials)

Allocation:

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2	Sequence	16a	Method of generating the allocation sequence (eg, computer-
3	generation		generated random numbers), and list of any factors for stratification.
4			(To reduce predictability of a random sequence, details of any
5			planned restriction (eg, blocking) should be provided in a separate
6			document that is unavailable to those who enrol participants or assign
7			interventions (N/A)
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10	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central
11	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
12	mechanism		describing any steps to conceal the sequence until interventions are
13			(N/A)
14			
15	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,
16			and who will assign participants to interventions (N/A)
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19	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial
20	(masking)		participants, care providers, outcome assessors, data analysts), and
21			how (N/A)
22			
23		17b	If blinded, circumstances under which unblinding is permissible, and
24			procedure for revealing a participant's allocated intervention during
25			the trial (N/A)
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Methods: Data collection, management, and analysis

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30	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other
31	methods		trial data, including any related processes to promote data quality (eg,
32			duplicate measurements, training of assessors) and a description of
33			study instruments (eg, questionnaires, laboratory tests) along with
34			their reliability and validity, if known. Reference to where data
35			collection forms can be found, if not in the protocol (Page9-13)
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38		18b	Plans to promote participant retention and complete follow-up,
39			including list of any outcome data to be collected for participants who
40			discontinue or deviate from intervention protocols (Page 13)
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42	Data	19	Plans for data entry, coding, security, and storage, including any
43	management		related processes to promote data quality (eg, double data entry;
44			range checks for data values). Reference to where details of data
45			management procedures can be found, if not in the protocol (Page
46			18)
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49	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.
50	methods		Reference to where other details of the statistical analysis plan can be
51			found, if not in the protocol (Page 18)
52			
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54		20b	Methods for any additional analyses (eg, subgroup and adjusted
55			analyses) (Page 18)
56			
57		20c	Definition of analysis population relating to protocol non-adherence
58			(eg, as randomised analysis), and any statistical methods to handle
59			missing data (eg, multiple imputation) (Page 18)
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Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed (Page 18)
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial (N/A)
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct (Page 10)
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor (Page 18)

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval (Page 3)
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) (Page 18)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) (Page 8)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable (N/A)
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial (Page 18)
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site (Page 29)
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators (Page 18)
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation (N/A)

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| Dissemination
policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions (Page 3) |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers (Page 29) |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code (Page 3) |

15 Appendices

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|-------------------------------|----|---|
| Informed consent
materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates (Appendix A) |
| Biological
specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable (N/A) |

25 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013
26 Explanation & Elaboration for important clarification on the items. Amendments to the
27 protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT
28 Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)"
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