Study Title: Randomized controlled study to investigate the impact of mobile health (mobile app and wearables) on the engagement with prescribed airway clearance techniques in patients with Primary Ciliary Dyskinesia (PCD)

Internal Reference Number / Short title: PCD-ENGAGE

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Sponsor declares no conflict of interest.

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, and members of the Research Ethics Committee, unless authorised to do so.

VERSION CONTROL

Version number	Date	Comments
V1.0	23-Feb-2022	Draft issued for peer-review
V1.1	10-May-2022	Peer-review feedback incorporated
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V2.0	04-Nov-2022	Feedback from REC incorporated
V3.0	24 May 2023	Amended for REC submission
V4.0	21 Nov 2023	Amended to incorporate details of updated consent, for REC submission.

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1. KEY CONTACTS

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2. LAY SUMMARY

Primary Ciliary Dyskinesia (PCD) is a rare, multisystem, genetic condition in which hair-like structures lining the airways, called cilia, do not function properly. In healthy people, cilia move like escalators to remove mucus and trapped pollution, viruses, and bacteria out of the airways and into the digestive tract, where it is destroyed. In PCD the faulty cilia cannot move mucus out of the airways efficiently, leading to it build up and cause recurrent respiratory infections. These infections affect the ears, sinuses and lungs, and cause irreversible lung damage called bronchiectasis. It is also associated with sub/infertility, congenital heart defects, organ laterality defects (e.g, organs in mirror image) and rare associations, such as polysplenia (having multiple small accessory spleens, rather than a single, normal spleen). PCD has a profound impact on patients' quality of life, as well as their airway function.

There is no bespoke treatment for PCD. Current treatments focus on preventing infections and managing the symptoms of the disease. Airway Clearance Techniques (ACTs) to improve mucus clearance, together with oral and/or intravenous antibiotics to treat upper/lower respiratory infections are the main approaches to treating PCD. There are many different types of ACTs used by patients, most of which involve repeated breathing exercises to move mucus through the airways. Some patients with PCD will use inhalers or nebulisers (e.g., hypertonic saline) prior to their ACT to loosen the mucus in the airways. Upper airway hygiene involves nasal rinsing with hypertonic saline and/or topical nasal corticosteroids and antibiotics to manage sinus and nasal symptoms. Regular exercise may be also recommended to increase mucus clearance and improve factors that can affect respiratory health (such as cardiovascular fitness, weight, and lung function).

Good engagement with ACTs may result in improved respiratory outcomes. However, engaging in a daily routine of ACTs is time-consuming and may be burdensome for PCD patients, which may lead to performing less efficient techniques or ultimately to the discontinuation of the routine. Furthermore,

some PCD patients, particularly young patients, view the performance of ACTs as a visible sign of 'being ill' and may be reluctant to carry them out systematically.

This study aims to demonstrate that use of mobile health in the form of a bespoke patient-facing app and a wrist-worn wearable device with behaviour change features tailored to patients' preferences, can support the engagement with prescribed airway clearance daily routine in PCD patients, which may result in improved quality of life and reduced exacerbation occurrence. Alongside the engagement data, wearable data will be collected to provide surrogate markers of exercise and high-intensity physical activity, related with lifestyle changes in PCD patients.

3. SYNOPSIS

Study Title	Randomized controlled study to investigate the impact of mobile health (mobile app and wearables) on the engagement with prescribed airway clearance techniques in patients with Primary Ciliary Dyskinesia (PCD)		
Internal ref. no. / short title	PCD-ENGAGE		
Study registration	Study identifier, registry name, registration number and date of registration.		
Sponsor	Aparito Ltd Unit 11, Gwenfro, Technology Park, Wrexham LL13 7YP, United Kingdom		
Funder	Dr. Elin Haf Davies Aparito Ltd elin@aparito.com +44 1978 896191 Lucy Dixon PCD Support UK chair@pcdsupport.org.uk PCD Support UK, PO Box 2233, Buckingham, MK18 9DX		
Study Design	Two-arm randomized controlled study to assess a behaviour change intervention using mobile health		
Study Participants	Patients diagnosed with primary ciliary dyskinesia performing airway clearance techniques by recommendation of their physiotherapist specialist		
Sample Size	Behavioural intervention group, n=44 Control group, n=44		
Planned Study Period	Recruitment period is 8 weeks Total study follow-up time is 12 weeks Total study duration is 20 weeks Extension phase of 12 weeks, after the 12-week study period		
Planned Recruitment period	Indicate start and end dates for recruitment Updated dates for recruitment: Prolong 8 additional weeks from REC approval (see section 9.1)		
	Objectives	Outcome Measures	Timepoint(s)
Primary	To compare the effect of a bespoke app and wrist-worn	Change in engagement with recommended airway clearance	Baseline and 12 weeks, and

	wearable device customized with behaviour change features to support engagement with own prescribed airway clearance techniques (ACTs) in patients with PCD followed for 12 weeks	techniques (ACTs) in patients with PCD followed for 12 weeks. Engagement with recommended ACTs is defined as the proportion of completed sessions out of prescribed sessions. Participants will also report the time spent in active clearance. Engagement data will be self-reported daily.	continuously monitored throughout the study.
Secondary	Change in quality of life (QoL) at the end of the 12-week study period	PCD-specific QoL instrument: QOL-PCD adult and adolescent (13-17) versions.	At baseline, 6 weeks and at the end of the 12-week period
	Change in exacerbation rate at the end of the 12-week study period	Exacerbation rate is defined as the number of exacerbations/related symptoms occurred at the end of the study period. Past exacerbations are defined as any hospitalizations (related with an exacerbation) and/or any rescue antibiotic treatment during the past 3 months prior entering the study.	Past exacerbations will be captured at baseline. Exacerbation rate during the study will be calculated at the end of the 12-week period
Intervention(s)	Behavioural change intervention via a mobile health app and wrist-worn wearables to support engagement with airway clearance techniques		
Comparator	Self-reported engagement with airway clearance techniques using a mobile app only with no behaviour change features		

4. ABBREVIATIONS

ACT	Airway clearance techniques
CI	Chief Investigator
GCP	Good Clinical Practice
HRA	Health Research Authority
ICF	Informed Consent Form
PCD	Primary ciliary dyskinesia
PI	Principal Investigator
PIS	Participant/ Patient Information Sheet
REC	Research Ethics Committee
SOP	Standard Operating Procedure

5. BACKGROUND AND RATIONALE

Primary ciliary dyskinesia (PCD) is a rare genetic condition usually diagnosed in childhood, in which mucus clearance is impaired due to abnormal function of the cilia that line the respiratory epithelium.

Mucus build-up leads to upper and lower respiratory infections causing lung exacerbations (Lucas et al. 2019) and progressive bronchiectasis (i.e., lung airway widening). As a result, lung structure and function as well as the quality of life of people living with PCD are severely impacted (1). As motile cilia are also present in fallopian tubes and the spermatozoan flagella, PCD patients may present with fertility problems. During foetal development, a type of motile cilia determines organ laterality, which if impaired leads to situs inversus and other problems such as congenital heart disease (2).

The presence of sinonasal symptoms (e.g., rhinosinusitis) or recurrent middle ear infections (leading to hearing loss) is common and requires routine daily care, which may be time consuming and burdensome for patients. Pulmonary exacerbations can result in a reduction of lung function, which might not be recovered despite antibiotic treatment and physiotherapy (3). It is estimated that patients lose 0.8% of their forced expiratory volume (FEV1, i.e., a measure of lung capacity) per year (1). Therefore, prevention of exacerbations is key to preserve lung function and overall quality of life.

Treatment of PCD relies on prevention and management of disease complications. Airway clearance therapy to improve mucus clearance, together with oral and/or intravenous antibiotics to treat upper/lower respiratory infections are the two mainstay approaches. Specialist multidisciplinary service to support children with PCD has been used in England (4).

Airway clearance therapy involves different options including the use of mucolytics (e.g., N-acetylcysteine) and hyperosmolar agents (e.g., nebulized hypertonic saline) and physiotherapy applying airway clearance techniques (ACTs). Upper airway hygiene involving nasal rinsing with hypertonic saline and/or topical nasal corticosteroids and antibiotics helps manage the sinonasal symptoms (1). Also, regular exercise is usually prescribed to increase general wellbeing and presumably mucus clearance (5).

ACTs are prescribed by physiotherapy specialists and involve positioning, manual techniques (percussion, vibrations), positive pressure adjuncts, breathing techniques, and oscillatory devices (5). In addition, regular exercise is suggested to help mucus clearance and produce bronchodilation in PCD and may be recommended due to its positive effects on general wellbeing, in addition to other airway clearance approaches (5–7). However, exercise should not be recommended in isolation to replace ACT (5). For patients living with PCD, nose and sinus rinsing is considered part of this airway clearance routine, which needs to be carried out daily for efficient infection prevention.

Good engagement with ACTs may result in improved respiratory outcomes. However, engaging in a daily routine of ACTs is time consuming and results in treatment burden for PCD patients, which may lead to performing less efficient techniques or ultimately to the discontinuation of the routine. Furthermore, some PCD patients, particularly young patients, view the performance of ACTs as a visible sign of 'being ill' and may be reluctant to perform them systematically (5).

Adherence to treatment is key for the success of an intervention, but it is known that in chronic diseases it is generally below 50% (8). Thus, improved engagement with prescribed airway clearance therapy will likely result in improved quality of life of PCD patients and better disease management.

Engagement with preventive treatment in chronic conditions, such as PCD, is challenging and involves establishing a new routine and therefore sustained behaviour change (9). Habit formation appears to be key in self-care management strategies as they persist regardless of individual motivation, and it has been the basis for improving objectively measured adherence in self-management intervention strategies in cystic fibrosis (10).

The use of mobile health technologies (e.g., wearables, health apps) in promoting physical activity has become popular in the past recent years. Commercial wearables (like fitness trackers) come with built-in behaviour change techniques that have variable effects on the user as they are not tailored to the specific individual behaviour (11). For example, some people might need more specific reminders than others or different incentives/rewards. Thus, wearables and health apps are attractive tools to encourage behaviour change and facilitate the formation of good health habits (12). In addition, commercial wearables allow remote monitoring and continuous data capture of activity levels and physiological parameters such as heart rate and oxygen saturation, which may be used as surrogate markers of exercise and high-intensity activity.

We hypothesize that the use of mobile health (mHealth) in the form of a bespoke patient-facing app and a wrist-worn wearable device with behaviour change features tailored to patients' preferences, may improve engagement with prescribed airway clearance daily routine in PCD patients, which may result in improved quality of life and reduced exacerbation occurrence. Alongside the engagement data, we expect wearable data to provide with: 1) surrogate markers of exacerbations and 2) surrogate markers of exercise and moderate-to-high-intensity physical activity, related with lifestyle changes in PCD patients. Additionally, we will explore whether the effect of the mHealth intervention may be associated with increased engagement in patient's self-management of health and care. We will use the Patient Health Engagement (PHE) model, a psychosocial theory model aimed at explaining patient engagement as a developmental process from a passive to an active approach to managing healthcare (13,14). The PHE model has also been found a potential mechanism to increase patient activation and adherence to treatment (15). Study outcomes might be useful for clinical decision making in recommending technology-mediated behaviour change intervention strategies to improve patient self-management of PCD.

This study has been co-designed with the PCD Support Group, UK-based charity dedicated to support people living with PCD and to champion PCD research. For patients living with PCD, building a good engagement with ACTs should be embedded in a broader, more holistic treatment strategy that considers ACTs and exercise as part of a healthy lifestyle to achieve better disease management and health outcomes. PCD Support UK conducted a survey in January 2021 to explore the views and preferences of PCD patients towards a digital tool for the management of their condition. Results of the analysis (n= 60) showed that PCD patients were in favour of a technology tool that could help with lifestyle changes without adding treatment burden. Consultation with International PCD Physiotherapists Network physiotherapy specialists corroborated the need to better understand the engagement of PCD patients with ACTs and to explore habit-formation strategies in improving this engagement, which has shown success in cystic fibrosis (10). The use of technology may be also more appealing to younger patients.

Building a solid habit is not straightforward as it depends on both individual's intrinsic and external factors according to the Capability, Opportunity Motivation-Behaviour (COM-B) model (16). Individual's capability (i.e., necessary knowledge and skills) together with intrinsic motivation and external opportunity that make the behaviour possible, are the components that underpin this behaviour change framework. The COM-B model served as theoretical underpinning of a self-management intervention to support treatment adherence in cystic fibrosis, which resulted in increased objectively measured effective adherence (10). In the present study, we followed the COM-B framework as a guiding principle to define preferences regarding the behaviour change intervention, i.e., how to customize

app/wearables, during a focus group with patient representatives from the PCD Support UK. Outcomes of this discussion highlighted that engagement with ACTs might be linked to different individual factors, such as social activity (e.g., more engagement during covid-19 lockdowns), flexibility (fixed vs flexible time of the day to carry out ACT routine), daily routine (e.g., school), self-efficacy (higher ability in ACT performance means less time invested, and therefore higher engagement). Positive feedback and tracking own progress were found important to incentivize carrying out ACTs in a consistent manner. Participants to the focus group found that setting engagement goals and obtaining rewards for achieving them, having reminders, reinforcers and gamification options, were good motivators to increase engagement. These preferences have been considered into the design of the behaviour change features embedded in the app.

6. OBJECTIVES AND OUTCOME MEASURES

We hypothesize that the use of mobile health in the form of a bespoke patient-facing app and wearables with behaviour change features tailored to patients' preferences, may improve engagement with prescribed airway clearance daily routine in PCD patients, which may result in improved quality of life and reduced exacerbation occurrence. Alongside the engagement data, we expect wearable data to provide surrogate markers of exercise and high-intensity physical activity, related with lifestyle changes in PCD patients.

Primary objective

- To compare the effect of a mobile health in the form of a bespoke app and wrist-worn wearable device customized with behaviour change features to support engagement with prescribed ACTs in patients with PCD followed for 12 weeks. Participants will self-report engagement with their prescribed ACT regimen using the mobile app, i.e., type of techniques and frequency. Engagement with prescribed ACTs is defined as the proportion of completed sessions out of prescribed sessions. Participants will also report on the quality of the ACT regimen the time spent in active clearance and how they felt after the session was completed.

ACTs are advised by physiotherapists and may include the following physiotherapy techniques: positioning, manual techniques (percussion, vibrations), positive pressure adjuncts, breathing techniques, and oscillatory devices (5). Usually, ACTs are prescribed as daily routine sessions. In this study, information about adjuncts to physiotherapy such as nose/sinus rinsing using saline/hypertonic saline solutions, mucolytics (such as DNAase) or bronchodilators will also be collected.

ACT regimen (type and frequency of ACTs) may change during the 12-week period due to the occurrence of lung infections or other factors. Participants will be able to record changes in their recommended ACT regimen and engagement will be recalculated using the new regimen parameters. Additionally, we will capture data on the patient's perspective on the quality of the physiotherapy regimen.

Secondary objectives

- To investigate the impact of engagement with ACTs on quality of life (QoL) measured with validated and specific PCD instrument (QOL-PCD) (17–19) at baseline, 6 weeks, and at the end of the 12-week study period. The adolescent version (Adolescent version 2, June 2016, ©Dell, Lucas, Leigh & Quittner) will be used for participants from 14-17 and the adult version (Adult version 2, March 2016, ©Lucas, Leigh & Quittner) for those aged 18 or above.

- To investigate the impact of engagement with ACTs on the exacerbation rate, defined as the number of exacerbations/related symptoms at the end of the 12-week study period compared with baseline exacerbation rate, i.e., number of exacerbations in the previous 3 months). Exacerbation rate at the end of the extension phase (12 additional weeks, see Section 7) will also be measured.

A pulmonary exacerbation is defined by the presence of three or more of the below events (3):

1) increased cough
2) change in sputum volume and/or colour
3) increased shortness of breath
4) decision to start or change antibiotic treatment because of perceived pulmonary symptoms
5) malaise, tiredness, fatigue or lethargy
6) new or increased haemoptysis, and
7) temperature >38°C.

This definition was suggested to be used as a patient-reported outcome (PRO) measure by Lucas et al. and is currently being validated in an observational study conducted by the BEAT-PCD network (20).

Exploratory objectives

- To investigate the potential clinical utility of passively collected wearable data as surrogate markers of exercise and moderate-to-vigorous intensity activity. Data will include heart rate, step count, motion type and intensity (low, moderate, high) and time spent in moderate-to-vigorous activity.

  Exercise is often advised before physiotherapy to enhance chest clearance in PCD patients, to help increase air flow to smaller airways and help mobilise mucus. However, PCD patients may also do it after if they find retained secretions limit their ability to exercise. Exercise alone must never replace ACTs (5). Please see exercise under exploratory objectives.

- To investigate the clinical utility of passively collected wearable data to identify a potential surrogate marker for exacerbations. Data will include heart rate, step count, time spent in moderate-to-vigorous activity and sleep. In addition, spirometry readings (FVC, FEV1) will be collected to be correlated with wearable data and exacerbation diary.

- To investigate whether the mHealth intervention has an effect on patient engagement in self-management of health care by using the self-administered Patient Health Engagement scale (14).

Objectives	**Outcome Measures**	**Timepoint(s) of evaluation of this outcome measure (if applicable)***
Primary Objective To compare the effect of a bespoke app and wrist-worn wearable device customized with behaviour change features to support engagement with own prescribed airway clearance techniques (ACTs) in patients with PCD followed for 12 weeks	Change in engagement with own prescribed airway clearance techniques (ACTs) in patients with PCD followed for 12 weeks. Engagement with prescribed ACTs is defined as the proportion of completed sessions out of prescribed sessions. Participants will also report the time spent in active clearance. Engagement data will be self-reported daily	At baseline and at 12 weeks, and continuously monitored throughout the study.

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)*
Secondary Objectives Change in quality of life (QoL) at the end of the 12-week study period	PCD-specific QoL instrument (QOL-PCD)	At baseline and at the end of the 12-week period
Change in exacerbation rate, at the end of the 12-week study period	Exacerbation rate is defined as the number of exacerbations/related symptoms occurred at the end of the study period	Exacerbation rate at baseline will be calculated by asking participants about exacerbations occurred 3 months prior study start. Ongoing exacerbations will be captured as they happen during the 12-week study period and exacerbation rate will be calculated
Exploratory Objectives To investigate the potential clinical utility of passively collected wearable data as surrogate markers of exercise and moderate-to-vigorous activity, and as surrogate markers of exacerbations.		Heart rate Step count per day Motion type and intensity (low, medium, high) Time spent in moderate/vigorous intensity activity Sleep
To investigate whether the mHealth intervention has an effect on patient engagement in self-management of health care.	Patient Health Engagement scale	At baseline and at the end of the 12-week period

*All variables will also be measured at the end of the extension phase (12 additional weeks, see Section 7) in those participants that have remained.

7. STUDY DESIGN

This is a parallel group decentralized controlled study in which participants will be randomized to two different arms:

- Behaviour change intervention arm. Participants will download a bespoke mobile app on their phone to self-report their engagement with recommended ACTs and will receive a consumer-grade CE-marked Garmin Vivosmart® 5 wearable activity tracker [1]. The bespoke app will integrate the activity tracker with behaviour change features tailored to patients' preferences regarding the formation of habits with the aim to support engagement with recommended ACTs and with physical activity/exercise.

[1] See Garmin Vivosmart® 5 product manual and information sheet at https://support.garmin.com/en-GB/?partNumber=010-02645-10&tab=manuals

- Control arm: Participants will self-report their engagement with ACTs using a bespoke app (see details below).

In both arms, patient-reported outcomes such as quality of life at the start and end of the study, exacerbation events occurring 3 months prior and during the study period and spirometry readings will be collected as well.

The data platform that will be used in this study is Atom5™, a fully configurable, multilingual platform designed to support remote patient monitoring through the use of text, videos, photos, voice and wearable integration. Participants download a specific app on their own smartphone (platform is compatible with both iOS and Android) in order to participate in the study.

Using Atom5™ platform we will design a bespoke app for the collection of patient-reported outcomes. A consumer-grade wearable device will be integrated into the app, i.e., Garmin Vivosmart® 5. In the intervention arm, both the app and wearable will be configured with behavioural change features tailored to patients' preferences, prioritizing those that help with the formation of new habits. Additionally, the wearable device will passively collect data such as heart rate (HR), activity levels (step count), motion type and intensity, time spent in moderate-to-vigorous activity, and sleep. In the intervention arm, participants will be able to track their own data, receive reminders for specific tasks and rewards when certain goals regarding ACTs and physical activity are attained.

In the control arm, behaviour change features will not be included in the app. Only messages will be sent to prompt that participant logs requested data on a regular basis to ensure enough engagement with the technology to collect the data

The total follow-up time of patients within the study is 12 weeks.

Extension phase

Once the 12-week study period is finished, all participants in the control arm will be able to voluntarily cross over to the intervention group, will receive the activity tracker and will be followed for up to 24 weeks. Participants in the intervention group will be able to continue in this group for up to 24 weeks. Participants crossing over from the control group will provide consent (and assent were applicable) to continue in the extension phase. In this phase, the assessments described in section 9.8 will be performed. An additional analysis of study objectives will be performed with data from the extension phase (See Section 11 Statistics and analysis).

8. PARTICIPANT IDENTIFICATION

8.1. Study Participants

Participants are patients with primary ciliary dyskinesia aged 14 upwards that are eligible for the study by meeting the inclusion/exclusion criteria described below.

8.2. Inclusion Criteria

- Adolescents (from 14 upwards) and adults diagnosed with PCD (written proof such as letter of diagnosis from their reference specialist centre will be required, and/or genetic information, if known) and performing regular airway clearance techniques (ACTs).

- Able and willing to provide consent or, if appropriate, participants having an acceptable individual capable of providing consent on their behalf, e.g., parent or guardian of a child under 18 years of age.
- Able to speak and understand English.
- Able and willing to engage with the technology.
- Access to internet-connected smartphone with iOS or Android system.

8.3. Exclusion Criteria

- Severe / acute disease, including:
    - Severe haemoptysis 6 months prior study start
    - Congenital heart defects, other than dextrocardia
    - Cardiac disease
    - Ongoing exacerbation (as defined by Lucas et al.(3)). Once their exacerbation is resolved, they could be considered eligible for the study.

9. PROTOCOL PROCEDURES

This is a fully decentralized study. There is not a trial site and therefore no onsite visits will take place. Participants will carry out all assessments through the app from home. See Annex A Study Flow Chart.

The patient-reported outcome (PRO) questionnaires used in this study will be scored according to each instrument's scoring algorithm. Appropriate agreements with the copyright owners will be in place for use of each of these questionnaires in this study.

9.1. Recruitment

Recruitment of participants will be supported by PCD Support UK through a national campaign (see Appendix D Communication plan) using their usual contact channels that may include, but not restricted to:

- Social media communications. The campaign will be disseminated through PCD Support UK's Twitter, Facebook and Instagram channels.
- Flyers that will be shared with PCD physiotherapist and consultants at PCD specialist centres in the UK
- PCD Support UK Newsletter
- PCD Support UK website that will host a dedicated study page.

Through these channels PCD Support UK will disseminate study information, instructions to access the study web portal and information related to the screening and eligibility assessments. A dedicated 'PCD Live' webinar (i.e., PCD Support UK webinar series dedicated to raise awareness of PCD and support the PCD community) will be conducted to inform about the study to potential participants.

The study website will host a video that will provide potential participants with information about the study, the consent process and contact details of study staff (see Appendix E for further details).

Participants will be recruited over a period of 8 weeks. Aimed study sample is 44 participants per arm. Recruitment rate will be analysed 2 weeks after the launch of the recruitment campaign. If recruitment rate is lower than 11 patients per week, recruitment strategy will be revised accordingly and included in an amendment to the protocol. Study went live on 17 Apr 2023. On 5 May 2023, only 4 participants

successfully onboarded on to the study platform and have been enrolled in the study. Sixteen participants have created an Atom5™ account which is the first step to enrol in the study, but only 8 signed the consent and 4 were finally included.

Participants	**N**
Account created	16
E-consent signed	8
Eligibility questionnaire completed	6
Proof of diagnosis submitted	5
Validated diagnosis	4
More information requested	1
Patients enrolled	**4**
Intervention	1
Control	3

The recruitment strategy was reviewed with PCD Support UK and identified the following:

- Fewer than scheduled social media posts were sent due to temporary lack of staff resources at PCD Support UK Communications. It is worth noting that PCD Support UK is a charity fully run by volunteers living with PCD. The first corrective action is to increase social media outreach with weekly posts across the different channels to reactivate recruitment and prolong the recruitment period by 8 additional weeks from REC approval (see Revised Communications strategy in separate file).
- Some participants had created an account (first step to engage with the digital platform), but did not progress to read and sign the e-consent. This may be explained due to the fact that the web portal is designed to be accessed from a laptop/computer to ease reading and uploading of proof of diagnosis. However, many potential participants are accessing it through their mobile phones and encountering difficulties. Together with PCD Support UK we agreed to contact these participants via email and offer them clarification and technical assistance if needed.

We have also identified issues related to engagement with the study app:

- Of the participants that enrolled, we noticed that in some cases the workflow to answer questionnaires was not entirely clear for participants. Video instructions for both the control and the intervention group have been created, which will be watched mandatorily after download of the study platform before proceeding to respond questionnaires. The instructions will be available in the app to rewatch (See Script and Video screenshots in a separate file).
- One participant in the intervention group needed to re-pair the Garmin watch to the study app and got in touch via email to get support. Additional Garmin watch troubleshooting instructions have been developed and will be available in the Information module.

9.2. Screening and Eligibility Assessment

The study web portal will provide potential participants with a detailed description of the study, what it will involve for the participant; the implications and constraints of the protocol and any risks involved in taking part. If a participant would like to enrol in the study, they will provide consent (see Section 9.3) and proceed to answer screening questions and upload proof of diagnosis (e.g., letter from their specialist). Screening questions will include:

- Age
- Sex
- Year of diagnosis
- Performance of ACTs as part of their routine PCD management
- Proof of PCD clinical diagnosis and genetic information (if available)
- Presence of acute lung disease (ongoing pulmonary exacerbation)
- Presence of congenital heart defects and/or cardiac disease
- Severe haemoptysis occurring up to 6 months before study start
- Able to speak and understand English
- Access to smartphone with iOS or Android system

Proof of PCD clinical diagnosis and genetic information will be uploaded by participants into the study web portal. Only medical personnel will have access to this documentation through the study portal to verify it and confirm participant's eligibility. Following this verification step, proof of diagnosis documentation will be permanently deleted and no longer be stored in the platform.

Participants eligible for the study will be asked to download the study app on their smartphone. Once onboarded, participants will be assigned a study ID. No identifiable patient personal data will be stored in the platform.

9.3. Informed Consent

Potential participants will be asked to consent to participate in the screening phase and provide diagnostic information. If they provide consent to be involved in the screening phase, they will have access to a full informed consent form (ICF) that will detail the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, without affecting their legal rights, and with no obligation to give the reason for withdrawal.

Participant will sign the ICF through the built-in DocuSign software and download a countersigned copy for their records. DocuSign offers modules to support your compliance with the electronic signature practices set forth in the U.S. Food and Drug Administration's 21 CFR Part 11.

If participant is below 18 years of age, their parent/guardian or legally authorised representative should sign the informed consent form, while the participant will sign an assent form.

The participant will be allowed as much time as wished to consider the information and will have the opportunity to question the Investigator (contact details included in the ICF), their GP or other independent parties to decide whether they will participate in the study.

Amendment 21 Nov 2023:

- A related qualitative research study that will explore engagement with the mHealth devices will be conducted by Ben Ainsworth PhD, Associate Professor at the University of Southampton. Participants within the PCD-ENGAGE trial, who have provided consent to be contacted in the main trial, will be invited to take part in an interview. Semi-structured interviews with 10-12 patients will be conducted with those who express interest in taking part. Interviews will be recorded and transcribed. Interviews will be up to 1 hour. Interviews will take place online via Microsoft Teams. Participants will be asked about their experiences, views and engagement with ACT via the PCD-ENGAGE app. For this study, separate Ethics approval will be obtained by researchers at the University of Southampton.
- In addition, quantitative data related to compliance with the study procedures (e.g., compliance with the ACT diary) will be obtained via a Data Sharing Agreement between Aparito and the University of Southampton. Qualitative and quantitative data will be triangulated to understand engagement and experiences with the PCD-ENGAGE app.

The Aparito study team will reach out participants through different means:

- Via the Atom5TM study app, participants will receive the updated consent form (see separate document) for review and e-consent via tick box.
- For participants that have already finished the study, we will send them the updated consent form via email for review. And if they agree, they will be able to sign it through DocuSign.

The consent form will be updated to consider that Aparito team will ask participants to contact Southampton researchers on whether they consent to their email address being shared with Southampton study team and their quantitative anonymized data will be shared with the University of Southampton.

9.4. Randomisation

Participants will be randomized in a 1:1 fashion to the intervention or control arm after being screened and complying with the eligibility criteria through the Atom5^{TM} platform. The platform has a built-in feature that randomly allocates participants to the control or intervention group once eligibility has been confirmed.

9.5. Blinding and code-breaking

No blinding or codebreaking is applicable to this study

9.6. Description of study intervention(s), comparators and study procedures (clinical)

This is a parallel group study with an intervention and a control arm.

9.6.1. Description of study intervention(s)

The study intervention is a behaviour change intervention to help form health habits and support engagement with airway clearance techniques in patients with PCD. The COM-B framework (10,16) served as theoretical underpinning and also as guidance to define behaviour change intervention.

Engagement session with PCD Support UK patient representatives informed the choice of Atom5™ features.

Participants in the intervention arm will download the study app on their phones and will receive a Garmin Vivosmart® 5 activity tracker. An information module in the app will instruct participants on how to connect the activity tracker to the study app and general instructions on its functioning. Participants will be prompted to record their prescribed airway clearance techniques daily, any occurrence of an exacerbation, spirometry readings and to answer the QOL-PCD quality of life instrument. The wearable will passively record their heart rate, step count, motion type and intensity, the time spent in high-intensity activity and their sleep. A combination of alerts (e.g., reminders to perform ACTs), rewards (e.g., options like badges, points, etc.) and relevant information will be issued to the participant. Participants will be instructed on how to synchronize their data to the app.

Alerts can include:

- Reminders to log daily ACTs. They could be issued daily at a fixed time (e.g., every day at 7am and 6 pm) and/or recurrently after a certain number of days that participant fails to log data.
- Real-time data monitoring and targeted completion reminders.

Rewards can include:

- Tracking own ACT data:
    - Weekly ACT engagement reports, to see previous week's percentage of completed ACT sessions. Encouraging notifications are sent together with the report.
    - Cumulative progress reports. Participant will have the option to see progress reports up to date.

  Engagement with ACT will be automatically calculated by the platform. Every time a goal is achieved a performance badge will be issued:
    - Complete all ACT sessions 3 days in a row: earn a bronze badge
    - Complete all ACT sessions 7 days in a row: earn a silver badge
    - Complete all ACT sessions 14 days in a row: earn a gold badge

- Tracking own exercise data: Participants will be able to monitor their physical activity through the app by recording their physical activity (e.g., swimming, cycling, running, sports). The Garmin wearable will record the step count and time spent in moderate/vigorous intensity activity.
    - Each week, participants will receive a progress report including step count and time spent in moderate-to-high-intensity activity. Other parameters like sleep data and heart rate (resting and during activity) will be included in the report.

  The app has an information module informing participants about the recommendation of the UK Medical Officer Physical Activity Guidelines[2]:

[2] https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/832868/uk-chief-medical-officers-physical-activity-guidelines.pdf

For adults:

- Do at least 150 min of moderate intensity (i.e., increased breathing, able to talk) physical activity throughout the week. Example of activities: Swim, brisk walk, cycle
- Do at least 75 min of vigorous intensity physical activity (i.e., breathing fast, difficulty talking) throughout the week. Example of activities: run, stairs, sport

For children and young people (5-18 years):

- Aim for an average of at least 60 min per day across the week. This can include all forms of activity such as physical education, active travel, after-school activities, play and sports.

Relevant information can include:

- Signpost to useful resources regarding ACT/physiotherapy and exercise, e.g., PCD Support UK website or the above-mentioned physical activity guidelines. These will be general knowledge, not personalised advice.

9.6.2. Description of comparator(s)

In the control arm, participants download the app only and do not receive any wearable. They will be instructed to log data about their daily ACTs, past and ongoing exacerbations, spirometry data to complete the PCD-specific validated quality-of-life instrument and the Patient Health Engagement scale. The app will not be customized with the behaviour change features described in 9.6.1. Participants will only receive standard periodical notifications to log requested data.

9.6.3. Description of study procedure(s)

During the 12-week study period, participants in both arms will report 5 types of patient-reported outcomes:

- Diaries to report daily ACT routine
- Exacerbation events
- Spirometry readings
- Medications
- Quality of life
- Social interactions
- Patient Health Engagement

This is a fully decentralized study in which participants do all assessments from home via the study app.

9.7. Baseline Assessments

Baseline assessments

<u>ACT routine</u>

At baseline participants will fill in an initial questionnaire in the app to report which is their prescribed ACT daily routine:

- Please choose the following ACT options that best describe the daily routine recommended by your physiotherapist; you can choose more than one:
    - Breathing techniques (e.g. Active Cycle of Breathing, huff coughing, autogenic drainage)
    - Manual techniques (percussion, vibrations)
    - Positioning, i.e., body positions to help mobilize secretions
    - Positive Expiratory Pressure (PEP) (e.g. TheraPEP®)
    - Oscillatory PEP (Flutter®, Acapella®, Aerobika®)
- How many times a day? (for each of the options above)
    - Once daily
    - Twice daily
    - Other, please describe

- In addition to your physiotherapy, are you doing any of the following?
    - Nose/sinus rinsing with saline/hypertonic saline solution
    - Mucolytics, e.g. DNAase
    - Bronchodilator medicines (inhalers)

This selection will be considered the prescribed ACT routine throughout the study. Participants may be able to report any changes in their prescribed routine.

Past exacerbation events

Participants will be required to report past exacerbation events according to the definition by Lucas et al. 2019, any hospitalizations (related with an exacerbation) and/or any rescue antibiotic treatment during the past 3 months prior entering the study. The app will feature a questionnaire to capture past exacerbations.

Spirometry readings

Participants will be required to provide spirometry readings (e.g., FEV1, FVC) at baseline, 6-week and 12-week time points. If participant does not have a spirometer at home, they could provide the most recent spirometry data performed at the clinic, if available.

Quality of life

Participants will complete the validated PCD-specific health-related quality of life instrument QOL-PCD that includes 48 items covering the following seven domains: Physical Functioning, Emotional Functioning, Treatment Burden, Respiratory and Sinus Symptoms, Ears and Hearing, Social Functioning, and Vitality and Health Perceptions (17–19).

Patients from 14-17 years of age will complete the QOL-PCD questionnaire Adolescents Ages 13 to 17 years version; and patients 18 and older will complete the QOL-PCD questionnaire Adults Ages 18 and older (19).

Patient Health Engagement Scale

The Patient Health Engagement scale is used to assess the psychological experience of engagement and has shown robust psychometric properties (14). It is a quantitative scale only comprising five items

where patient describes their experience along a continuum of engagement. This scale was designed to be self-administered by the patient. Adult participants will be required to complete the PHE scale at baseline and at the end of the study period. The scale is not validated for children and young patients

Drug treatments

At baseline, participants will also be asked to complete a medication diary to record all prescribed drug treatments and changes in their medication regimen throughout the study. This information will allow rule out potential confounders on heart rate values, to identify conditions that could potentially influence engagement with ACTs (e.g., anxiety and depression) and to track any medications and medication changes that could potentially influence the occurrence of exacerbations (e.g., prophylactic antibiotics withdrawal).

9.8. Subsequent assessments

We report here subsequent assessments to be performed throughout the study period.

Baseline, day 42 (6 weeks) and day 84 (12 weeks) assessments

At baseline, 6 and 12 weeks, participants will complete the validated QOL-PCD quality of life instrument and report on spirometry data.
At baseline and day 84, the PHE scale will also be sent to participants for its completion.

Daily assessments

ACT performance diaries.

Participants will complete a daily ACT diary containing the following questions:

- I have performed session 1/session 2/all sessions/no session
- I have spent XX minutes in active clearance during each session
- How do you think the session went? Please score it from 0 (worst) to 10 (best)
- Please select the options that best reflect your experience:
  - It was easy to clear / hard to clear
  - I coughed up more / less / same as usual
  - My chest was tighter than usual
  - I had pain / no pain

Weekly assessments

Social interactions

Increased social interaction can be a risk factor for respiratory infections. A weekly questionnaire will be sent to the participants asking about their level of social interactions, including frequency of social encounters, travel, time spent in public transportation (21,22).

Ongoing assessments

Exacerbation events

Exacerbations may be reported as they occur during the study period. Participants will have three options:

- **Weekly reports**: Participants will be prompted by the app to log any occurrence of the events described in Section 6, including any hospitalizations (related with an exacerbation) and/or any rescue antibiotic treatment in the past 7 days.
- **Spontaneous reports**: Patients can also spontaneously log any occurrence of the events described in Section 6, including any hospitalizations (related with an exacerbation) and/or any rescue antibiotic treatment, as they happen.
- Participants may report any **signs or symptoms** that, according to their experience and using their own words, could be **indicative of an exacerbation**. We aim to capture additional descriptors indicative of an exacerbation that might not be included in the criteria described by Lucas et al. 2019 (3).

Medication/ACT routine changes

At any point during the study, participants will be able to report any new medication prescribed, or report medication withdrawal. Similarly, they will be able to report any changes to their ACT routine recommended by their physiotherapist.

Continuous wearable data collection

Participants in the behaviour change intervention arm will receive a wrist-worn activity tracker (Garmin Vivosmart® 5) that they will be asked to wear during daytime and night-time, which will capture the following data:

- Heart rate
- Number of steps per day
- Time spent in moderate-to-vigorous intensity activity
- Sleep
- Oxygen saturation

9.9. Sample Handling

No samples will be taken.

9.10. Early Discontinuation/Withdrawal of Participants

During the course of the study a participant may choose to withdraw early from the study at any time. This may happen for several reasons, including but not limited to:

- Inability to comply with study procedures
- Participant decision

Participants may withdraw their consent, meaning that they wish to withdraw from the study completely.

1) Participants can withdraw from the study but permit data obtained up until the point of withdrawal to be retained for use in the study analysis. No further data would be collected after withdrawal.
2) Participants can withdraw completely from the study and withdraw the data collected up until the point of withdrawal. The data already collected would not be used in the final study analysis.

The type of withdrawal and reason for withdrawal will be recorded in the study platform. Withdrawn participants will not be replaced.

9.11. Definition of End of Study

The end of study is the point at which all the study data has been entered.

10. SAFETY REPORTING

Safety reporting is not applicable to this study as the study intervention is non-pharmacological. No data concerning adverse effects of medications that participants might be taking as part of their usual regimen will be collected.

11. STATISTICS AND ANALYSIS

11.1. Statistical Analysis Plan (SAP)

The plan for the statistical analysis of the study is outlined below. There is not a separate SAP document in use for the trial.

11.2. Description of the Statistical Methods

Preliminary analyses

We will use univariate and bivariate descriptive statistics (e.g., means, standard deviations, correlations, cross-tabulations) and plots (e.g., histograms, scatterplots) to examine distributions of and associations among study variables, to screen for potential data entry errors and biologically implausible values, and to characterize the degree and patterns of missingness.

Baseline characteristics

Descriptive statistics will be presented. Categorical data will be summarised by frequencies and percentages. Continuous data will be summarised by mean (standard deviation), median (interquartile range) and range. No formal statistical testing will be undertaken.

Final analyses

The final analyses will be conducted following availability of the 12-week data for the last patient randomised for the intervention group. The control participants to be included in the analysis must be those recruited contemporaneously to the intervention being evaluated.

The primary outcome is engagement with ACTs at week 12 and we will test the hypothesis that there is a higher engagement with ACTs in the intervention arm than in the control arm using a two-sample unpaired t-test.

To assess any potential age-related differences on the intervention effect, measures of engagement with ACTs for 14-17 years of age (teenagers and young adults) and ≥18 years of age (adults) will be assessed separately as subgroup analysis.

To assess potential changes in quality of life and exacerbation rate at the end of the 12-week study period, we will use paired two-sample t-tests to compare the baseline measures to the 12-week outcomes. As a subsidiary analysis we will investigate the effect of potential confounders of exacerbations (social interactions, time of the year…) on the intervention effect and changes from baseline using an analysis of covariance. Relationships between exacerbation occurrence and spirometry readings will be explored in a correlation analysis.

Actual change from baseline will be calculated as (12-week outcome – baseline measure). Percent change from baseline will be calculated as (actual change from baseline/baseline measure)* 100.

Wearable data will be explored to evaluate the relationships between infections and increased heart rate, decreased oxygen saturation levels, disturbed sleep pattern.

The primary and secondary outcomes will be tested with a 5% significance level

11.3. Sample Size Determination

We have conducted power calculations based on the primary outcome being the change in self-reported engagement at week 12 compared to the control arm. We estimated necessary power for a medium effect (d=0.61) based on the average effect sizes found in studies examining the effects of similar interventions on airway therapy adherence in patients with obstructive sleep apnoea. Power calculations indicated that with N=88 (44 in each arm) we will have sufficient power (i.e., 80%) to detect a medium effect with a two-sided Type 1 error of 0.05 for the two-sample t-test analysis that forms the primary methods of analysis for assessing the primary outcome.

We then adjusted the sample size for an estimated 10% dropout rate. The resulting sample size is N = 98.

11.4. Analysis populations

All randomised study subjects completing the whole study period. This will be seen as the primary population for the analysis.

11.5. The Level of Statistical Significance

All applicable statistical tests will be two-sided and will be performed using a 5% significance level.

12. DATA MANAGEMENT

The plan for the data management of the study is outlined below. There is not a separate Data Management document in use for the study.

All data collected in the context of this study will be collected, stored, and evaluated in accordance with the protocol and regulatory requirements and applicable guidance for electronic records.

Aparito will collect the raw data using Atom5^{TM}, a digital platform owned by Aparito, designed for electronic devices and web surveys. The Atom5^{TM} platform operates under ISO143485 Quality Management System (QMS) and ISO/IEC 27001 ISMS accreditations and is FDA CFR21 Part 11 and GDPR compliant. It has also attained the trusted privacy seal “ePrivacyApp '' awarded by ePrivacyseal GmbH for the protection and security of data. Atom5^{TM} is Cyber Essentials certified, a UK government program for

information assurance and is the minimum certification that is required for a government supplier responsible for handling personal information in the UK. Cyber Essentials Plus has the Cyber Essentials trademark simplicity of approach but includes a hands-on technical verification (For more details please see https://www.aparito.com/regulatory-compliance/)

Following completion of each assessment, data are transferred and temporarily stored on Aparito cloud servers located in Cardiff, UK. Meta-data like geo-location, movement, will not be captured. All data capture and data storage tools used for the study will be validated. This validation will include a mutually agreed upon user acceptance test (UAT) created by Aparito. PCD Support UK will participate in the UATs, with support from Aparito. All systems will be only used in practice after passing UAT.

During data entry, online automatic checks will indicate participants entering the data of any non-plausible or incoherent errors which have been made. A data cleaning process will involve a variety of defined automated computer checks to be run on the data, as well as manual checks (e.g., identification of missing values or values which are outside pre-defined range, logical and consistency checks). Missing or unclear data will not be queried.

Medical staff appointed by PCD Support UK involved in confirming the diagnosis PCD during this study are bound by medical confidentiality and are obliged to comply with data protection. During diagnosis confirmation, all entry of clinical information in the database is carried out in an anonymised manner (as described in ICF). All the documents provided by the patient/caregiver during diagnosis confirmation will be destroyed once they have been reviewed by the medical staff in charge of confirming the diagnosis.

To ensure the confidentiality of research participants and throughout the study, all data will be collected and stored with restricted access according to all current standards for hard- and software security as dictated by applicable international, national, and European data protection legislations. National and international data protection laws as well as regulations on observational, non-interventional studies will be followed. For data processing technical and organisational measurements according to Art. 32 of the EU general data protection regulation 2016/679 (GDPR) will be followed. The software platform hosting European patient data records is compliant with the UK GDPR 2021 and Data Protection Act 2018 . Patient data will be held on an Aparito hosted server in the UK (Cardiff).

12.1. Source Data

Personal data captured on the consent form will include name and year and month of birth. Once consent has been taken participants will be assigned an anonymous identification (ID) number, which confirms data anonymity for the remainder of the study. Demographic data captured under anonymous ID number will include age and duration of disease.

12.2. Access to Data

Data should only be accessible to approved personnel as per the user access log, which should be used to provide and revoke access during the study where necessary.

Aparito and PCD Support UK staff involved in the design and writing of the protocol will not have access to individual participant study results during the study duration, but could have access to aggregated data. Aparito will assign a Data Monitor who will be able to monitor study progress and participant

compliance with study procedures. Aparito Senior Data Scientist will be responsible for analysis of study data.

In accordance with GCP, quality control (QC) checks must be implemented for each stage of the data handling process to ensure that all data are reliable and have been processed correctly. For electronic CT data, the following is maintained:

- A security system preventing unauthorised access to the data with a list of individuals who are authorised to make changes (Access request Log).
- A fully auditable trail of data queries and corrections. If data are transformed during processing, it should always be possible to compare the original data and observations with the processed data.

Aparito staff have no unauthorised access to patient identifiable data captured in the study system.

12.3. Data Recording and Record Keeping

Aparito will retain the study documents and participant records for at least 7 years after the completion or discontinuation of the study.

13. QUALITY ASSURANCE PROCEDURES

13.1. Risk assessment

A risk assessment and monitoring plan will be prepared before the study opens and will be reviewed as necessary over the course of the study to reflect significant changes to the protocol or outcomes of monitoring activities.

13.2. Study monitoring

Aparito will assign a Data Monitor who will be able to monitor study progress and participant compliance with study procedures

13.3. Study Committees

An independent Data Monitoring Committee (DMC) will be appointed. The DMC will review accumulating data to assess the progress of the study and will provide recommendations regarding the study modification, continuation or termination, if applicable.

14. PROTOCOL DEVIATIONS

A study related deviation is a departure from the ethically approved study protocol or other study document or process (e.g., consent process or administration of study intervention) or from Good Clinical Practice (GCP) or any applicable regulatory requirements. Any deviations from the protocol will be documented in a protocol deviation form and filed in the study master file.

A standard operating procedure should be in place describing the procedure for identifying non-compliances, escalation to the central team and assessment of whether a non-compliance /deviation may be a potential Serious Breach.

15. SERIOUS BREACHES

A "serious breach" is a breach of the protocol or of the conditions or principles of Good Clinical Practice which is likely to affect to a significant degree

(a) the safety or physical or mental integrity of the trial subjects; or

(b) the scientific value of the research.

16. ETHICAL AND REGULATORY CONSIDERATIONS

16.1. Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

16.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

16.3. Approvals

Following Sponsor approval, the protocol, informed consent form/assent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), and HRA (where required) for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

16.4. Other Ethical Considerations

As specified in section 9.3, if participant is below 16 years of age, their parent/guardian or legally authorised representative should sign the informed consent form, while the participant will sign an assent form.

16.5. Reporting

The CI shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, HRA (where required) host organisation, Sponsor and funder (where required). In addition, an End of Study notification and final report will be submitted to the same parties.

16.6. Participant Confidentiality

The study will comply with the General Data Protection Regulation (GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. The processing of the personal data of participants will be minimised by making use of a unique participant study number only on all study documents and any electronic database(s). All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data.

16.7. Expenses and Benefits

Participation in the study is completely voluntary. Participants, who have completed all assessments at the end of the 12-week study period will receive a £20 GBP Amazon voucher as an expression of appreciation for their participation. Amazon vouchers will be issued through the study app.

Participants in the intervention group, and those who give their consent to participate in the extension phase of the study (see 7. Study design) will keep the Garmin wearable device at the end of the study.

17. FINANCE AND INSURANCE

17.1. Funding

Aparito Ltd is and PCD Support UK are the funder and co-funder of this trial, respectively.

17.2. Insurance

Aparito Ltd, UK has contracted an indemnity insurance policy of £5m GBP cover by Markel (UK) Ltd combined with underwriting by CFC (https://www.cfcunderwriting.com/en-gb/).

17.3. Contractual arrangements

Appropriate contractual arrangements will be put in place with the Data Monitoring Committee members and other third parties, if applicable.

18. PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by Aparito Ltd. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged. Aparito and PCD Support UK will be co-authors of any publications arising from the study.

Study results will be communicated to the PCD community in lay language with the support from the PCD Support UK for their dissemination.

19. DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY

Any generation of intellectual property derived from the study (i.e., joint invention) will be shared between Aparito and PCD Support UK. Both parties shall agree in good faith on the filing and commercial exploitation of the joint Inventions in a license agreement. The terms of the license agreement should ensure that PCD Support UK has the right to obtain royalties derived from the commercial exploitation of the joint invention.

20. ARCHIVING

The anonymised data we use for analysing the results will be on Aparito's secure servers for one year and then deleted.

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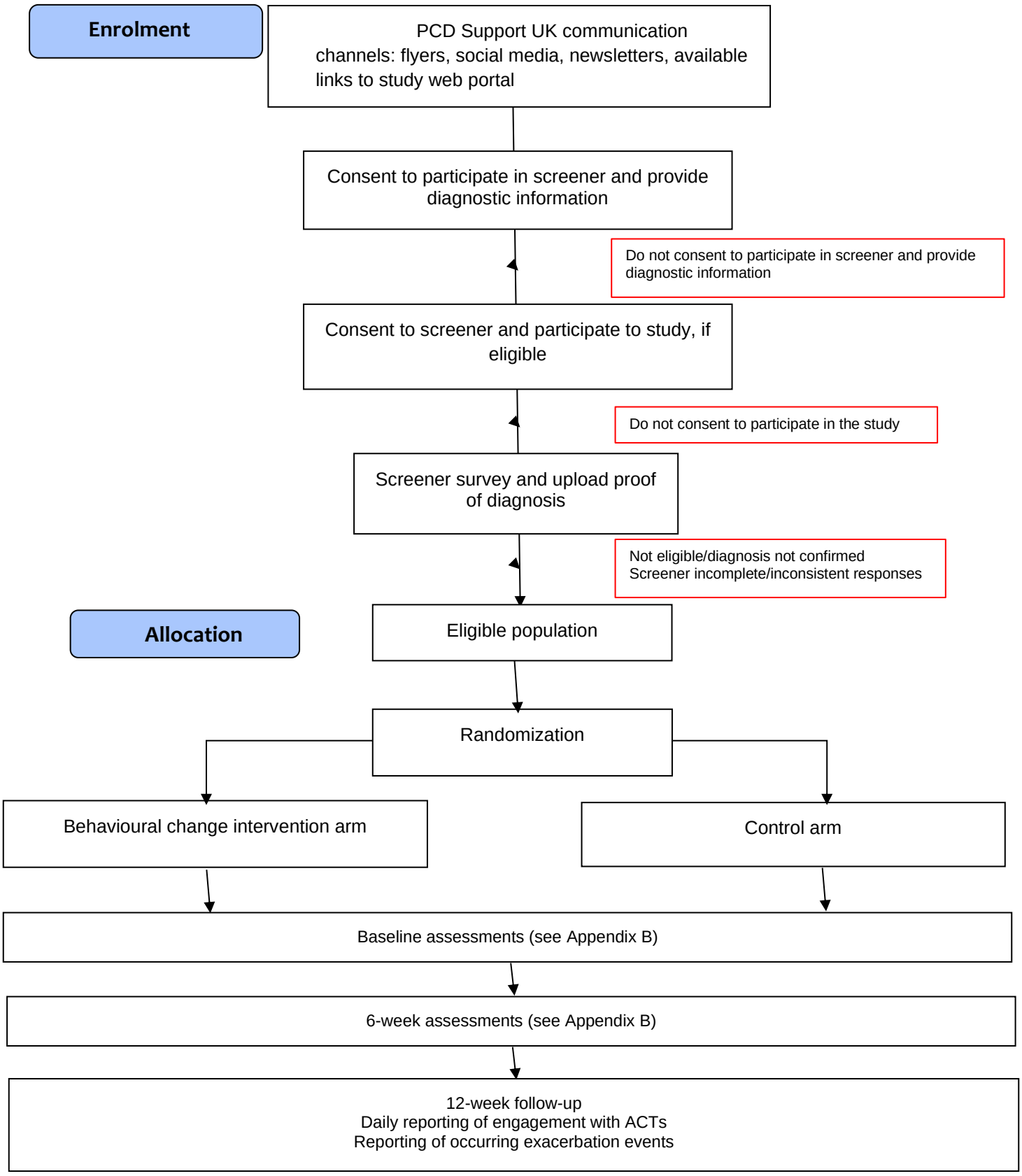
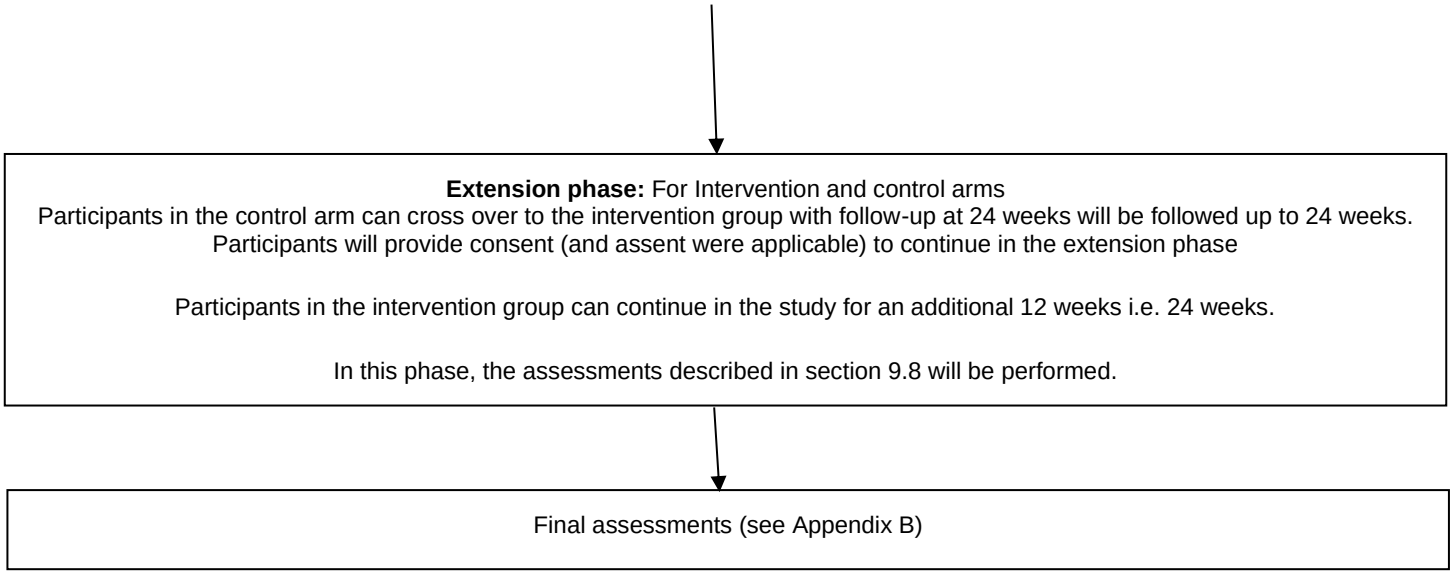
22. APPENDIX A: STUDY FLOW CHART




Extension phase: For Intervention and control arms
Participants in the control arm can cross over to the intervention group with follow-up at 24 weeks will be followed up to 24 weeks.
Participants will provide consent (and assent were applicable) to continue in the extension phase
Participants in the intervention group can continue in the study for an additional 12 weeks i.e. 24 weeks.
In this phase, the assessments described in section 9.8 will be performed.
Final assessments (see Appendix B)

23. APPENDIX B: SCHEDULE OF STUDY PROCEDURES

Procedures during the 12-week study period

Procedures	Day 0 Screening	Day 1 Baseline	Day 42	Day 84	Daily	As they happen	Weekly	Continuously
Eligibility assessment	x							
Informed consent	x							
Randomisation	x							
QoL-PCD assessment		x	x	x				
Past exacerbations		x						
Ongoing exacerbations						x		
Spirometry readings (FEV1, FVC)		x	x	x				
Engagement with ACTs		x			x			
Patient Health Engagement (PHE scale)		x		x				
Social interactions							x	
Wearable data								x

Procedures during the 12-week extension phase

Procedures	Day 84	Daily	As they happen	Weekly	Continuously
QoL-PCD assessment	x				
Ongoing exacerbations			x		
Spirometry readings (FEV1, FVC)	x				
Engagement with ACTs		x			
Patient Health Engagement (PHE scale)	x				

Social interactions				x	
Wearable data					x