An exploratory study of a novel, low-cost sleep apnoea screening device to compare its capability to identify apnoeas and hypopneas with current standard sleep apnoea test devices.

SHORT TITLE: Sleep Apnoea Breathing Record Exploratory Study (SABRES)

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Chief Investigator:	Dr Ajit Thomas
NHS sites	Royal Stoke University Hospital
Sponsor:	University Hospitals of North Midlands
Funder:	Innovate UK through Apnea-Tech Limited

AMENDMENT HISTORY

Amendment No.	Protocol Version	Date Issued	Author(s)	Details

1. LAY SUMMARY

1.1 Background

During sleep, many people have times when they breathe shallowly or completely stop. If a person stops breathing for more than 10 seconds, this is called an 'apnoea'. If shallow breathing, where the airflow drops by 30% or more, lasts for more than 10 seconds and results in the oxygen level in the person's blood decreasing by 3% or more, it is called a 'hypopnoea'. If a person has these events frequently, it disrupts their sleep and they do not awake refreshed. The tiredness can be so significant that it affects their life and can leads to accidents. These breathing events can also put strain on the heart, leading to cardiovascular conditions. These sleep disorders, usually called 'Sleep Apnoea', and can be treated for most people using 'continuous positive airways pressure', CPAP.

1.2 Why is this study important?

Sleep Apnoea diagnosis currently takes place at a specialist clinic, primarily because the diagnostic devices are complicated to use and interpret, as well as expensive. The standard tests, which patients wear overnight, do not measure actual breathing but rely on a series of other measurements which indicate that the person has stopped or reduced their breathing.

1.3 What is the test?

The new test is very simple. It just requires the user to wear a mask, similar to ones used for CPAP treatment, overnight and then return the mask for data analysis. The mask contains a small sensor to measure changing pressures in the user's breathing during the night, which records when the user has an apnoea or a hypopnea.

1.4 How does the device work?

Over the past two years, a newly formed company, Apnea-Tech Limited, has developed a simple, low-cost device to assist medical professionals in screening for sleep apnoea and hypopnea. It has been awarded taxpayer funding through Innovate UK to develop its novel device. The screener, called Apne-Scan, uses a mask fitted with a pressure sensor to monitor actual breathing.

1.5 The Key Question

Can the simple, low-cost screener assist a clinician in diagnosing sleep apnoea as well as the more expensive standard sleep apnoea test?

1.6 How are we going to answer this question?

In this study, patients will be invited to take part if they have been referred by a clinician to the sleep clinic for a standard diagnostic test. Participation in the study does not change their NHS care pathway for their condition but could eventually lead to others being screened earlier, reducing NHS costs. If they agree to take part, at the same time as the standard test, participants will wear an Apne-Scan mask to capture details of their actual breathing. They will also complete a short questionnaire answering questions about their age, sex, weight, measurements and about using the mask. Having worn Apne-Scan overnight, they will return the device to the sleep clinic, with the standard test, for data analysis by Apnea-Tech. Apnea-Tech will not receive any personal information about the user. The company will only receive their study participant number, the data captured by their Apne-Scan device, the participant's oxygen saturation level data captured by the standard test and the participant's questionnaire answers.

1.7 What is the potential public health impact of this study?

Independent research indicates that treating Sleep Apnoea reduces overall NHS costs. It also suggests that, in the U.K. alone, better diagnosis of Sleep Apnoea could lead to a reduction of up to 40,000 fatigue-related accidents per year.

1.8 How will this research be used?

The results from analysing the data from the Apne-Scan device will be compared with those from the standard test to establish the comparability of the two methods. The study results will be published in either a journal or at a conference. Apnea-Tech will also use the results to develop a data analysis program to assist clinicians in diagnosing sleep apnoeas and hypopneas.

1.9 Who are the key people involved?

The key people involved are:

- Dr. Ajit Thomas, an experienced respiratory consultant in the Sleep Clinic at the Royal Stoke University Hospital. He will be the Chief Investigator in this exploratory study.
- Jeremy Walsh, Technical Director of Apnea-Tech Limited, will oversee the analysis of the Apne-Scan data collected in the study and present it to the Chief Investigator for comparison with the data from the standard sleep apnoea tests.

1.10 The 'Apne-Scan' screening device


Figs 1, 2 and 3: The Apne-Scan device (close up), being worn (front) and being worn (side)

2. ABBREVIATIONS

ADE	Adverse Device Effect
AE	Adverse Event
ASADE	Anticipated Serious Adverse Device Effect
CE	EU Conformity Assessed
CI	Chief Investigator
CSA	Central Sleep Apnoea
DMC	Data Management Committee
DUID	Device User ID
EHR	Electronic Healthcare Record
GCP	Good clinical practice
GDPR	General Data Protection Regulations
GP	General Practice / General Practitioner
HCP	Healthcare professional
HYP	Hypopnea
IHE	Indicative Hypopnea Event
IFU	Instructions For Use
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
OSA	Obstructive Sleep Apnoea
PI	Principal Investigator
PIS	Participant Information Sheet
R&D	Research and Development
REC	Research Ethics Committee
SA	Sleep Apnoea (CSA, OSA and HYP)
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Effect
SPO2	Oxygen saturation level in the blood
TSC	Trial Steering Committee
USADE	Unanticipated Serious Adverse Device Effect
UKCA	UK Conformity Assessed

3. SYNOPSIS

STUDY TITLE	An exploratory study of a novel, low-cost sleep apnoea screening device to compare its capability to identify apnoeas and hypopneas with current standard sleep apnoea test devices.
INTERNAL REF. NO.	G001-23
PROBLEM STATEMENT	Sleep apnoea (SA) has been estimated to affect nearly 1 billion people worldwide (Reference 1) but only 15-20% of people with the condition are diagnosed and treated. It is estimated that about 20% of the people with SA have Central Sleep Apnoea (CSA) and the remaining 80% have Obstructive Sleep Apnoea (OSA). Cost effective treatments for OSA exist, e.g., CPAP, which have a significantly beneficial effect on the patient, reduce tiredness and the onset of co-morbidities[4-6]. Current diagnostic aids are expensive, tend not to monitor the user's actual breath pathway, are complicated for the user and time consuming for the clinical team to interpret. An easier to use, low cost device could streamline the diagnostic pathway and release capacity in the sleep clinic for treatment.
PRIMARY HYPOTHESIS	Use of Apne-Scan DC1 to screen patients for possible sleep apnoea supports the clinician in reaching a diagnosis and identifies people who do not have the symptoms of sleep apnoea.
SECONDARY HYPOTHESES	Apne-Scan DC1 has the potential to reduce the cost of diagnosis for sleep apnoea.
	Apne-Scan DC1 is easy-to-use for both clinicians and patients.
	Apne-Scan DC1 has the potential to reduce patient visits to the Sleep Clinic and hence reduce the hospital's CO_2 footprint.
SAFETY HYPOTHESIS	Apne-Scan DC1 does not indicate that users with moderate or severe sleep apnoea or hypopnea do not have the conditions.
STUDY DESIGN	Simple comparative
STUDY PERIOD	One night per participant
STUDY PARTICIPANTS	**Inclusion criteria** The study participants must: • Have been referred by a clinician to the sleep clinic for diagnosis of a sleep disorder, possibly sleep apnoea. • Be about to be screened for possible sleep apnoea using a standard sleep apnoea test device. • Be between the ages of 18 and 75 and have provided informed consent for the study. **Exclusion criteria** People who: • Have not been referred by a clinician to a sleep clinic for diagnostic tests for sleep disorders other than for possible sleep apnoea. • Cannot tolerate wearing a mask overnight.

	• Have a neurological condition, learning or physical difficulties such that they are unable to remove a mask should they become distressed. • Are not capable of understanding the English language version of Apne-Scan DC1's IFU. • Are under the age of 18 years old or over 75 years old. • Are not capable of giving informed consent.
PLANNED SAMPLE SIZE	The study will recruit 25 participants on initial referral to the sleep clinic for diagnostic tests for possible sleep apnoea. A total of 40 Apne-Scan DC1 devices will be available for use by the clinical team and study participants.
PRIMARY OBJECTIVE	The primary objective of this exploratory study is to assess Apnea-Tech's UKCA Class I Apne-Scan DC1 sleep apnoea screening device in assisting a clinical diagnosis of sleep apnoea in comparison to standard sleep apnoea test devices (ResMed NOX T3 and Phillips Alice Night One).
SECONDARY OBJECTIVES	The secondary objectives of this exploratory study are: To review whether the effectiveness of Apnea-Tech's Apne-Scan DC1 low-cost screener seems to be impacted by the severity of the user's condition determined by a standard sleep apnoea test device as: • Mild sleep apnoea • Moderate sleep apnoea • Severe sleep apnoea To review whether the effectiveness of Apnea-Tech's Apne-Scan DC1 low-cost screener seems to be impacted by the severity of the user's condition determined by a standard sleep apnoea test device as: • Mild hypopnoea • Moderate hypopnoea • Severe hypopnoea To review whether there are artifacts in the Apne-Scan data which can be used to accurately predict the change in the user's SPO2. To assess the usability and effectiveness of the device in capturing the minimum data required for screening for sleep apnoea.
OUTCOMES	<u>Primary Outcome</u> The primary outcome of interest is the data capture of the changing pressures in the user's breathing, whilst asleep, as recorded by the Apne-Scan DC1 device. Note: The minimum evidence for successful completion of the study is 60 hours of breathing data captured by a minimum of 15 participants. <u>Secondary Outcomes</u> • An overall comparison of the SA screening output from Apne-Scan DC1 with that from standard sleep apnoea test devices (ResMed NOX T3 and Phillips Alice Night One). • A comparison stratified by the severity of the SA indicated by standard sleep apnoea test devices.

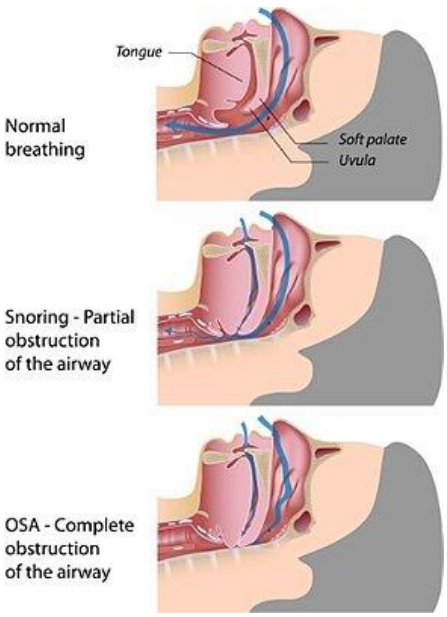
	• A comparison stratified by the severity of the hypopnoea indicated by standard sleep apnoea test devices. • A possible first-generation algorithm, based on the Apne-Scan data, to predict the user's SPO2 level.

4 BACKGROUND AND RATIONALE

4.1 Epidemiology

Sleep apnoea is a chronic condition where the person stops breathing for more than ten seconds (an apnoea) or shallow breathes for more than ten seconds (a hypopnea). Both events reduce the oxygenation of the blood. Less than 20% of sleep apnoea is caused by brain commands (central sleep apnoea) with more than 80% due to obstruction of the airways (obstructive sleep apnoea - OSA)[1].

OSA is a common, treatable condition. Recent research indicates that 936 million globally have mild-to-severe OSA, with 425 million with moderate-to-severe OSA[1]. Even in first-world countries, the vast majority (up to 80%) of those affected remain undiagnosed and therefore untreated[2-4]. The lack of an appropriate level of case identification is driven by three factors: patients are frequently unaware of their own symptoms of sleep apnoea since they are often identified either by a bed partner or family member; clinicians in most medical specialties, and especially within primary care, do not have access to a simple sleep apnoea screening device; and health care professionals often lack the necessary training to identify high risk people and screen for early intervention. An accessible diagnostic technology and improved knowledge of the risk factors leading to sleep apnoea are therefore crucial to properly screen those with the highest risk.



1.5 million people in the UK have OSA. Up to 4 per cent of middle-aged men and 2 per cent of middle-aged women in the UK have OSA. It also affects 3 per cent of children in the general population; and as many as 50 per cent of children who are obese or have specific disabilities or other health conditions. Older people are even more at risk, with 15 to 20 per cent of those aged 70 and more estimated to have the condition. This means that OSA is the most common chronic respiratory condition, and the numbers affected are believed to be rising due to more people being overweight.[4] Currently, due to the cost of the diagnostic equipment, OSA is diagnosed at specialist sleep clinics. More than 25% of the people referred to these centres are snorers, who could be screened out by Apne-Scan, releasing much needed specialist diagnostic capacity.

Due to the proven association between OSA and cardiovascular or metabolic pathology, it is clear that undiagnosed moderate-to-severe OSA results in significant additional healthcare costs. In the UK out of the 1.5 million people believed to have OSA, currently only 330,000 are treated[4]. In September 2014, the Office of Health Economics Consulting and British Lung Foundation (now Asthma+Lung UK) concluded that increasing treatment rates to 45% of OSA patients (effectively all moderate-to-severe OSA) would save the NHS £28 million per year and produce 20,000 QALYS annually[5]. Additionally, they estimated a reduction of 40,000 road accidents annually due to a reduction in fatigue. Case–control studies in the UK and USA have consistently shown that OSA patients use more healthcare resource, with more frequent hospital admissions in the years before diagnosis, when compared to subjects

without OSA[6-11]. This is exampled by a case–control study of 97 obese patients with severe OSA which reported that in the 2 years prior to diagnosis, OSA patients spent 251 nights in the hospital compared with 90 nights for the control group (p,0.001)[6].

4.2 Current screening/diagnostic methods

ResMed's NOX T3

Current screening and diagnostic devices for sleep apnoea are complicated, expensive and do not measure the breath pathway, they measure proxies for cessation of or reduction in respiration. They are also complicated and, even with the recent introductions of WatchPat™ and AcuPebble™, the median cost of current diagnostics is still in the region of £2-£3K per device plus consumables. This includes ResMed's NOX T3 diagnostic device illustrated above. Polysomnography (PSG) diagnostic devices can cost over £10,000 per unit depending on functionality. Some of the shortcomings with current 'home use' screening devices include**,** but are not limited to, the requirement for calibration, user error (complicated functionality), only nasal breath detection if respiration is monitored at all (most OSA patients breathe through their mouth), home damage and loss of device (not returned by patients).

4.3 The Apne-Scan Device

Apne-Scan DC1 is a newly developed Class I UKCA screening device to assist clinicians to identify sleep apnoea and hypopnea. It is designed to be a low-cost, simple-to-use, single user, single use device.

4.4 Comparator Devices

ResMed's NOX T3 and Phillips Alice NightOne are market leading sleep apnoea test devices which will be used as the reference devices in this exploratory clinical study.

5. PRELIMINARY STUDIES AND EXPERIENCE OF INVESTIGATORS

5.1 Investigator Experience

The Chief Investigator for this study will be Dr Ajit Thomas, an experienced consultant respiratory physician in the Sleep Clinic at Royal Stoke University Hospital. Dr Thomas also runs one of the largest domiciliary ventilation units in the U.K., with over 1,500 patients. He is also an honorary lecturer at Keele University School of Medicine, focused on clinical methods in respiratory medicine. Dr Thomas has been involved in clinical research for many years and has published seven clinical papers and numerous research abstracts.

5.2 Previous studies

The Apne-Scan DC1 device is newly developed and has been accredited as a UKCA and CE Class 1 data collector device. Prototypes and development versions of the device have been tested both in the laboratory and overnight by people involved with its development. During these tests it was found to be safe and comfortable. It also recognised cessation of breathing (in effect, an apnoeic event) and shallow breathing (a hypopnea), delivering both the reduction in signal from the sensor during the event and also the duration of the event.

6. AIMS AND OBJECTIVES

6.1 Overall Study Aim

The overall study aim of the study is an initial assessment of whether screening patients with possible sleep apnoea using Apne-Scan DC1 can support the clinician in reaching a diagnosis of sleep apnoea and whether Apne-Scan identifies people who do not have the symptoms of sleep apnoea.

6.2 Primary Objective

The primary objective of this exploratory study is to assess Apnea-Tech's UKCA Class I Apne-Scan DC1 sleep apnoea screening device in assisting a clinical diagnosis of obstructive sleep apnoea in comparison to standard sleep apnoea test devices (ResMed NOX T3 and Phillips Alice Night One).

6.3 Secondary Objectives

- To review whether the effectiveness of Apnea-Tech's Apne-Scan DC1 low-cost screener seems to be impacted by the severity of the user's condition determined by a standard sleep apnoea test device as:
    - Mild sleep apnoea
    - Moderate sleep apnoea
    - Severe sleep apnoea

- To review whether the effectiveness of Apnea-Tech's Apne-Scan DC1 low-cost screener seems to be impacted by the severity of the user's condition determined by a standard sleep apnoea test device as:
    - Mild hypopnoea
    - Moderate hypopnoea
    - Severe hypopnoea

- To review the participant's Apne-Scan data in comparison with their oxygen saturation levels from the standard test to identify the possibility of using the Apne-Scan data to predict the user's SPO2 level.

- To assess the usability and effectiveness of the device in capturing the minimum data required for screening for sleep apnoea.

7. STUDY DESIGN

7.1 Summary of Study Design

A simple exploratory comparative study between two screening devices.

7.2 Outcome Measures

7.2.1 Research outcomes:

Primary Outcome

The primary outcome of interest is the data capture of the changing pressures in the user's breathing, whilst asleep, as recorded by the Apne-Scan DC1 device.

Note: The minimum evidence for successful completion of the study is 60 hours of breathing data captured by a minimum of 15 participants.

Secondary Outcomes

- An overall comparison of the OSA screening output from Apne-Scan DC1 with that from standard sleep apnoea test devices (ResMed NOX T3 and Phillips Alice Night One).
- A comparison stratified by the severity of the OSA indicated by standard sleep apnoea test devices.
- A comparison stratified by the severity of the hypopnoea indicated by standard sleep apnoea test devices.
- A possible first-generation algorithm, based on the Apne-Scan data, to predict the user's SPO2 level.

7.2.2 Safety Outcomes:

- Any adverse events (AEs) reported while performing the study procedures.
- Any adverse device effects (ADEs).

8. STUDY PARTICIPANTS

8.1 Study Setting

Recruitment for this research study will take place from among the patients who have been referred for diagnosis of a possible sleep disorder, possibly sleep apnoea, to the sleep clinic at the Royal Stoke University Hospital.

8.2 Study Participants

The study participants have been referred by a clinician to the sleep clinic for diagnosis of a sleep disorder, possibly sleep apnoea.

8.3 Eligibility Criteria

8.3.1 Inclusion Criteria:

The study participants must:

- Have been referred by a clinician to the sleep clinic for diagnosis of a sleep disorder, possibly sleep apnoea.
- Be about to be screened for possible sleep apnoea using a standard sleep apnoea test device.
- Be between the ages of 18 and 75 and have provided informed consent for the study.

8.3.2 Exclusion Criteria:

People who:

- Have not been referred by a clinician to a sleep clinic for diagnostic tests for sleep disorders other than for possible sleep apnoea.
- Cannot tolerate wearing a mask overnight.
- Have a neurological condition, learning or physical difficulties such that they are unable to remove a mask should they become distressed.
- Are not capable of understanding the English language version of Apne-Scan's Instructions For Use (IFU).
- Are under the age of 18 years old or over the age of 75 years old.
- Are not capable of giving informed consent.

9. SAMPLE SIZE CALCULATION

This is an exploratory study and the sample size of twenty-five participants reflects this. The outcomes of the study will be used to inform the design and outcomes of a planned, appropriately powered clinical utility and effectiveness study, which will also assess the health economic impact of Apne-Scan's use.

10. STUDY PROCEDURES

10.1 Recruitment

Potential participants for this study will be invited to take part in the study when they present at the sleep clinic at the Royal Stoke University Hospital. They will be provided with the Participant Instructions Sheet and given adequate time to consider enrolling.

10.2 Enrolment

Potential participants will be identified as follows:

Aged between 18 and 75 years.

Capable of giving informed consent.

The study team will qualify them through enquiring about their capability to remove a mask should they become distressed and their understanding of the ASDC-1's Instructions for Use.

10.3 Study Assessments

10.3.1. Schedule of Assessments

- Informed consent
- Demographic information (all standard care)
    - Age
    - Sex
    - Ethnicity
- Basic health criteria (all standard care)
    - Weight
    - Height
    - Neck circumference
    - Smoker/reformed smoker/non-smoker
    - Completes Epworth Sleepiness Questionnaire (validated)
    - Baseline Saturations at rest
- Issue of the Apne-Scan DC1 device, together with card documenting participants demographic information and basic health criteria
- Explanation to the participant of use of Apne-Scan at the same time as the standard sleep apnoea test device (either ResMed NOX T3 or Phillips Alice Night One)
- Participant uses the device overnight, at the same time as using the standard sleep apnoea test device.
- Participant completes short user questionnaire.
- Participant returns the Apne-Scan DC1 device and the completed participant questionnaire to the sleep clinic, at the same time as they return the standard sleep apnoea test device to the sleep clinic (standard care).
- Apnea-Tech analyses the data collected by Apne-Scan and provides to the clinical team.
- Output of Apne-Scan compared by clinical team to the output of the standard sleep apnoea test device used by the participant.

Schedule of study events					
Event	**Enrolment**	**Baseline**	**Study**	**Analysis**	**Remarks**
Clinical Data					
Informed Consent	X				
Age	X	X			
Sex		X			
Ethnicity		X			
Weight and height		X			
Neck circumference		X			
Smoking history		X			
Epworth Sleepiness questionnaire		X			
Baseline Saturations at rest		X			
Demonstration of use of Apne-Scan DC1		X			
Issue of Apne-Scan DC1 kit		X			
Apne-Scan Device					
Use of Apne-Scan DC1 overnight			X		
Post Apne-Scan Use					
Short participant experience questionnaire			X		
Return the device and questionnaire to the sleep clinic.			X		
Apne-Scan DC1 data is downloaded and secured together with clinical data and experience questionnaire, and participant's SPO2 data from the standard test for analysis				X	

10.3.2. Study Device

10.3.2.1 Description

Each Apne-Scan DC1 kit consists of the following items.

Item	Description
ASDC1	Apne-Scan DC1 device
ASDC1 IFU	Apne-Scan DC1 Instructions for Use
ASDC1 PUQ	Post use questionnaire

10.3.2.2 Infection Prevention Control

The Apne-Scan DC1 has been developed as a single user single use device. It is manufactured in a clean and ready to use state. There is no requirement for a cleaning regime, as it will only be used once.

10.3.2.3 Device Usage and Data Flow

The Apne-Scan DC1 device is a single user, single use device. It has a single flow sensor which records the pressure in the breath pathway twice per second. The definitions for diagnosing sleep apnoeas and hypopneas are all relative, based on percentage changes in sensor readings. The device will only recognise Indicative Hypopnea Events, because it does not confirm desaturation, unless the captured data can be used to accurately predict the user's SPO2 level at any time. There is no need for any calibration by the clinician or the user.

Once the device has been started, it continues to monitor the pressure in the breath pathway until the battery runs flat, which is targeted at over eight hours. The pressure readings are recorded sequentially on the internal memory for later download. They remain in the memory when the battery has run down.

After use the study participant return the used Apne-Scan DC1 and completed questionnaire, with the standard test, to the sleep clinic. The Apnes-Scan data, together with the post-use questionnaire and the standard test's SPO2 level data, will be securely stored by participant number by the company and then analysed for possible apnoeas, indicative hypopneas and prediction artifacts within the Apne-Scan data of changes in SPO2 levels.

10.3.2.4 Supply, Packaging and Storage

The Apne-Scan DC1 kit will be provided to the study participant by the sleep centre. It will contain all the items outlined in 10.3.2.1 above. Apnea-Tech do not believe that there are any requirements for secure packaging or long-term storage. The shelf life of the batteries is the current limitation on use, and this is over 24 months.

10.3.2.5 Administration

The study team will maintain a Device Register which will identify to which participant each device was issued, so that they can be tracked.

10.3.2.6 Disposal of items

Once returned to Apnea-Tech, the Apne-Scan is dismantled, with the battery and electrical components recycled appropriately (under WEEE). The mask, sensor and Apne-Scan enclosure will be recycled according to their specific requirements.

10.3.3 Assessment questionnaire

After using the Apne-Scan DC1, each study participant will complete a short questionnaire which is on the back of the study participant's baseline details completed by the study team after informed consent (age, sex, ethnicity, weight, neck circumference, smoking history, Epworth score and baseline saturations at rest). The questionnaire, which is not a validated questionnaire, enables the participant to record their experience in using the Apne-Scan DC1.

10.4 Discontinuation/Withdrawal of Participants from the study

Participants will be free to withdraw from the study at any time without any consequences or compromise to their standard clinical care. Participants will consent at the start of the study to allow

for their anonymised study data (baseline information, questionnaire data and Apne-Scan data) to be retained and analysed by the study team in the event that they withdraw from the study.

10.5 Definition of End of Study

The end of study is the date at which the final participant completes the study and returns their device to Apnea-Tech. The minimum evidence for successful completion of the study is at least 15 participants capturing between them sixty hours of breathing data.

11. SAFETY

11.1 Safety Reporting Definitions

Adverse Event Categorisation

<table>
<tr><th>Adverse Events</th><th>Non-Device-Related</th><th colspan="2">Device- or Investigational Procedure-Related</th></tr>
<tr><td>Non-Serious</td><td>Adverse Event (AE)</td><td colspan="2">Adverse Device Effect (ADE)</td></tr>
<tr><td rowspan="3">Serious</td><td rowspan="3">Serious Adverse Event (SAE)</td><td colspan="2">Serious Adverse Device Effect (SADE)</td></tr>
<tr><td>Anticipated</td><td>Unanticipated</td></tr>
<tr><td>Anticipated serious adverse device effect (ASADE)</td><td>Unanticipated serious adverse device effect (USADE)</td></tr>
</table>

11.1.1 Adverse Event (AE)

An untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in participants, users or other persons, whether or not related to the investigational medical device and whether anticipated or unanticipated.

An AE can, therefore, be any unfavourable or unintended sign, symptom or disease temporarily associated with the use of the device, whether or not this has a causal relationship with the device under investigation.

11.1.2 Adverse Device Effect (ADE)

An adverse event related to the use of an investigational medical device.

Note 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

Note 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

ADEs are all untoward and unintended medical occurrences in response to a medical device. All cases judged by either a medically qualified professional or the sponsor as having a reasonable suspected causal relationship to the device qualify as a device effect. This also includes any event resulting from insufficiencies or inadequacies in the instruction for use or deployment of the device and includes an event that is a result of a user error.

11.1.3 Serious Adverse Events (SAE)

An adverse event that led to any of the following:

- Death
- Serious deterioration in the health of the participant, users, or other persons as defined by one or more of the following:
    - A life-threatening illness or injury
    - A permanent impairment of a body structure or a body function including chronic diseases
    - In-patient or prolonged hospitalisation
    - Medical or surgical intervention to prevent life-threatening illness or injury, or permanent impairment to a body structure or a body function
    - Foetal distress, foetal death, a congenital abnormality, or birth defect including physical or mental impairment

Note: Planned hospitalisation for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered a serious adverse event.

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Other events that may not result in death, are not life-threatening or do not require hospitalisation, may be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

11.1.4 Anticipated Serious Adverse Device Effects (ASADE)

A serious adverse device effect which by its nature, incidence, severity or outcome has been identified in the risk assessment.

11.1.5 Unanticipated Serious Adverse Device Effects (USADE)

A serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current risk assessment.

11.1.6 Serious Adverse Device Effects (SADE)

An adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

A SADE does not necessarily have to have a causal relationship with the device under investigation. However, a SADE is defined as any untoward medical occurrence seen in a participant that can be attributed wholly or partly to the device which resulted in any of the characteristics or led to the characteristics of a SAE. A SADE is also an event that may have led to these consequences if proper action had not been taken or intervention had not been made or if circumstances had been less opportune. A SADE will be documented on a SAE form.

11.1.7 Serious Health Threat (SHT)

A signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in participants, users or other persons, and that requires prompt remedial action for other subjects, users or other persons.

Note: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.

11.2 Recording & Reporting of Adverse Events

11.2.1 Sponsor Responsibilities

The Sponsor is responsible for the following activities:

- In collaboration with the Device Manufacturer, perform on-going safety evaluation of the trial device and report any findings that may affect the health of participants to the Device Manufacturer.
- Promptly notify all Investigators, REC and MHRA (if required), of any findings that may affect the health of participants.
- Keep detailed written reports of all AEs reported by PI(s) and review the PI's evaluation of the AE's seriousness, causality and expectedness.
- Report all relevant safety information and SAEs to the CI, REC and MHRA (if required) within the relevant timelines given in the protocol.
- Break treatment codes before submitting expedited reports to MHRA and REC for specific participants, even if the Investigator has not broken the code.
- Submit the annual safety report to REC.
- Submit summary reports to the MHRA (if required).

11.2.2 Chief Investigator Responsibilities

The Chief Investigator has overall responsibility for the conduct of the study and will provide the Sponsor with details of all AEs identified in the protocol as critical to the evaluation of safety.

11.2.3 Principal Investigator Responsibilities

The Principal Investigator will be a different person to the Chief Investigator and will:

- Inform the Sponsor (UHNM) of all adverse events that occur at their site.
- Inform the Sponsor within 24 hours of being notified that the event has occurred.
- Assess the AE severity, causality and expectedness and update the Sponsor on the results of their assessment within 48 hours of being notified that the event has occurred.
- Supply the Sponsor, and the MHRA and REC (where necessary), with any supplementary information they request.

11.3 Recording & Reporting of Adverse Events

Participants will be asked to report any AEs to the clinical study team. AEs will be assessed by the CI for causality, intensity, seriousness and expectedness. Only AEs that have a reasonable possibility of being attributable to the device and any other AE considered to be of clinical significance by the CI as causing harm to the participant will be recorded and reported to the Sponsor. Any SAEs that do occur and are considered by the CI to be related to the device will be expedited to the Sponsor and the REC within 7 days. Lists of the AEs will be provided by the Sponsor when requested.

11.3.1 Assessment of Adverse Events

Initial assessment of AEs must be made by the Principal Investigator using the relevant safety reporting form. The outcome of this assessment should be forwarded to the Sponsor for Sponsor review **within 48 hours** of the AE being detected by the research team. If the AE is determined to be serious, it must then be reviewed by the CI.

Each AE must be assessed for seriousness, causality and expectedness. Where the PI and Sponsor's reviews do not concur, the AE must be followed up as the more serious event.

11.3.2 Assessment of Seriousness

The assessor (PI / CI / Sponsor) should make an assessment of seriousness in the following manner:

11.3.2.1 Assessment of Expectedness

The assessor must consult the current version of the protocol to determine whether an event is expected or unexpected. Events that are anticipated (or 'expected') are listed below. An unanticipated (or unexpected) effect is anything not listed in the protocol.

Anticipated (Expected) Events:

Code	Event	Frequency
01	Breathlessness/intolerance to mask	High
02	Apnoeas/cessation of breathing	High
03	Hypopneas/shallow breathing	High
04	Snoring	High
05	Restlessness/poor sleep	High
06	Snoring	High
07	Irregular breathing	High
08	Any other event directly related to diagnosis of suspected sleep apnoea	High
09	Any other event directly related to the participant's existing medical conditions	High

If the event is classified as an anticipated effect (i.e. expected), which by its nature, incidence severity or outcome has been previously identified in the Protocol, then the event does not require reporting to the Regulatory Agencies (MHRA and REC) but must be recorded in the medical records and the relevant safety reporting form. The sponsor must be informed of this event **within 48 hours** of becoming aware of the event. This document must be retained with the CRF.
Where an event could be related to the medical device and is unanticipated, in relation to the protocol (i.e. a USADE or unexpected SAE), the PI must report this event to the Sponsor **within 24 hours** of becoming aware of the event. The Sponsor will report this event to both the Manufacturer and to the Regulatory Agencies within the required timelines.

11.3.2.2 Assessment of Causality

The assessor of any causality assessments will use clinical judgement to determine the relationship between the event and the medical device. The assessor must consult the current version of the Protocol. When making a causality assessment, the following definitions should be used:

Not Related	There is no evidence of causal relationship to the Investigational Device.
Unlikely	There is little evidence to suggest there is a causal relationship. There is another reasonable explanation for the event (e.g. the participant's clinical; condition, other concomitant events or medication).
Possible	The relationship with the use of the investigational medical device is weak but cannot be ruled out completely

Probable	The relationship with the investigational medical device seems relevant and/or the event cannot reasonably be explained by another cause.
Causal Relationship	The serious event is associated with the investigational medical device beyond reasonable doubt.

11.4 Reporting Adverse Events

11.4.1 Reporting Adverse Events

The PIs assessment of seriousness, expectedness and causality of all AEs should be reported to the Sponsor **within 48 hours** of the research team becoming aware of the AE occurring. The Sponsor will then also undertake a review to ensure they agree with the PIs assessment of seriousness, expectedness and causality.

11.4.2 Reporting Non-Serious Adverse Events

If the PI reports to the Sponsor that the AE is non-serious, and the Sponsor agrees, there is no need to escalate further or report to regulatory bodies (REC / MHRA). All AE and ADEs must be observed to ensure that they do not escalate to an SAE/SADE. All AEs should be reported to the DMC and presented at the next TSC.

If the Sponsor does not agree with the PI's assessment, the AE must be treated as a more serious event and reported as described in section 11.5.3 below.

11.4.3 Reporting Serious Adverse Events

Reporting to Sponsor:

If the PI determines that the AE is serious, the relevant safety reporting form must be used to report all SAEs/SADEs/USADEs/ASADEs to the Sponsor. This form and any documents provided to the Sponsor in support of the SAE/SADE/USADE must be depersonalised (labelled with trial ID number) and must NOT contain any patient identifiable data.

The PI/research team at the site where the AE occurred must provide any additional information as required to complete the report. The PI/research team at site must actively following-up the affected participant(s) until either:

- The SAE/SADE/USADE resolves, or
- Until 30 days after the discontinuation of use of the medical device

Review and sign-off of SAEs:

The CI is responsible for the review and sign-off of all serious adverse events/effects. In the event that the CI is unable to sign the report immediately, the research team/site should not delay sending the report to the Sponsor. However, a CI signed copy must be forwarded to the Sponsor as soon as possible (and within 48 hours of the initial reporting).

Should the CI be unavailable, serious adverse events/effects can be signed off by Dr Francis Gilchrist.

Reporting to the MHRA:

Device related events involving a CE/UKCA marked device being used within its intended purpose/proof of concept studies in a post market surveillance study must be reported to the MHRA Adverse Incident Centre https://aic.mhra.gov.uk/. Reporting to the MHRA of such occurrences is undertaken by the Sponsor. Individual guidance on the reporting requirements for certain types of devices can be found on the MHRA website https://www.gov.uk/government/collections/medical-devices-guidance-for-manufacturers-on-vigilance

Reporting to REC:

The following SAEs/SADEs are considered reportable to the REC that gave the favourable ethical opinion:

- Those related to the administration of the medical device or any of the research procedures.
- USADEs - i.e. unanticipated events not listed in the Protocol as an anticipated occurrence.

Reports to REC should be submitted, by the Sponsor, within 15 days of the CI becoming aware of the event using the Non-CTIMP Safety Report Form to the REC published on the HRA website http://www.hra.nhs.uk/.

The CI is also required to include a report of the safety of participants in the annual progress report to the REC.

Individual reports will be reviewed by the REC at a subcommittee or committee meeting. Any requests for further information should be provided as applicable and all correspondence should be copied to the Sponsor.

Reporting to NHS Trust:

SAEs, SADEs, USADEs or Device Deficiencies which occur at site must be reported on the Trust's electronic incident reporting system (e.g. Datix). Reporting of incidents must be carried out in accordance with the Trusts Incident and Accident reporting policy. All SAE/SADE/USADE reported to the Sponsor will be reviewed at the R&I COG and by the Director of R&I.

11.4.4 Follow-up of Adverse Events by Sponsor

Acknowledgement will be issued to the Investigator from the Sponsor via email within 7 days of receipt of a fully completed form, and this must be filed in the TMF/ISF.

Each SAE/SADE/USADE will be registered on the recognised Sponsor database and reviewed by the Sponsor or their delegate. This review may lead to queries being issued by the Sponsor/delegate to request signed documentation, clarify information or complete event outcome. All queries will be sent via email and must be responded to within the stated timeframe.

All SAEs and SADEs will be recorded on a SAE Form and will be reported within 24 hours of awareness to Apnea-Tech. This will be sent by email using the SAE Form to the company's Chief Technical Officer who is responsible for the medical device vigilance of this study.

Reports must be sent to:	Copied to:
Apnea-Tech's Chief Technical Officer	Sponsor's Clinical research Lead:

Apnea-Tech will notify the Competent Authority as soon as the Company becomes aware of any Medical Device Reportable (MDR) events.

11.5 Device Deficiencies

Inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance.

Note: Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling.

All device deficiencies device shall be documented throughout the trial and reported on the relevant device deficiency form and retained with the CRF. The Sponsor shall take, where applicable, appropriate corrective and preventive actions to protect the safety of participants, users, and other persons.

Device deficiencies that did not lead to an adverse event but could have led to a serious adverse device effect will be reported as specified in section 11.3.2. if:

a. suitable action had not been taken,

b. intervention had not been made, or,
c. circumstances had been less fortunate.

11.6 Quarantine of Devices

If a device is found to be defective or deficient then it should be withdrawn from the study and quarantined. If the device is off-site with a participant, it should be recalled using the contact information provided on the loan form and device accountability documentation.
If the device is assessed by the PI to be defective in a way which could have led to a Serious Adverse Device Event if used or usage had continued, then the MHRA must be contacted, by the Sponsor, within 1 week of the PI being made aware of the occurrence.
The device must not be returned to the manufacturer until the MHRA has been given the opportunity to carry out/complete an investigation. In addition, the device should not be:

- Discarded
- Repaired
- Returned to the manufacturer

All material evidence that may be required by the MHRA to undertake their investigation i.e. devices/parts that have been removed, replaced or withdrawn from use following an incident, instructions for use, records of use, repair and maintenance records, packaging materials, or other means of batch identification must be:

- Clearly identified and labelled
- Stored securely

This evidence should not be interfered with in any way, except for safety reasons or to prevent its loss. Where appropriate, a record should be made of all readings, settings and positions of switches, valves, dials, gauges and indicators, together with photographic evidence and eyewitness reports.

The Chief Investigator and the Sponsor will undertake any requirements outlined in the MHRA investigation and follow-up as instructed.

12. DATA HANDLING AND RECORD KEEPING

12.1 Data Handling

All data will be handled in accordance with the General Data Protection Regulations (GDPR), Apnea-Tech's SOPs and the participant's consent form. No data will be accessed for any patients who have not consented to be part of this study. Apnea-Tech or its analysis team at Keele University will not have any direct access to participant identities and participants' medical notes; participant information will be managed securely by the clinical research team.

12.2 Data Collection

Data collection will comprise of:

- The Baseline data, provided by the study team.
- The Participant Questionnaire.
- The recording of changes in flow downloaded from the participant's Apne-Scan DC1.

12.3 Data Management, Quality, Security

- All study data will be held by participant number. Apnea-Tech will have no access to any patient identifiable information.

- Any Apne-Scan device not returned by post will be noted and the study team will have the option of confirming with the participant whether it was used and posted.
- Apnea-Tech will review the data provided and assess its completeness and quality. Any missing Baseline data will be requested from the study team. Missing or poor-quality participant-supplied data will be noted in the study data log.
- All data will be retained in a secure data repository for seven years.

13. DATA ANALYSIS

13.1 Analysis of Endpoints

13.1.1 Summary Statistics

The summary statistics produced from this exploratory study will be:

% participants successfully using the Apne-Scan DC1

Comparisons of primary diagnostic metric, AHI, between the standard sleep apnoea test device and Apne-Scan (based on recorded apnoeas and indicative hypopneas).

Primary Data Analysis

Comparison of primary diagnostic metric, AHI, between the standard sleep apnoea test device and Apne-Scan DC1.

Secondary Data Analysis

Comparison of primary diagnostic metric, AHI, segmented into mild, moderate and severe sleep apnoea, between the standard sleep apnoea test device and Apne-Scan DC1

Comparison of primary diagnostic metric, AHI, segmented into mild, moderate and severe hypopnoea, between the standard sleep apnoea test device and Apne-Scan DC1

Comparison of the participant's Apne-Scan data with their oxygen saturation levels from the standard test to identify the possibility of using the Apne-Scan data to predict the user's SPO2 level, possibly resulting in a first-generation algorithm, based on the Apne-Scan data, to predict the user's SPO2 level.

Analysis of the usability and effectiveness of the device in capturing the minimum data required for screening for sleep apnoea.

13.2 Interim analysis and criteria for early study termination

Not planned or required

14. REGULATORY & ETHICS

14.1 Participant Confidentiality

Participants will be identified with a random unique identifier by the clinical study team.

All study documents (e.g., consent forms) will be stored securely and will only be accessible by the clinical study team and authorised personnel. The study will comply with the GDPR, and all other relevant Data Protection Regulations.

14.2 Ethical Considerations

The study will not commence before the protocol, participant information sheets, consent forms and all other supporting study materials, have received a favourable opinion from the relevant Research Ethics Committees (REC), and any National Health Service (NHS) Research & Development (R&D)

departments. Any changes to protocol or relevant study documents will be approved by the CI and Sponsor. Should an amendment be made that requires REC approval, defined by REC as a substantial amendment, the changes will not be implemented until the amendment has been reviewed and received favourable opinion from the REC (and any R&D departments). A protocol amendment intended to eliminate an immediate hazard to participants may be implemented immediately, approval will be requested and the REC will be notified as soon as possible. Minor amendments (non-substantial amendments), may be implemented immediately, and the REC will be informed.

All participants will be given time to consider participation in the study, as per Good Clinical Practice (GCP) guidelines.

14.3 Informed Consent

The process for obtaining consent will be under the REC guidance, and GCP and any other regulatory requirements that might be introduced. The participant will be provided with sufficient time to consider participating in the study

The decision to participate in the study is entirely voluntary, and this will be emphasised to patients.

14.4 Declaration of Helsinki and ICH Guidelines for Good Clinical Practice

The study will be performed in accordance with, and in the spirit of, the declaration of Helsinki, the Good Clinical Practice Guidelines (GCP) the protocol and any applicable local regulatory requirements and laws. The clinical study team must hold evidence of appropriate GCP training or undergo GCP training before undertaking any responsibilities on this study. This training should be updated every 3 years.

15. FINANCING AND INSURANCE

15.1 Research Costs

This research is funded by a grant of taxpayer funds awarded through a funding competition by Innovate UK to Apnea-Tech Limited.

15.2 Service Support Costs

There are no service support costs.

15.3 Study Sponsorship

This study is sponsored by Royal Stoke University Hospital.

16. RESOURCES AND EQUIPMENT

The Apne-Scan DC1 kits will be provided as free-issue stock to the sleep clinic at Royal Stoke University Hospital.

17. DISSEMINATION AND OUTCOME

Results generated by this study will be formalised for submission to a peer-reviewed journal or conference. The manuscript will be drafted by Apnea-Tech and authorship will be determined by

agreement. Apnea-Tech must review any subsequent publications and presentations prepared by Investigators.

18. INSURANCE AND LIABILITY

The study is insured through the standard NHS clinical study insurance cover. Apnea-Tech has commercial liability insurance, as well as product liability insurance for its Class 1 Apne-Scan DC1 device.

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