

Study Title: COPD tRansforMation of diagnOstic pathways in pRimary cAre using N-Tidal

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Please declare any/no potential conflicts of interest.

HA, GH, CB, MG, SF, PT, JW, RKK, JC, CLB, LJ and CR are employees of the University of Oxford. They receive no payments or support from TidalSense, and will retain ownership and governance of research data.

AP and JC are shareholders of TidalSense Limited. GL, HL and EM are employees of TidalSense Limited.

LC is our lay advisor.

Confidentiality Statement

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

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1. KEY CONTACTS

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2. LAY SUMMARY

Chronic obstructive pulmonary disease (COPD) is a lung condition that causes breathing problems and is usually caused by smoking. Although common, many people do not know they have it: in the UK, almost half of people affected have not been diagnosed. This is a big problem because people are often diagnosed after too much lung damage has been done, and their quality of life is already poor. Diagnosing COPD early would mean more could be done to prevent the condition getting worse and give the option of treatments, giving patients a better chance of living a longer, active life.

The difficulties of performing spirometry, the test used to diagnose COPD, contribute to missed or late diagnosis. It involves blowing hard and fast into a machine that measures lung capacity, which is difficult for people to do. It is also time-consuming and must be done by a trained healthcare professional, which uses up staff time in GP surgeries.

TidalSense has built an easy-to-use device called the N-Tidal Handset. The N-Tidal Handset is CE marked which means that the product complies with European law with regards to medical devices. Patients breathe in and out normally and the N-Tidal Handset measures a gas that everyone breathes out called Carbon Dioxide (CO₂). The device shows how the level of CO₂ in the breath changes as the patient breathes in and out. It is easier and faster to train healthcare professionals to use the N-Tidal Handset compared to spirometry.

TidalSense has collected results from people already diagnosed with various breathing conditions using the N-Tidal Handset across a range of healthcare settings. Using artificial intelligence (AI), TidalSense developed software called N-Tidal Diagnose that can distinguish between those with and without COPD. It does this by looking at the pattern of CO₂ in the breath, a pattern recorded using the N-Tidal Handset. New patients can now use the N-Tidal Handset, and the N-Tidal Diagnose software can say if they have COPD or not. This process, from turning on the device to a result being generated, takes under 5 minutes.

This research will gather evidence on the value of N-Tidal Diagnose in primary care, the setting where it would be most used. This study will test the accuracy of N-Tidal Diagnose in patients who are not yet diagnosed but might have COPD.

TidalSense spoke to patients and doctors from the very beginning of developing N-Tidal to make sure it fits their needs. In each study, TidalSense invited patients to review the study plan, progress, and help communicate results to participants and the public. This study will be no exception: patients recruited from Asthma and Lung UK's network of 100,000 people with lung conditions will give the team feedback throughout the project and we have a lay representative as part of the study team.

3. SYNOPSIS

Study Title	COPD tRansforMation of diagnOstic pathways in pRimary cAre using N-Tidal
Short title	CORMORANT
Study Registration	ISRCTN18133836
IRAS number	329554
CPMS	56530
Ethics ref	25/SC/0103
Sponsor	University of Oxford Research Governance, Ethics & Assurance Team (RGEA) University of Oxford, Boundary Brook House, Churchill Drive, Headington, Oxford, OX3 7GB RGEA.Sponsor@admin.ox.ac.uk
Funder	i4i Challenge Awards, NIHR and NIHR HRC in Community Healthcare
Study Design	Diagnostic Accuracy Study with nested qualitative sub-study
Study Participants	Adults aged ≥35 years, for whom diagnostic spirometry has been requested where COPD has been considered a potential diagnosis
Sample Size	500 participants Approximately 20 of the main study participants and approximately 20 healthcare professionals (40 interviews combined) will partake in the optional qualitative sub-study
Planned Study Period	31/03/2025 – 30/09/2026
Planned Recruitment Period	March 2025 – September 2026
Summary definitions used in objectives below Further details of reference standard definitions and independent technical interpretation and clinical diagnosis are provided later in the protocol (Section 8.8 and 12). <u>N-Tidal Diagnose</u> – Novel diagnostic test for COPD diagnosis, conducted here for research purposes only, results not used to inform clinical care. The results output from the test will give the probability of COPD diagnosis through 5 different categories: COPD highly likely (++), likely (+), indeterminate (?), unlikely (-) or highly unlikely (- -). The result outputs will be analysed as follows: • N-Tidal binary diagnosis of COPD (++) or not (- -) (i) Index test • N-Tidal binary diagnosis of COPD (++ / +) or not (- - / -) (ii) Index test • N-Tidal individual prediction categories (++ / + / ? / - / - -) (iii) Reference test <u>Spirometry</u> – Standard diagnostic test used in COPD diagnosis, conducted here as part of usual care	

Spirometry measurements indicate presence or absence of airway obstruction, which is required for formal diagnosis of COPD. The administration of salbutamol in between two recordings can determine whether this obstruction is reversible (consistent with asthma) or remains present (consistent with COPD). Spirometry results require a degree of technical interpretation to ensure results are valid for use in clinical diagnosis. Spirometry traces in this study will have:

- Usual care interpretation around/shortly after time of test.
- Expert technical spirometry interpretation at a later date by independent trained assessor(s) – for quality assessment and binary presence/absence of airway obstruction
- Expert independent clinical consensus interpretation at a later date for quality assessment and binary presence/absence of airway obstruction **(iv)**

Clinical diagnosis of COPD – Decision on whether someone has COPD on the basis of clinical history (symptoms), presence of risk factors (e.g. smoking, age) and results of spirometry. This is set out in NICE/GOLD clinical guidelines.

- Usual care clinical diagnosis around/shortly after time of test – how this is done and recorded will vary between sites, but we will attempt to capture this in data collection where available
 - Usual care binary diagnosis of COPD (+) or not (-) **(v)**
- Expert independent clinical consensus assessment at a later date, blinded to N-Tidal Diagnose results.
 - Consensus binary diagnosis of COPD (+) or not (-) **(vi)**
 - Consensus prediction categories of COPD (mirroring N-Tidal Diagnose categories) – COPD highly likely (++), likely (+), indeterminate (?), unlikely (-) or highly unlikely (- -) **(vii)**

N.B. Regarding N-Tidal Diagnose software version

As software that incorporates machine learning models, N-Tidal Diagnose has the capacity to be updated with improved models. The software version used in the study will remain fixed for the duration of the study.

However, if a new release of N-Tidal Diagnose software has been formally issued incorporating updated machine learning models prior to statistical analysis, the updated version will be used in place of the original outputs generated at the time of data collection, in order that diagnostic accuracy is based on the most recent version and findings are as up-to-date as they can be.

	Objectives	Outcome Measures	Time point(s)
Primary	Determine diagnostic performance of N-Tidal Diagnose for the diagnosis of COPD in a primary care population	Diagnostic accuracy (PPV, NPV) of N-Tidal Diagnose compared to consensus diagnosis Index test: (i) Reference test: (vi)	N-Tidal and spirometry at study visit Consensus at end of study

Secondary	Compare diagnostic performance of N-Tidal Diagnose with diagnostic performance of usual care diagnosis of COPD	Diagnostic accuracy (PPV, NPV) of N-Tidal Diagnose compared to consensus diagnosis Index test: (i) and (ii) vs. Reference test: (vi) (i.e. primary outcome as above) Vs. Diagnostic accuracy (PPV, NPV) of usual care diagnosis compared to consensus diagnosis Index test: (v) Reference test: (vi)	N-Tidal and spirometry at study visit Consensus at end of study Notes review for usual care diagnosis at least one month following spirometry
	Determine the sensitivity and specificity of N-Tidal Diagnose prediction categories	Diagnostic accuracy (sensitivity, specificity, PPV, NPV) of all possible N-Tidal Diagnose prediction cut-offs compared to consensus diagnosis Index test: (iii) Reference test: (vi)	Consensus at end of study
	Assess feasibility and acceptability to clinicians and patients of use of N-Tidal Diagnose in primary care settings, compared to spirometry/existing diagnostic pathways	Visual Analogue Score following N-Tidal and spirometry Thematic analysis of semi-structured interviews with participating clinicians and participants, exploring feasibility and acceptability	At study visit Qualitative interviews post-recruitment
	Describe the quality of primary care spirometry performed in this study	Percentage of participants with adequate spirometry performed according to ARTP guidelines, determined by independent clinical consensus quality assessment (iv) Descriptive data on primary care spirometry quality control and training procedures at recruiting sites Thematic analysis of semi-structured interviews with participating primary care	Consensus at end of study Collected during Site set-up Qualitative interviews post-recruitment

		clinicians, exploring quality and accuracy issues	
	Evaluate the quality of N-Tidal Diagnose data capture	Percentage of participants with adequate N-Tidal Handset breath record capture, sufficient to generate a diagnostic output using N-Tidal Diagnose software	N-Tidal at study visit
Intervention(s) / Index test(s)		Primary: N-Tidal Diagnose Other index test definitions as described above	
Comparator(s) / Reference test(s)		Primary (Outcome measure vi): Consensus binary diagnosis of COPD using NICE/GOLD guidelines based on clinical history (symptoms), presence of risk factor(s), age and spirometry result Other reference standard definitions as described in Section 8.8 Reference Standard Outcome Definition.	
Study devices		N-Tidal Diagnose N-Tidal Handset N-Tidal Respiratory Sensor Paired Airway (RESPA) N-Tidal Mouthpiece	
Clinical Development Stage		Post-market	
Inclusion Criteria		- Participant is willing and able to give informed consent for participation in the study. - Participant is aged 35 years old or over. - Diagnostic spirometry has been requested by their clinician where COPD is a potential diagnosis (even if it is not necessarily the most likely)	
Exclusion Criteria		The participant may not enter the study if ANY of the following apply: - Participants who have previously had COPD confirmed by spirometry (participants who are having repeat spirometry as part of diagnosis can be included) - Participants who, in the opinion of the chief investigator, or their delegate, are unlikely to comply with the requirements of the study. - According to the recruiting clinician, participants unable to give fully informed consent - According to the recruiting clinician, participants who are acutely unwell, e.g. requiring hospitalisation - Patients unable to breathe through their mouths e.g. tracheostomy patients. - Participants who have already participated in the study	

Embedded Qualitative Interview Sub-study Criteria	• Study participants who have consented to be contacted • Health care professionals at study sites who have been involved in delivering the study There are no additional exclusion criteria for the qualitative study.
Statistical Considerations	The statistical aspects of the study will be fully described in a statistical analysis plan that will be finalised before analysis takes place. Based on a maximum sensitivity for N-Tidal of 90%, and estimated COPD prevalence of 55% in the cohort, 262 patients would be required to obtain a confidence interval with a half-width of 5% (i.e. a confidence interval from 85-95% if the sensitivity is 90%). 500 participants will be recruited to account for missing data or failure to complete study procedures. Unless otherwise specified, analyses will be carried out only on data from participants with a suitable quality post-bronchodilator spirometry result, or pre-bronchodilator spirometry adequate for diagnostic purposes under 2025 GOLD guideline update. A sensitivity analysis will be carried out using spirometry from all participants.
Authors/Reviewers of Plan	Chief Investigators and all Investigators

4. ABBREVIATIONS

AI	Artificial Intelligence
ARTP	The Association for Respiratory Technology & Physiology
CAT	COPD Assessment Test
CI	Chief Investigator
CO ₂	Carbon Dioxide
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CRN	Clinical Research Network
DALYs	Disability-Adjusted Life Years
DHSC	Department of Health and Social Care
EU MDR	REGULATION (EU) 2017/745 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC as amended.
FEV ₁	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GOLD Guidance	Global Initiative for Chronic Obstructive Lung Disease Guidance
GP	General Practitioner
HCP	Healthcare Professional
HRA	Health Research Authority
ICF	Informed Consent Form
IFU	Instructions for Use
MDCG 2020-10/1	Safety reporting in clinical investigations of medical devices under the Regulation (EU) 2017/745
MDCG 2024-3	Guidance on content of the Clinical Investigation Plan for clinical investigations of medical devices
mMRC Breathlessness Score	Modified Medical Research Council Breathlessness Score
NHS	National Health Service
NIHR	National Institute for Health and Care Research
NICE	National Institute for Health and Care Excellence
NPV	Negative Predictive Value
PC-CTU	Primary Care Clinical Trials Unit

PI	Principal Investigator
PIS	Participant/ Patient Information Sheet
PPV	Positive Predictive Value
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
RES	Research Ethics Service
RESPA	Respiratory Sensor Paired Airway (a consumable component of the N-Tidal Handset that forms the breath pathway together with the N-Tidal Mouthpiece)
RGEA	Research Governance, Ethics & Assurance
SAP	Statistical Analysis Plan
SaMD	Software as a Medical Device
SOP	Standard Operating Procedure
TBCO ₂	Tidal Breathing Carbon Dioxide
TMF	Trial Master File
TMG	Trial Management Group
UK	United Kingdom

5. BACKGROUND AND RATIONALE

5.1. Problem

Chronic Obstructive Pulmonary Disease (COPD) is an incurable respiratory disease, affecting >174M people globally [1]. It is the third most common cause of mortality worldwide, killing 30,000 people per year in the UK [2]. Early diagnosis and treatment is essential to slow the decline of lung function and improve quality of life [3]. Yet, half of the 3 million people with COPD in the UK are not diagnosed [4], while over-diagnosis occurs in up to 60% of cases in Europe [5].

Diagnostic challenges are in part due to lack of a simple, accurate test. According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidance the current standard for COPD diagnosis is spirometry. Spirometry assesses lung function by measuring the volume of air that a patient can forcefully exhale from the lungs after a maximal inspiration, with FEV₁ describing how much air you can exhale in 1 second and FVC total amount of air you can exhale. A FEV₁/FVC ratio of <0.7 would indicate a COPD diagnosis. This forced exhale manoeuvre is difficult for patients already experiencing potential COPD symptoms. Additionally, it is unreliable, with a positive predictive value (PPV) of only 63% [6], as many respiratory conditions produce similar results. Poorly performed spirometry commonly causes misdiagnosis: reliable testing and interpretation are time-consuming and require specifically trained healthcare professionals (HCPs). Spirometry was suspended in primary care during the COVID-19 pandemic and currently testing is yet to be restarted in a third of practices, exacerbating the significant diagnostic backlog: Almost a quarter of people (nearly one in four) surveyed had waited five years or more for a diagnosis after noticing symptoms, with 1 in 5 (21%) being unable to access key tests, such as spirometry, which are essential for an accurate diagnosis [19]. The 2022 Lancet COPD Commission concluded “current diagnostic approaches substantially underestimate the burden and morbidity of COPD and potentially prevent the development of curative treatments.” [7].

COPD is the second largest cause of emergency admission in the UK [4]. One third of patients admitted were not previously diagnosed [8]. At this stage, readmissions, disability, and acute worsening of symptoms are very common: COPD is one of the most expensive conditions for the NHS, costing £1.7bn/year in direct costs and £55bn/year in intangible costs (DALYs) [9]. The National Institute for Health and Care Excellence (NICE) specifically recommended improving access to reliable and accurate diagnostics in primary care [4].



Figure 1 - (left to right) N-Tidal Handset, RESPA (dark purple) and Mouthpiece (lavender)

TidalSense has developed and regulated the N-Tidal Handset, an easy-to-use, effort-independent medical device that measures the partial pressure of carbon dioxide (CO₂) during normal tidal breathing (Figure 1) [10]. Data collected using the device across five clinical studies has been used to develop and test fast and accurate machine learning diagnostic algorithms for COPD. These have been embedded in a software medical device called N-Tidal Diagnose [11]. This software medical device is in the final stages of regulatory approval as a Class 2a medical device under EU Medical Device Regulations.

The speed and ease of use with no requirement for extra breathing effort, and potentially improved PPV compared to spirometry, gives N-Tidal Diagnose the potential to create a paradigm shift in COPD diagnosis. However, NHS adoption necessitates an in-depth study of real-world performance and value in primary care.

5.2. Research Importance

The slow evolution of COPD means symptom onset is insidious and significant lung damage has usually occurred by the time of spirometry diagnosis. The disease progressively debilitates patients, resulting in disability, impaired quality of life, and frequent exacerbations. Earlier diagnosis and treatment are important to slowing disease progression and decline in quality of life [3,12,13].

Primary care clinicians undertake most COPD diagnosis and management. Yet over a third of practices do not regularly use spirometry, because of cost, time or personnel constraints, and lack of confidence in correctly administering/interpreting the test [14,15]. Even correctly-used spirometry misses early lung damage [7].

Implementation of N-Tidal Diagnose in primary care could rapidly benefit patients and the NHS within a year post-project:

1. Earlier, accurate diagnosis allows earlier treatment/management, delaying disability/acute symptoms, reducing NHS costs and burden on secondary care.
2. End to end use of N-Tidal Diagnose takes 5 minutes (spirometry=30 minutes), with only brief training required to administer the test, potentially freeing 300,000 appointments/year and incentivising routine use for COPD case-finding. [16]
3. The N-Tidal Diagnose automated output may aid ease of interpretation and clinical decision-making.

The next stage is to produce evidence to build the case for commissioners and NICE appraisal by:

1. Validating diagnostic performance in routine primary care use.
2. Assessing the health economic case for adoption, which requires real-world data on diagnostic accuracy in a primary care population.
3. Understanding barriers and facilitators to use in primary care settings.

6. OUTCOMES MEASURES AND OBJECTIVES

	Objectives	Outcome Measures	Time point(s)
Primary	Determine diagnostic performance of N-Tidal Diagnose for the diagnosis of COPD in a primary care population	Diagnostic accuracy (PPV, NPV) of N-Tidal Diagnose compared to consensus diagnosis Index test:(i) Reference test: (vi)	N-Tidal and spirometry at study visit Consensus at end of study
Secondary	Compare diagnostic performance of N-Tidal Diagnose with diagnostic performance of usual care diagnosis of COPD	Diagnostic accuracy (PPV, NPV) of N-Tidal Diagnose compared to consensus diagnosis Index test:(i) and (ii) vs. Reference test: (vi) (i.e. primary outcome as above) Vs. Diagnostic accuracy (PPV, NPV) of usual care diagnosis compared to consensus diagnosis Index test:(v) Reference test: (vi)	N-Tidal and spirometry at study visit Consensus at end of study Notes review for usual care diagnosis at least one month following spirometry
	Determine the sensitivity and specificity of N-Tidal Diagnose prediction categories	Diagnostic accuracy (sensitivity, specificity, PPV, NPV) of all possible N-Tidal Diagnose prediction cut-offs compared to consensus diagnosis Index test:(iii) Reference test: (vi)	Consensus at end of study

	Assess feasibility and acceptability to clinicians and patients of use of N-Tidal Diagnose in primary care settings, compared to spirometry/existing diagnostic pathways	Visual Analogue Score following N-Tidal and spirometry Thematic analysis of semi-structured interviews with participating clinicians and participants, exploring feasibility and acceptability	At study visit Qualitative interviews post-recruitment
	Describe the quality of primary care spirometry performed in this study	Percentage of participants with adequate spirometry performed according to ARTP guidelines, determined by independent clinical consensus quality assessment (iv) Descriptive data on primary care spirometry quality control and training procedures at recruiting sites Thematic analysis of semi-structured interviews with participating primary care clinicians, exploring quality and accuracy issues	Consensus at end of study Collected during Site set-up Qualitative interviews post-recruitment
	Evaluate the quality of N-Tidal Diagnose data capture	Percentage of participants with adequate N-Tidal Handset breath record capture, sufficient to generate a diagnostic output using N-Tidal Diagnose software	N-Tidal at study visit

7. STUDY DESIGN

This is a diagnostic accuracy study of N-Tidal Diagnose for the diagnosis of COPD in primary care. Binary, independent, consensus, clinical diagnosis of COPD based on post-bronchodilator spirometry (or pre-bronchodilator spirometry adequate for diagnostic purposes under 2025 GOLD guideline update[20]) along with symptom and risk factor information will be used as the reference / gold standard. We will recruit 500 participants from primary care across the UK, when they present with potential COPD and spirometry has been requested. There is a nested qualitative sub-study, where a selection of participants and clinicians (approximately 40 depending on data saturation) who have participated in the study will be invited to take part in a qualitative interview study assessing the acceptability and feasibility of N-Tidal Diagnose when used in primary care.

7.1. Study Participants

Adults aged ≥ 35 years, for whom diagnostic spirometry has been requested where COPD has been considered a potential diagnosis.

7.2. Inclusion Criteria

- Participant is willing and able to give informed consent for participation in the study.
- Participant is aged 35 years old or over.
- Diagnostic spirometry has been requested by their clinician where COPD is a potential diagnosis (even if it is not necessarily the most likely).

For the embedded qualitative interview sub-study:

- Study participants who have consented to be contacted
- Health care professionals at study sites who have been involved in delivering the study

There are no additional exclusion criteria for the qualitative study.

7.3. Exclusion Criteria

The participant may not enter the study if ANY of the following apply:

- Participants who have previously had COPD confirmed by spirometry (participants who are having repeat spirometry as part of diagnosis can be included).
- Participants who, in the opinion of the chief investigator, or their delegate, are unlikely to comply with the requirements of the study.
- According to the recruiting clinician, participants unable to give fully informed consent.
- According to the recruiting clinician, participants who are acutely unwell, e.g. requiring hospitalisation.
- Patients unable to breathe through their mouths e.g. tracheostomy patients.
- Participants who have already participated in the study.

8. STUDY PROCEDURES

A schedule of procedures can be found in Appendix A.

8.1. Recruitment

We will recruit through the Oxford Primary Care Clinical Trial Unit (PC-CTU) and its well-established links with Regional Research Delivery Networks (RRDNs) across the country, which in turn have links with research-active practices. We will recruit sites that enable a diversity of ethnicities, deprivations, and geography. This will be achieved with RDN guidance and by asking the sites questions about their patient cohort during recruitment. We will also ensure that we recruit sites with different pathways for diagnosing COPD e.g. GP practices performing in-house spirometry, Community Diagnostic Centres or diagnostic hubs.

Throughout the study recruitment and procedures, we will give options for participants to complete electronic forms over the telephone with the study team, for those who may struggle with a digital interface. They can also be completed by a carer. For participants who do not speak fluent English, we will

use translation services (as already used in routine NHS practice, so may vary between study sites) such as 'dals' (<https://dals.co.uk/>) to ensure quality of translation.

8.2. Screening and Eligibility Assessment

Eligible participants will be identified when diagnostic spirometry has been requested for potential COPD. This will be either at a recruiting GP Practice/Network or a Community Diagnostic Centre (the exact system will vary locally and this diversity will be captured within the study recruitment plans).

When possible, potential participants will be informed about the CORMORANT study by the usual clinical team, as soon as possible after spirometry has been requested, and will be sent a link to the study website, the Participant Information Sheet (PIS) and an online Informed Consent Form (ICF). Alternatively, participants will be identified and informed about the study when they attend their spirometry appointment by one of their clinical team and given a PIS to read, and if they would like to participate, they will be given the ICF to complete.

8.3. Informed Consent

The participant must personally sign and date the latest approved version of the Informed Consent Form (ICF) before any study specific procedures are performed. This will be done electronically using REDCap's electronic signature feature.

The PIS and ICF will be presented to the participants detailing no less than: the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol; 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.

The participant will be allowed time to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the study. Due to the low-risk nature of the study, where possible this will be completed electronically by the participant prior to attending their spirometry appointment. Electronic Informed Consent will be obtained by REDCap. A copy of the signed Informed Consent will be available for them to download and print from REDCap directly once they have signed. If the participant would like a copy later on, they will be able to email the trial team for one.

As part of the main consent process, participants will have the option to provide their contact details to potentially be asked to participate in a qualitative sub-study where they would be interviewed about their experience of using the N-Tidal device and spirometry (see Section 11 for details of qualitative sub-study).

8.4. Randomisation

There is no randomisation in the study. All participants will undergo both the N-Tidal Diagnose test and the spirometry test.

8.5. Blinding and Code-breaking

As all participants undergo both tests within this study there is no requirement for test blinding. It is not possible to blind the operator to the N-Tidal Diagnose results. Training will be given to the operator and it will be made clear within the PIS that N-Tidal Diagnose is being assessed for diagnostic accuracy and so the results will not affect their diagnosis or care they will receive following their standard spirometry test.

The assessors on the consensus panel will be blinded to the N-Tidal Diagnose results and will determine their consensus clinical COPD diagnosis based on clinical history (symptoms), presence of risk factor(s), age and spirometry results. To understand the extent of potential bias when using primary care diagnosis of COPD instead of independently-conducted consensus clinical diagnosis (**v** and **vi** respectively, (for more detail, please see Section 8.8 Reference Standard Outcome Definition) we will record whether the person interpreting the spirometry in primary care and/or making the clinical diagnosis is the same person who undertook the N-Tidal Diagnose testing.

8.6. Description of Study Intervention(s), Comparators and Study Procedures (Clinical)

Once Informed Consent has been given the participant will complete the baseline assessment questionnaire online, then attend their spirometry appointment. Here they will perform the N-Tidal Diagnose test in addition to spirometry. Spirometry will be conducted as per usual clinical practice: where spirometry is performed both pre- and post-bronchodilator, N-Tidal Diagnose will be measured a second time before the second spirometry. Procedures listed here may not always be completed in the same order as listed. Please see appendix A for the Schedule of Procedures.

8.7. Baseline Visit

Participant-facing questionnaires have been reviewed and piloted with patient groups through Asthma + Lung-UK. Where possible questionnaires will be completed in advance of any testing taking place, N-Tidal or spirometry, during or after the spirometry appointment where this has not been possible. We will collect the following information in addition to the N-Tidal Diagnose and spirometry results:

From the participant:

- Biological Sex
- Gender
- Age
- Ethnicity
- Smoking history
- Any existing respiratory diagnoses
- Reason for participant attending for spirometry
- Current respiratory symptoms
- Duration of symptoms
- Current or recent prescriptions for respiratory medications
- Number of chest infections in the last year including any hospitalisations
- Co-morbidities
- COPD Assessment Test (CAT) score
- Modified Medical Research Council (mMRC) breathlessness score
- Device Acceptability - Evaluation scores using Visual Analogue Scale of level of comfort and ease of use of N-Tidal and spirometry testing

From the health care professional:

- Weight
- Height
- Any comments on N-Tidal procedure
- Details of spirometry e.g. pre- or post-bronchodilator, timings of any inhalers, any comments on spirometry procedure
- Estimated time duration of N-Tidal procedure (for health economic analysis)(this will be cross-referenced with N-Tidal dashboard data which records exact times)
- Estimated time duration of spirometry procedure (for health economic analysis)

Alongside the spirometry appointment or afterwards as preferred, the health care professional or other clinical research staff will also enter (if possible/known, based on electronic health record):

- Reason for participant attending for spirometry
- Any existing respiratory diagnoses
- Current or recent prescriptions for respiratory medications
- Co-morbidities
- Chest X-ray and/or CT chest (including low-dose CT performed as part of Targeted Lung Health Check, if done) results and date (most recent only)
- Blood eosinophil count (most recent only)

The participant's full spirometry results will be sent to the study team to be redacted and uploaded in the database.

8.7.1. Description of Devices

N-Tidal hardware comprises the following components: N-Tidal Handset, the N-Tidal RESPA and N-Tidal Mouthpiece (the latter two together forming a replaceable breath pathway). Study participants will be required to breathe in and out through the N-Tidal Mouthpiece, through their mouth (not nose), using normal tidal breathing for 75 seconds. The N-Tidal Handset will record the concentration of carbon dioxide (CO₂) at regular intervals using a non-dispersive infra-red sensor. Once the recording has been complete, the CO₂ data will be uploaded to TidalSense's remote cloud-based platform via the mobile phone packet switched network, where it will be stored and processed.

N-Tidal Diagnose software is cloud-based software with a clinician-facing dashboard served through the web. The N-Tidal Diagnose software will receive respired carbon dioxide data, a breath record, from the N-Tidal Handset. No identifiable data will be entered into the N-Tidal Diagnose software. The healthcare professional administering the device is asked to enter the smoking history in pack years into the clinician-facing dashboard. The software will process the breath record to provide a diagnostic output using machine learning models, which will be presented to the clinician on the clinician-facing dashboard.

Where further spirometry is being carried out after administration of bronchodilator medication (termed pre- and post-bronchodilator spirometry, or reversibility testing), the N-Tidal Diagnose test will also be performed a second time prior to the second spirometry.

The results output of N-Tidal Diagnose provides likelihood of COPD diagnosis in 5 categories: COPD highly likely (++), likely (+), indeterminate (?), unlikely (-) or highly unlikely (- -). These outputs will be used as follows for analysis:

- N-Tidal binary diagnosis of COPD (++) or not (- -) (outcome measure i)
- N-Tidal binary diagnosis of COPD (++ / +) or not (- - / -) (outcome measure ii)
- N-Tidal individual prediction categories (++ / + / ? / - / - -) (outcome measure iii)

Refer to 9 DEVICES INFORMATION for further description of the devices used in this study.

8.7.2. Description of Comparator(s)

Spirometry is the standard for diagnosing COPD in those who are clinically suspected of having COPD. After completing use of N-Tidal Diagnose the participant will complete their spirometry test. UK NICE guidelines recommend that spirometry should be performed by a healthcare professional who has had appropriate training and who has up-to-date skills, and should be supported by quality-control processes. The Association for Respiratory Technology & Physiology (ARTP) produces guidance which details how to perform spirometry and sets out quality control processes, and the ARTP also provides formal assessment of competence of skills in performing spirometry.

However, standards are likely to vary across primary care settings and we will gather information on training and local procedures of those clinicians performing spirometry used in the study as part of the site recruitment and set-up. To assess the variation and standard of spirometry procedures, the sites will send all the spirometry traces to the study team where we will have an independent assessor interpret the traces for all study participants.

Spirometry will be carried out as it would be for the participant's standard-of-care testing. For COPD diagnosis, spirometry should be post-bronchodilator (measurements after bronchodilation using short-acting or long-acting bronchodilators), however pre- and post-bronchodilator spirometry (i.e. before and after bronchodilator administration) is often performed to look for reversibility (suggestive of an asthma diagnosis). All results and whether they are pre- or post-bronchodilator will be recorded however only post-bronchodilator results, or pre-bronchodilator results adequate for diagnostic purposes (GOLD guideline update 2025 [20]) will be used in the primary analysis (see Section 12 Statistics and Analysis below).

Performing spirometry has certain contra-indications and procedural components which will be carried out as they would normally be (as this is the standard-of-care diagnostic test), and so we will not provide study-specific direction on this. Usually, the participant will be asked to remain in a seated position for the test and place a soft clip on their nose to stop air escaping from it. They will be asked to inhale fully, so their lungs are completely filled with air, close their lips tightly around the mouthpiece and exhale as long as they can, making sure they empty their lungs fully. This will be repeated at least 3 times to ensure a reliable result. Following these 'relaxed blows' (which measure the 'vital capacity' (VC)) the participant repeats the blows but this time exhaling as quickly and forcefully as they can, again at least 3 times (this measures the 'forced vital capacity' (FVC) and 'forced expiratory volume in 1 second' (FEV₁)).

We will ask for the clinician to send the full spirometry result (graph traces and figures) to the study team who will redact any identifiable information and upload to REDCap. Therefore it can be independently assessed for quality as well as interpreted for use as the study reference standard. How this is done in practice will depend on the spirometer used by the site (how it outputs its results). See Section 12 Statistics and Analysis below for further details of spirometry interpretation and reference standard categorisation.

8.8. Reference Standard Outcome Definition

This section refers to determination of reference standard outcome for study purposes, not clinical diagnosis which will be undertaken as part of usual care using the standard-of-care spirometry trace.

The primary study reference standard will be a binary, independent, consensus clinical diagnosis of COPD based on clinical history (symptoms), presence of risk factor(s), age and spirometry. Since clinical diagnosis of COPD uses spirometry as per current (as of 2025) national guidelines, a high level of certainty regarding the quality and interpretation is essential, as this is known to be variable in primary care. This primary reference standard is referred to as **consensus binary diagnosis of COPD (outcome measure vi)** (see *c) Consensus binary diagnosis of COPD (outcome measure vi)* below).

Several steps will be taken to ensure the **consensus binary diagnosis of COPD (outcome measure vi)** is an accurate diagnostic label. They will be performed for all participants, with the exception of b) which will only be if this information is available.

a) ***Expert technical spirometry interpretation (outcome measure iv)***

Initially spirometry traces will be independently technically reported using ARTP guidance by two assessors who are deemed appropriately qualified by the study team to perform technical spirometry reporting e.g. ARTP certification or evidence of equivalent standard. They will be blinded to the N-Tidal result and any additional clinical information not included in the spirometry trace (age, sex, BMI and smoking status are usually provided on the trace). Where technical spirometry reporting has already been undertaken by an appropriate individual as part of usual care (for example, spirometry performed in the Community Diagnostic Centre is technically reported by a respiratory physiologist), only one further assessor will be required (blinded to the reporting already performed). All traces will be formally reported.

As an amendment, following issues with high levels of disagreement between spirometry technical reporters (who do not have access to any clinical details), the quality and spirometric outcomes will be determined by the expert independent clinical consensus panel, in order that they can be assessed in the clinical context, as would be the case in routine clinical practice. Only those spirometry results which are confirmed as post-bronchodilator (or pre-bronchodilator results adequate for diagnostic purposes (GOLD guideline update 2025 [20])) and are deemed sufficient quality to inform clinical COPD diagnosis, will be included in primary analysis.

b) ***Usual care binary diagnosis of COPD (outcome measure v)***

Where notes review is possible, a binary classification will be extracted from the primary care clinical record whether the participant received a clinical diagnosis of COPD or not. If they receive an alternative diagnosis, such as asthma, this will be recorded.

c) ***Consensus binary diagnosis of COPD (outcome measure vi)***

Participants will be classified into diagnostic categories by two independent assessors who will be clinicians deemed appropriately qualified by the study team to perform clinical interpretation of spirometry and respiratory diagnosis e.g. respiratory specialist or GP with respiratory expertise. Assessors will be provided with the spirometry result, technical report and clinical information provided by the participant in their questionnaire and entered into the CRF from their electronic health record.

d) ***Consensus prediction categories of COPD (outcome measure vii)***

These will be determined using the same methodology as for **Consensus binary diagnosis of COPD (outcome measure (vi))** but rather than provide a binary diagnosis, assessors will give a likelihood category that mirrors the N-Tidal Diagnose output (highly likely, likely, indeterminate, unlikely, or highly unlikely).

8.9. Subsequent Visits/Data Collection

After their testing appointment, there are no participant follow up visits.

At least one month after the spirometry appointment, the health care professional will complete an additional CRF stating the primary care clinician diagnosis / outcome following spirometry testing (e.g. COPD, alternative diagnosis, or diagnosis not yet arrived at), if they have access to the participant's clinical record. Please see appendix A for the Schedule of Procedures.

8.10. Sample Handling

There are no samples being collected within this study.

8.11. 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:

- The occurrence of device-related (Serious) Incidents (as defined under EU MDR) related to spirometry, N-Tidal Handset, N-Tidal RESPA, N-Tidal Mouthpiece or N-Tidal Diagnose device use
- Inability to comply with study procedures
- Participant decision

Participants can withdraw from the study, but data obtained up until the point of withdrawal will be retained for use in the study analysis. No further data would be collected after withdrawal.

In addition, the Investigator may discontinue a participant from the study treatment at any time if the Investigator considers it necessary for any reason including, but not limited to:

- Ineligibility (either arising during the study or retrospectively having been overlooked at screening)
- Significant protocol deviation
- Clinical decision

The type of withdrawal and reason for withdrawal will be recorded in the withdrawal CRF.

8.12. Definition of End of Study

The end of study is the point at which all the study data has been entered into the study database and all data queries have been resolved.

9. DEVICES INFORMATION

9.1. Description of the Study Devices and Their Intended Purposes

Device(s)	Intended Use and role in CORMORANT	Device Description	Purpose of data collected in CORMORANT
N-Tidal Handset	The N-Tidal Handset is intended to be used in combination with the N-Tidal Mouthpiece and N-Tidal RESPA to capture the pattern of respired CO ₂ , and transmit this data to remote servers running TidalSense medical device software.	The N-Tidal Handset is a handheld, battery-operated device incorporating a III-V infrared LED CO ₂ sensor, that reports CO ₂ measurements at 50Hz, and transmits these to a remote TidalSense cloud server.	Post Market Surveillance safety data
N-Tidal RESPA	The N-Tidal Mouthpiece is intended to be used in combination with the N-Tidal Handset and N-Tidal RESPA.	The N-Tidal RESPA and N-Tidal Mouthpiece form a replaceable breath pathway through which a handset user (participant) breathes for 75s with relaxed, tidal, breathing.	
N-Tidal Mouthpiece	The N-Tidal RESPA is intended to be used in combination with the N-Tidal Handset and N-Tidal Mouthpiece.		
(Class 1 EU MDD)	All devices will be used within their intended use on the CORMORANT study.		
N-Tidal Diagnose	N-Tidal Diagnose is intended to be used in combination with the N-Tidal Handset, for recording and displaying respiratory function by recording the pattern of respired carbon dioxide (CO ₂) from the N-Tidal Handset user's breath, and using this data to support confirmation of or rule out a diagnosis of Chronic Obstructive Pulmonary Disease (COPD). Where clinically relevant, the software will also output disease severity.	SaMD that is intended to incorporate simple, interpretable COPD diagnostic ML algorithms to support confirmation of or rule out a diagnosis of COPD using data collected and transmitted using the N-Tidal Handset. One of five categories is output as a diagnostic result: Highly likely COPD, Likely COPD, Indeterminate, Unlikely COPD and Highly Unlikely COPD.	Post Market Surveillance safety and performance data (Primary Outcome)

Table 1 Medical devices used in the CORMORANT study

9.1.1. Manufacturer of the study devices

Name: TidalSense Limited

Address: The Vinery, 15a Vinery Road, Cambridge, CB1 3DN

9.1.2. Model/type

N-Tidal Diagnose 1 v1.0.

9.1.3. Summary of required training/experience needed

Training will be provided to participating sites by initially distributing a training video and the N-Tidal Diagnose and N-Tidal Handset Instructions for Use (IFU). These will be followed up with an interactive virtual or in-person training session, to be delivered by members of the TidalSense team.

9.2. List of Features of the Devices to be evaluated (per MDCG 2024-3)

Objective(s)	Feature description (technical or functional)	Expected clinical performance outcome	Safety or performance characteristic
Determine diagnostic performance of N-Tidal Diagnose for the diagnosis of COPD in a primary care population	Diagnostic performance as specified in IFU	Diagnostic accuracy meets state of the art performance threshold	Performance
Determine the sensitivity and specificity of N-Tidal Diagnose prediction categories	Diagnostic performance as specified in IFU	Diagnostic accuracy meets state of the art performance threshold	Performance
Evaluate the quality of N-Tidal Diagnose data capture (used in combination with N-Tidal hardware)	Capture and transmit the pattern of respired CO ₂ (N-Tidal Handset)	Percentage of participants with adequate N-Tidal Handset breath record capture, sufficient to generate a diagnostic output using N-Tidal Diagnose software	Performance
Assess feasibility and acceptability to clinicians and patients of use of N-Tidal Diagnose in primary care settings, compared to spirometry/existing diagnostic pathways	Devices are safe to use as intended	Identify possible misuse, risks or unknown side effects of device	Safety

9.3. Device Traceability Accountability

The medical devices used in this study (N-Tidal Handset, N-Tidal RESPA, N-Tidal Mouthpiece and N-Tidal Diagnose) will only be used in the study and according to this protocol and will be used and stored in line with contractual obligations agreed between the parties. TidalSense will provide the site with instructions for use and technical support.

TidalSense will keep the following records related to their medical devices: name(s) of study personnel to whom devices were shipped; how many devices were shipped (including batch / lot numbers as relevant) to study sites; the date of shipment, and records of delivery (delivery notes); device identifiers (for N-Tidal Handsets); dates and contents of return shipments; servicing records; details of study staff with system access (for software).

At the end of the study, N-Tidal Handsets and unused N-Tidal RESPAs and N-Tidal mouthpieces will be returned to TidalSense; and access for study teams to N-Tidal Diagnose software will be revoked.

10. SAFETY REPORTING

This is a low risk, post-market study: participants have one visit, the intervention consists of one, 75 second test involving normal tidal breathing, and there is no participant follow up or change to the standard diagnostic pathway. Although any risks/side effects from the N-Tidal device are likely to be minimal, spirometry is associated with certain risks and adverse events, which are checked for and counselled about as part of standard-of-care routine clinical practice (which we are not changing in the study). In order to be able to compare the two tests in terms of risk and adverse event profile, we will be collecting adverse events (AEs) and serious adverse events (SAEs) as outlined below. Recruiting sites will be required to report AEs and SAEs which are felt to be clinically related to the test procedures, based on the judgement of the clinician administering the tests. This may be during the study visit or be reported by the patient in the hours or days following the visit. Sites will be asked to report SAEs to the PC-CTU within 24 hours of becoming aware of the event and AEs as soon as possible after becoming aware of the event, using the respective AE and SAE CRFs in REDCap.

SAEs will be followed up until the event resolution/stabilisation or the end of the study, whichever is sooner. For SAEs or AEs related to the N-Tidal test, incident reporting will occur as per 10.2.2 Device Incident Reporting.

10.1. Definitions

10.1.1. Incident

Per EU MDR Article 2(64): “Any malfunction or deterioration in the characteristics or performance of a device made available on the market, including use-error due to ergonomic features, as well as any inadequacy in the information supplied by the manufacturer and any undesirable side-effect”

10.1.2. Serious Incident

Per EU MDR Article 2(65); Any incident that directly or indirectly led, might have led or might lead to any of the following: (a) the death of a patient, user or other person, (b) the temporary or permanent serious deterioration of a patient’s, user’s or other person’s state of health, (c) a serious public health threat.

10.1.3. Adverse Event

“Adverse event means any untoward medical occurrence, unintended disease or injury or any untoward clinical signs, including an abnormal laboratory finding, in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational device.” (EU MDR Article 2(57))

10.1.4. Serious Adverse Event

Serious adverse event refer to “any adverse event that led to any of the following:

- a) death,
- b) serious deterioration in the health of the subject, that resulted in any of the following:
 - i. life-threatening illness or injury,
 - ii. permanent impairment of a body structure or a body function,
 - iii. hospitalisation or prolongation of patient hospitalisation,
 - iv. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
 - v. chronic disease,
- c) foetal distress, foetal death or a congenital physical or mental impairment or birth defect”
(EU MDR Article 2(58))

We will not consider hospitalisation for elective or planned surgery or that do not require overnight hospitalisation (i.e. A&E visit) to be a SAE.

10.2. Recording and Reporting

10.2.1. Side effects, Incidents and Serious Incidents

The Principal Investigator or an authorised designee will ensure all incidents and serious incidents related to N-Tidal devices are reported (as per usual vigilance reporting) in addition to completing the AE/SAE in the CRF as appropriate.

Reporting of Serious Incidents will occur in line with vigilance reporting requirements in EU MDR (Article 87, 89) and UK MDR (per MEDDEV 2.12/1 rev 8). Side-effects and non-serious incidents will also be reported by the Principal Investigator or an authorised designee.

It is the responsibility of TidalSense to perform Serious Incident reporting to the competent authority (MHRA); but it is the responsibility of the study sponsor to inform TidalSense of any side effects, incidents or serious incidents. All Incidents and side-effects that are related to N-Tidal devices (both hardware and software) or that may *possibly* be related to N-Tidal devices shall be reported to TidalSense via the TidalSense HelpDesk. The mechanism for reporting is via the ‘Contact Support’ tab in the left-side menu of the N-Tidal Diagnose dashboard. All side-effects and incidents (serious or otherwise) shall be reported as quickly as possible.

Any serious incidents which are defined under EU MDR Article 2(65) as: “any incident that directly or indirectly led, might have led or might lead to any of the following: a) the death of a patient, user or other person, b) the temporary or permanent serious deterioration of a patient's, user's or other person's state of health, c) a serious public health threat” must be reported to TidalSense via the HelpDesk immediately and in any case within 1 calendar day of the Sponsor becoming aware of the serious incident in order for TidalSense to be able to perform its obligations for vigilance reporting under EU MDR.

10.2.2. Reporting Procedures for Adverse Events

Any AE during the study visit will be reported on the AE form within the study database by the recruiting site based on their clinical judgment. If the AE meets the criteria of an Incident, or Serious Incident, the vigilance process in 10.2.1 must be followed in parallel.

10.2.3. Reporting Procedures for Serious Adverse Events

In cases where an AE is determined to be an SAE based on the definition given in 10.1.4 above with an established causal relationship to study procedures during the study visit, it will be reported by the recruiting site on the SAE form within the study database or directly to the trial team.

An SAE occurring to a participant should be reported to the REC that gave a favourable opinion of the study where, in the opinion of the Chief Investigator, the event was 'related' (resulted from administration of any of the research procedures) and 'unexpected' in relation to those procedures (i.e. SAEs which are related to spirometry will not be reported to the REC, as this is not a research procedure and these are also not unexpected). Reports of related and unexpected SAEs should be submitted within 15 working days of the Chief Investigator becoming aware of the event, using the HRA report of serious adverse event form (see HRA website).

If the SAE meets the criteria of a side effect, Incident, or Serious Incident, the vigilance process in 10.2.1 must be followed in parallel.

11. EMBEDDED QUALITATIVE SUB-STUDY

11.1. Aim

To explore the experiences of HCPs involved in the use of N-Tidal Diagnose, their perceptions of the usability of the test and the feasibility of introducing it into primary care settings; and to explore the experiences of patients in using N-Tidal Diagnose in relation to their diagnostic pathway.

11.2. Objectives

To gather information about how the HCPs view the test, how they might implement it as part of consultation for patients with potential COPD, how this impacts on their practice, as well as barriers and facilitators to its use; and to understand from patients their experiences of N-Tidal Diagnose compared to spirometry and its potential place in the diagnostic pathway.

11.3. Study Design

A qualitative methodology is highly appropriate for capturing and exploring people's experiences and perceptions of phenomena – in this case a new rapid test for consultations with patients attending primary care for potential COPD – from the perspectives of the HCPs who will be administering the test and the patients experiencing it. We will conduct semi-structured interviews with the HCPs and patients who have taken part. This method of data collection is well suited to capturing experiences and perceptions and has considerable power to explain actions, decisions and processes. Topic guides for HCP and patient interviews will be developed from the existing literature and previous experiences of the research team in conducting such research into diagnostic testing.

Inclusion criteria for the sub study are:

- Participant completed the main study (patient or HCP)
- Participant has given consent to be contacted regarding the sub-study

There are no exclusion criteria for the sub study.

11.3.1. Staff

Gaining qualitative input on clinician experiences of using N-Tidal Diagnosis is a key part of the study and there will therefore be an expectation in recruiting sites that one or more of the clinicians recruiting for the study will take part in the nested qualitative component. During the site set-up phase, the CORMORANT research team will also outline the embedded qualitative study as part of required tasks for participating as a recruitment site. HCPs who have been involved in administering and using the new test will be asked to take part in an interview. The purpose of the interview study will be explained and further details will be provided as requested. The PIS and the Informed Consent Form (ICF) will be sent to the HCPs. The HCPs will also be informed of the options for timing, location, and format of the interview. It is anticipated that all the interviews will be conducted via telephone or through an online platform such as Microsoft Teams. The HCPs will have the opportunity to ask any questions, to receive further information, and also to decline to participate. HCPs will be informed that they will be able to speak freely at the interview without any negative implications or repercussions on employment. Any HCP who requests not to participate further in the study will be reassured that this will in no way impact upon their current or future working. If the HCP is happy to proceed, an interview will be arranged. Before commencing the interview, the CORMORANT research team will ensure that participating HCPs have read and understood the PIS, have had an opportunity to have all questions and concerns addressed, and that they are willing to give their consent for the interview to proceed. The interviewer will capture the participant's informed consent remotely during the audio-recorded interview. This will be recorded in the relevant sub-study Remote Informed Consent Form. A copy of this will be sent to the participant.

11.3.2. Patients

Patients who have given their consent to be contacted about the qualitative sub-study will be contacted with further details about the interview study, including the PIS and ICF. Patients will have the opportunity to ask any questions, to receive further information, and also to decline any further contact regarding the qualitative sub-study. They will be informed that they will be able to speak freely at the interview without any negative implications or repercussions on their care. If they are interested in taking part, they should respond to the research team. The interview will take place at a time and format to suit them (most likely via video call).

At the start of the interview, the CORMORANT research team will ensure that patients have read and understood the PIS, have had an opportunity to have all questions and concerns addressed, and that they are willing to give their consent for the interview to proceed. A Remote Informed Consent form (ICF) (additional to the main study) will be captured remotely during the audio-recorded interview and a copy will be sent to the participant.

11.4. Sampling

We will aim to interview a range of practice staff/trained operators and patient participants involved in the use of the new test across a range of the GP practices and other sites. We would anticipate conducting up to 40 interviews (20 HCPs, 20 patients) incorporating views from a varied sample of HCPs, with different involvement in the process, around the potential use and communication of results. We will also purposively target patient participants who have given particularly high or low acceptance scores in relation to the device use at their appointment. Recruitment for the qualitative study will continue until we are able to build up a sufficiently detailed picture of, and explanatory power for the findings around

the test. The decision to stop interviewing will be discussed and agreed among members of the research team.

11.5. Analysis

We will use an adapted Framework approach to thematic analysis of qualitative data. This will allow us to transfer data around the characteristics of the test, and how it fits into the clinical setting, into matrices. Other thematic material will also be coded and categorised. This ongoing process will be discussed with the members of the research team, and further developed and refined as interviewing and analysis proceeds, to allow flexibility and incorporation of new information as the clinical study progresses.

12. STATISTICS AND ANALYSIS

12.1. Statistical Analysis Plan (SAP)

The statistical aspects of the study are summarised here with details fully described in a statistical analysis plan that will be finalised before any analysis takes place. Please see Section 11 Embedded Qualitative Sub-study for details on the analysis of qualitative data.

12.2. Description of the Statistical Methods

12.2.1. Index test definitions

These have been described in Section 8.8 and the methodology used to generate them in Section 8.7.1.

The index test, N-Tidal Diagnose, provides an output in the form of a 5-level indication of diagnostic certainty for COPD (highly likely / likely / indeterminate / unlikely / highly unlikely). The following abbreviations for these levels will be used:

- Highly likely: ++
- Likely: +
- Indeterminate: ?
- Unlikely: -
- Highly unlikely: - -

The following N-Tidal Diagnose outcome measures will be used:

- **N-Tidal binary diagnosis of COPD (++) or not (- -) (outcome measure i)**
- **N-Tidal binary diagnosis of COPD (++ / +) or not (- - / -) (outcome measure ii)**
- **N-Tidal individual prediction categories (++ / + / ? / - / - -) (outcome measure iii)**

Usual care clinical diagnosis of COPD around/shortly after time of test:

- **Usual care binary diagnosis of COPD (+) or not (-) (outcome measure v) (also used as reference standard in sensitivity analysis only)**

12.2.2. Reference standard definitions

These have been described in section 8.8 and the methodology used to generate them in section 8.7.1. A summary has been reproduced for reference:

Expert independent clinical consensus assessment, blinded to N-Tidal Diagnose results:

- **Consensus spirometry interpretation** for quality assessment and binary presence/absence of airway obstruction (**outcome measure iv**)
- **Consensus binary diagnosis of COPD (+) or not (-) (outcome measure vi)**. This reference standard for the primary analysis will be a binary independent consensus clinical diagnosis of COPD using NICE/GOLD guidelines based on clinical history (symptoms), presence of risk factor(s), age and spirometry results, referred to hereafter as consensus binary diagnosis of COPD (see section 8.7.2).
- **Consensus prediction categories** (mirroring N-Tidal categories) – COPD highly likely (++), likely (+), indeterminate (?), unlikely (-) or highly unlikely (- -) (**outcome measure vii**)
Exploratory analysis will be carried out using this 5-level indication of diagnostic certainty as determined by independent clinical consensus.

12.3. Descriptive Statistics

We will report descriptive statistics for both the total sample and for individual centres.

12.4. Primary Analysis

The primary analysis will be the diagnostic accuracy (PPV and NPV) of N-Tidal Diagnose in the following scenario compared to **consensus binary diagnosis of COPD (outcome measure vi)**:

Where a positive test result is defined as ++ and negative test result is defined as - - **N-Tidal binary diagnosis of COPD (++) or not (- -) (outcome measure i)**

12.5. Secondary Analyses

12.5.1. Accuracy of grouped N-Tidal Diagnose prediction categories

The diagnostic accuracy (PPV and NPV) of N-Tidal Diagnose will be calculated in the following scenario compared to **consensus binary diagnosis of COPD (outcome measure vi)**:

Where a positive test result is defined as ++ or + and a negative test results is defined as - - or - **N-Tidal binary diagnosis of COPD (outcome measure ii)**

12.5.2. Usual care diagnosis versus N-Tidal Diagnose

Diagnostic accuracy (PPV and NPV) of **usual care binary diagnosis of COPD (outcome measure v)**, compared to **consensus binary diagnosis of COPD (outcome measure vi)**. These results will be compared to the results of the primary analysis by presentation with 95% confidence intervals.

12.5.3. Accuracy of N-Tidal Diagnose prediction cut-offs

Diagnostic accuracy of cut-offs defined by **N-Tidal individual prediction categories** (++) / + / ? / - / --)
(**outcome measure iii**)

compared to **consensus binary diagnosis of COPD (outcome measure vi)**. This will be presented as a 4x2 table, and Se/Sp + PPV/NPV pairs for each possible cut-off. ROC and precision-recall curves will be presented and the area under the curves calculated.

12.5.4. Assessing the quality of data capture

Quality of spirometry

The proportion of participants with spirometry meeting quality standards determined by independent consensus will be reported (**expert clinical consensus spirometry interpretation (outcome measure iv)**) – see section 8.8 for details of reporting used to determine quality of spirometry records.

Quality of N-Tidal Diagnose data capture

The proportion of participants with adequate N-Tidal Handset breath record capture, sufficient to generate a diagnostic output using N-Tidal Diagnose software will be reported.

12.5.5. Acceptability of spirometry and N-Tidal assessment

Visual analogue score

Visual analogue scores for the acceptability of spirometry and N-tidal measurement procedures will be compared using paired non-parametric statistics (Wilcoxon signed-rank test).

Number of AEs and SAEs

The number of AEs and SAEs associated with the two tests (spirometry and N-tidal) will be reported. The proportion of participants experiencing either an AE or an SAE with each test will be reported, and tested for significance.

12.6. Sensitivity Analysis

The following sensitivity analyses will be carried out for the primary analysis and secondary analyses using alternative index test definitions.

12.6.1. Including all spirometry results

The analyses will be repeated using all spirometry results, regardless of quality, or if post-bronchodilator. This will also be carried out for the secondary analysis using primary care diagnosis as the index test.

12.6.2. Using spirometry only as the outcome

The analyses will be repeated using spirometry only to determine the binary outcome (**outcome measure iv**). This will also be carried out for the secondary analysis using primary care diagnosis as the index test.

12.6.3. Using primary care diagnosis as the outcome

The analyses will be repeated using the **usual care binary diagnosis of COPD** (+) or not (-) (**outcome measure v**) to determine the binary outcome (instead of consensus clinical diagnosis). This will not be done in analyses involving primary care diagnosis as the index test.

12.7. Exploratory Analyses

12.7.1. Clinical confidence

A 5x5 table will be presented for the **consensus prediction categories (outcome measure vii) vs N-Tidal individual prediction categories (outcome measure iii)**. The results will be explored descriptively.

A 5x2 table will be presented for the **consensus prediction categories (outcome measure vii) and expert technical spirometry interpretation (outcome measure iv)**. The results will be explored descriptively.

12.7.2. Subgroup analysis

Sensitivity cut-offs defined by the 5 levels of the N-Tidal Diagnose results will be presented by the following subgroups (subgroup analysis 1):

- GOLD airflow obstruction grades 1, 2, 3 and 4
- GOLD group (A, B or E)

Sensitivity, specificity, PPV and NPV for cut-offs defined by the 5 levels of the N-Tidal Diagnose results will be presented by the following subgroups (subgroup analysis 2):

- Participant age group (under or over 60; age <40, 40-49, 50-59, 60-69, 70-79, ≥80)
- Participant sex (male or female, as assigned at birth)
- Ethnicity

Subgroup analysis will only be carried out where there is a minimum of 50 participants in a subgroup; and, for subgroup analysis 2, where at least 10 participants in the subgroup are in each reference diagnosis category (COPD or not). Where this is not the case, subgroups may be combined, or if this is not practical, the subgroup analysis will not be carried out.

12.7.3. N-Tidal algorithm development

After completion of primary and secondary outcomes, TidalSense will be provided with diagnostic labels for the participants using the **consensus binary diagnosis of COPD (outcome measure vi)** to form the labels. These will be used to develop further iterations of the N-Tidal Diagnose diagnostic algorithms. The diagnostic accuracy of these algorithms, (measured in the same way as for **outcome measures i, ii, and iii**) will then be assessed against the **consensus binary diagnosis of COPD (outcome measure vi)**. To conduct this analysis, the data will be split into training/testing and independent performance validation datasets.

Additional exploratory models may be developed and tested included but not limited to:

- Classification by GOLD status (1-4 and A, B or E) using N-Tidal breath record in isolation and/or with additional clinical parameters.
- Classification of COPD using pre and post-bronchodilator N-Tidal breath records (where these are available) in isolation and/or with additional clinical parameters.

12.7.4. Agreement of duplicate outcome definitions

Inter-observer agreement measures of the duplicate clinical (**outcome measure vi**) and spirometric (**outcome measure iv**) outcomes will be calculated. Inter-observer agreement between expert spirometric interpretations will also be investigated.

12.8. N-Tidal Diagnose software version use

As software that incorporates machine learning models, N-Tidal Diagnose has the capacity to be updated with improved models. The software version used in the study will remain fixed for the duration of the study.

However, if a new release of N-Tidal Diagnose software has been formally issued incorporating updated machine learning models prior to statistical analysis, the updated version will be used in place of the original outputs generated at the time of data collection, in order that diagnostic accuracy is based on the most recent version and findings are as up-to-date as they can be.

12.9. Sample Size Determination

Based on a maximum sensitivity for N-Tidal Diagnose of 90%, and estimated COPD prevalence of 55% in the cohort, 262 patients would be required to obtain a confidence interval with a half-width of 5% (i.e. a confidence interval from 85- 95% if the sensitivity is 90%). We will aim to recruit 500 participants in case of any missing data or failure to complete study procedures e.g. unable to complete spirometry, requiring recruitment of an estimated 24 CRN-linked practices.

12.10. Analysis Populations

Unless otherwise specified, analyses will be carried out only on data from participants with either a suitable quality post-bronchodilator spirometry result, or a pre-bronchodilator result adequate for diagnostic purposes under 2025 GOLD guidelines.

A sensitivity analysis (see section 12.6) will be carried out using spirometry from all participants.

12.11. Decision Points and Interim Analysis

We will assess the following after the recruitment of approximately 150 and 300 participants:

- Total number recruited
- Recruitment rate (number/time) actual vs. expected
- Number of participants with a good quality, post-bronchodilator spirometry measure
- Number of participants with an N-Tidal diagnose result of “highly likely” (++) or “highly unlikely” (--)
- Number of participants with both of the above
- Number of participants with an “indeterminate” N-Tidal diagnose result
- Prevalence of COPD

Based on these results, the proportion of participants who will be eligible for the primary analysis will be calculated, along with the likely accuracy of estimates of PPV, NPV, sensitivity (Se) and specificity (Sp) after full recruitment.

No calculation of diagnostic accuracy will be performed until after sample size adjustments have been confirmed (if required).

The results of the interim analyses will be disclosed to and discussed by the TMG, who will then determine whether additional recruitment is required.

12.12. Stopping Rules

No formal stopping rules will be applied to this study. Interim analysis will only be used to determine any need for additional recruitment in the event that insufficient data is available for the main analyses.

12.13. The Level of Statistical Significance

95% confidence intervals will be used to express statistical uncertainty. Where appropriate, a p-value threshold (alpha) of 0.05 will be applied to determine statistical significance.

12.14. Procedure for Accounting for Missing, Unused, and Spurious Data

Analysis will only be carried out where results are available for both spirometry (forced ratio) and N-Tidal Diagnose (complete case analysis). It is expected that the proportion of missing data will be low.

Missing data will be reported with reasons given, where available, and the missing data pattern will be examined to see whether missingness is related to a specific variable and can be corrected or accounted for.

12.15. Procedures for Reporting any Deviation(s) from the Original Statistical Plan

The SAP will be finalised prior to analysis of any results. Any deviations from this plan will be clearly justified and discussed in the final report, with reference to the fact that they are a deviation from the original plan. Where additional analyses are carried out, these will be clearly specified as post-hoc analyses in both an updated version of the SAP, and in the final report, and results from these analyses will be treated with appropriate caution.

12.16. Health Economics Analysis

Aim: To understand the economic implications of introducing N-Tidal Diagnose in primary care

Objective: Assess the resource use, costs and benefits related to introduction of N-Tidal Diagnose in existing diagnostic pathways and produce an economic model to determine optimal implementation strategies.

Methods: We will use information collected through previous and ongoing TidalSense studies, the embedded qualitative study, existing literature, and expert opinion to accurately map the common current

diagnostic pathways for COPD. These pathways are expected to include but would not be limited to: Individual GP practices delivering spirometry; Primary Care Networks delivering spirometry through a local spirometry hubs; Referrals to Community Diagnostic Centres; Referrals to secondary care. These current diagnostic pathways along with the diagnostic accuracy data from this study will enable the development of a health economic model to ascertain the potential economic impact of implementing the N-Tidal Diagnose diagnostic test in terms of costs and benefits.

13. DATA MANAGEMENT

13.1. Source Data

Source documents are defined as where data are first recorded, and from which participants' CRF data are obtained. However, CRFs may themselves be source data if this is where the data are first recorded.

In this study we will primarily obtain the participant information from the participant questionnaire(s), electronic medical record and results of spirometry and N-Tidal. Additional source data may be collected from, but not limited to, GP surgery records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, readouts from medical devices, laboratory and pharmacy records, diaries, and correspondence.

The CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant number/code, not by name.

Consent for the main study will be taken digitally within REDCap, the eConsent form will be downloaded and held securely by the central study team on an access-restricted University of Oxford server. These will be held during and after the end of the study according to the legally required retention period and made available for inspection where required.

Consent for optional sub-study will be captured remotely during the audio-recorded interview. The sub-study interview transcripts and sub-study ICFs will be held during and after the end of the study according to the legally required retention period and made available for inspection where required.

13.2. Access to Data

Direct access to the CRF will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit study-related monitoring, audits and inspections of the study to ensure compliance with regulations. Summary results data will be included on the study registration database within 12 months of the end of study. Requests for data (anonymised study participant level data excluding all data or analysis related to N-Tidal) will only be provided to external researchers who provide a methodologically sound proposal to the study team (and who will be required to sign a data sharing access agreement with the Sponsor) and/or in accordance with the NIHR's guidance. Participant consent for this is included in the ICF. Data Recording and Record Keeping

The study is being run as part of the portfolio of studies in the PC-CTU. The data management will be run in accordance with the PC-CTU SOPs, which are fully compliant with Good Clinical Practice (GCP). The data

management aspects of the study are summarised here with details fully described in the Data Management Plan.

A PC-CTU data manager will be assigned to the study, as delegated by the CI, and will be responsible for overseeing the receiving, entering, cleaning, querying, analysing and storing of all data that accrues from the study by designated persons.

All participants will be assigned a unique ID. A document that links the participant's personally identifiable data with the participant ID will be stored separately from all other research data.

The study data will be entered directly into the participants' CRFs in an electronic format by the participant or study team (using REDCap). The use of REDCap is compliant with Good Clinical Practice via differentiated user roles and privileges, password and user authentication security, SSL encryption, de-identification of Protected Health Information. Data will be hosted on network servers/drives which are maintained by University of Oxford Medical Sciences Division's and are backed up every 24 hours and firewalls and authentication are in place to block any inappropriate access.

While all study data will be directly entered into electronic Case Report Forms (eCRFs), paper versions will be provided only if access to the online CRF is not possible. In this case the original copy of the CRF will be returned to the study team and a copy will be held at the research site. All CRFs (electronic or paper) will be date stamped upon receipt. A full pre-entry review and electronic data validation for all data entered into the clinical database will be provided by study specific programmed checks. All paper data will be locked in secure cabinets and only the researchers will have access to the files. A separate database will be used to securely store all identifiable patient information required to contact patients and permit follow up. Access to this information will be strictly on a need-to-know basis and databases will be password protected on a secure server.

Qualitative interviews will be audio recorded using an encrypted digital audio recorder and/or using the recording and transcribing function of Microsoft Teams. Recordings will be held temporarily on these audio-recording devices for no more than 24 hours before being securely transferred to a restricted access folder on the University of Oxford IT Network where they will be stored separately from all other research data in a restricted access OneDrive folder. The audio recording will be either i) transcribed by a member of the research team, or ii) sent securely via OneDrive to professional transcribers, Bristol Transcription and Translation Services who have a contract with the university (and who has been subject to and found to comply with recommendations from a TPSA, including confidentiality agreements). The transcriber will be required to delete all audio files after returning the verbatim transcription to the research team.

On completion of the study and data cleaning, the study documentation will be transferred to a secure, GCP compliant archiving facility. This excludes any research documents with personal information, such as consent forms, which will be held securely at the University of Oxford for five years after the end of the study. Qualitative interview transcripts will be retained securely to support publications of findings from the study until they are no longer required. Prior to database lock, the Data Manager and the Study Statistician will undertake a dataset review. Digitised consent forms, and an electronic record of consent completed online will be stored for five years after the study is complete, and then securely destroyed. The linkage information will be permanently destroyed at the end of the study. Audio-recordings will be transcribed verbatim, and transcriptions thoroughly checked. Once transcribed, the audio-recordings will

be destroyed. The transcripts will be archived securely for 5 years after the end of study and then will be destroyed.

In addition, to facilitate retraining of the COPD Diagnostic algorithms and for the purposes of the exploratory analyses, clinical data (including participant baseline questionnaire data, symptoms, spirometry results, imaging results and final diagnosis where available) will be shared with TidalSense. This will be conducted under a contractual agreement between TidalSense and the University of Oxford.

Pseudonymised data (anonymous in context) shared with TidalSense will be retained indefinitely by TidalSense for the purpose of regulatory compliance (EU and UK Medical Device Regulation). No retained data will be identifiable.

14. QUALITY ASSURANCE PROCEDURES

The study will be monitored regularly in accordance with the current approved protocol, GCP, relevant regulations, standard operating procedures and the study-specific monitoring plan. Data will be evaluated for compliance with the protocol and accuracy in relation to the source documents. Following written standard operating procedures, the monitors will verify that the study is conducted, and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

The level of monitoring will be determined using a risk adaptive approach based on a formal risk assessment, planned monitoring activities (onsite and / or central monitoring) and the involvement of the Trial Management Committee (TMG).

14.1. Risk Assessment

In line with standard PC-CTU procedures, a study specific risk assessment will be carried out. The risk assessment will identify any study specific risks to participants' safety or well-being or that may impact on the integrity or reliability of the resulting data. The risk assessment will detail how all identified risk will be minimised and inform a study specific monitoring plan.

The Chief Investigator (CI) will ensure that the study is conducted at all times in line with the currently approved version of the protocol, PC-CTU SOPs and all applicable regulations. 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.

14.2. Study Monitoring

Regular monitoring will be performed according to the study specific Monitoring Plan, which will be produced before the study commences recruitment. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents as these are defined in the study specific Monitoring Plan. Following written standard operating procedures, the monitors will verify that the clinical study is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements. The study Risk Assessment and Monitoring Plan document will be referred to, to ensure that regular monitoring is carried out as planned and the document is kept up to date.

14.3. Study Committees

A Trial Management Group (TMG) will be appointed in line with standard CTU procedures. The responsibilities of this group is to monitor the day-to-day running of the study, including monitoring all aspects of the study and ensuring that the protocol is being adhered to and that recruitment is progressing in a satisfactory manner.

Due to the low-risk nature of this study there will be no Trial Steering Committee or Data Monitoring Committee. The TMG will oversee the running of this study and report directly to the ethics board, and sponsor. TidalSense are responsible for reporting to the funder.

More details about the roles and responsibility of TMG members is outlined in the CORMORANT TMG charter.

15. 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 trial master file (TMF). Where required, sites will be asked to provide details of corrective and preventative actions.

The investigator is not allowed to deviate from the protocol except in the case of an urgent safety measure to protect clinical study participants from any immediate hazard to their health and safety, in which case such deviations shall be documented and reported to PC-CTU as soon as possible.

A standard operating procedure (SOP) 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.

16. 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 study subjects; or
- (b) The scientific value of the research.

Investigators must notify the study team within 1 working day if a serious breach is suspected. In the event that a serious breach is suspected, the Sponsor must be contacted within 1 working day. In collaboration with the C.I., the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the approving REC committee and the relevant NHS host organisation within seven calendar days.

17. ETHICAL AND REGULATORY CONSIDERATIONS

17.1. Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki. N.B. The 2008 Declaration of Helsinki provides detail on what must be included in a protocol: funding, sponsorship, affiliations and potential conflicts of interest, incentives to participate and compensation for harm.

17.2. Guidelines for Good Clinical Practice

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

17.3. Approvals

Following Sponsor approval the protocol, informed consent form, participant information sheet and any other participant facing materials will be submitted to an appropriate Research Ethics Committee (REC), and HRA (where required) and host institutions 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.

The N-Tidal Handset, RESPA and Mouthpiece by TidalSense are CE-marked and known to be safe for use in our target population; in this research study the devices will be used within their intended use that they were CE-marked for.

17.4. Other Ethical Considerations

In the study we are collecting data on quality of primary care spirometry, as well as clinician-made diagnosis. It is well-known that quality of primary care spirometry provision in terms of both performing and reporting/interpretation is variable and it is likely that we will come across specific examples of this. Diagnosis of respiratory disease is made using a variety of clinical information including spirometry, and it is very unlikely that a higher standard of technical reporting of spirometry, potentially carried out well after the spirometry assessment, would make any tangible difference to patient outcomes.

In the highly unlikely event that we notice anything about a patient's care which we feel poses a serious risk to their health or safety, we would have a duty to report this to the appropriate manager(s) at their GP surgery and their health care professional's regulatory body. This would be discussed with the CI and contact made with the site to identify the participant. A theoretical example of this might be where a chest x-ray report were seen to identify a potential malignancy but it wasn't clear whether this had been followed up (free text boxes will be provided in the CRF to reduce the chances of such eventualities).

17.5. Reporting

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

17.6. Transparency in Research

Prior to the recruitment of the first participant, the study will have been registered on a publicly accessible database. Where the study has been registered on multiple public platforms, the study information across all platforms will be kept up to date during the study, and the CI or their delegate will upload results to all those public registries within 12 months of the end of the trial declaration.

17.7. Participant Confidentiality

The study will comply with the UK 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.

The following University of Oxford's documents will be adhered to:

Data Protection Checklist <https://researchsupport.admin.ox.ac.uk/policy/data/checklist>

Practical Considerations <https://researchsupport.admin.ox.ac.uk/policy/data/practical>

The N-Tidal Diagnose software will receive respired carbon dioxide data, a breath record, from the N-Tidal Handset. No identifiable data will be entered into the N-Tidal Diagnose software therefore TidalSense will not have any direct access to participant identities and participants' medical notes. Participant information will be managed securely by the clinical research team. Information gathered in this study may be used to develop future clinical and diagnostic pathways including medical tests, and anonymised data may be stored indefinitely for this purpose.

17.8. Expenses and Benefits

As participants are not required to attend any additional visits and there is no participant follow up, there are no expenses or benefits that will be paid to participants in the main diagnostic study. For the Qualitative Sub-study, a £40 voucher is available for the HCP participants (or this can be paid to their practice as part of research costs, as preferred), and a £10 voucher is available for the patient participants who take part in the qualitative interview.

18. FINANCE AND INSURANCE

18.1. Funding

This study is being funded by the National Institute for Health and Social Care Research (NIHR) i4i Challenge Award (NIHR206532).

18.2. Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment that is provided.

18.3. Contractual Arrangements

Appropriate contractual arrangements will be put in place with all third parties, in line with the requirements of the NIHR (the Department of Health and Social Care, DHSC) grant terms signed between DHSC and TidalSense.

19. PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. The intention is to publish this research in peer-reviewed scientific journals on completion of the study and analysis. Authors will acknowledge that the study was funded by NIHR i4i Challenge Award and is taking place under the umbrella of the NIHR HealthTech Research Centre in Community HealthCare, with standard NIHR disclaimers. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

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

Ownership and exploitation of IP are in line with the NIHR (the Department of Health and Social Care, DHSC) contractual grant terms between DHSC and TidalSense, which are passed through in contractual agreements between the University of Oxford and TidalSense.

21. ARCHIVING

Storage of study materials will be entirely electronic.

Following the end of the study and the completion of all analyses and all reporting the study will be archived. Electronic documents will be stored on the University of Oxford computers for five years. Participant contact details at sites will be deleted within three months of the end of the study.

Data collected by the device software, N-Tidal Diagnose, will be stored anonymously by TidalSense indefinitely to comply with legal obligations under EU Medical Device Regulations.

22. REFERENCES

1. Chronic Obstructive Pulmonary Disease: How common is it? National Institute for Health and Care Excellence (NICE) <https://cks.nice.org.uk/topics/chronic-obstructive-pulmonary-disease/background-information/prevalence/incidence/>
2. Chronic obstructive pulmonary disease (COPD), Fact Sheets. World Health Organization. [https://www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-\(copd\)](https://www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-(copd))
3. Welte T, Vogelmeier C, Papi A. COPD: early diagnosis and treatment to slow disease progression. International journal of clinical practice. 2015 Mar;69(3):336-49.
4. National Institute for Health and Care Excellence (NICE). Health and social care directorate. Quality standards and indicators. Briefing paper. Chronic obstructive pulmonary disease (COPD) update. 2015
5. Ho T, Cusack RP, Chaudhary N, Satia I, Kurmi OP. Under-and over-diagnosis of COPD: a global perspective. Breathe. 2019 Mar 1;15(1):24-35.

6. Schneider A, Gindner L, Tilemann L, Schermer T, Dinant GJ, Meyer FJ, Szecsenyi J. Diagnostic accuracy of spirometry in primary care. *BMC pulmonary medicine*. 2009 Dec;9(1):1-0.
7. Stolz D, Mkorombindo T, Schumann DM, Agusti A, Ash SY, Bafadhel M, Bai C, Chalmers JD, Criner GJ, Dharmage SC, Franssen FM. Towards the elimination of chronic obstructive pulmonary disease: a Lancet Commission. *The Lancet*. 2022 Sep 17;400(10356):921-72.
8. Bastin AJ, Starling L, Ahmed R, Dinham A, Hill N, Stern M, Restrick LJ. High prevalence of undiagnosed and severe chronic obstructive pulmonary disease at first hospital admission with acute exacerbation. *Chronic respiratory disease*. 2010 May;7(2):91-7.
9. Respiratory Disease. NHS. <https://www.england.nhs.uk/ourwork/clinical-policy/respiratory-disease/>
10. Bate SR, Jugg B, Rutter S, Graham S, Perrott R, Rendell R, Altrip J, Foord J, Carter J, Haines M, Walsh J. N-Tidal C: A Portable, Hand Held Device for Assessing Respiratory Performance and Injury. In A74. *Respiratory Health: altitude, environmental exposures, and rehabilitation*. 2018 May (pp. A2371-A2371). American Thoracic Society. Available from:
https://www.atsjournals.org/doi/abs/10.1164/ajrccmconference.2018.197.1_MeetingAbstracts.A237
11. Talker L, Neville D, Wiffen L, Selim AB, Haines M, Carter JC, Broomfield H, Lim RH, Lambert G, BRS study team, Weiss ST. Machine Diagnosis of Chronic Obstructive Pulmonary Disease using a Novel Fast-Response Capnometer. *medRxiv*. 2023 Feb 24:2023-02.
12. Csikesz NG, Gartman EJ. New developments in the assessment of COPD: early diagnosis is key. *International journal of chronic obstructive pulmonary disease*. 2014 Feb 27:277-86.
13. Celli BR. Chronic obstructive pulmonary disease: from unjustified nihilism to evidence-based optimism. *Proceedings of the American Thoracic Society*. 2006 Mar;3(1):58-65.
14. Kaminsky DA, Marcy TW, Bachand M, Irvin CG. Knowledge and use of office spirometry for the detection of chronic obstructive pulmonary disease by primary care physicians. *Respiratory care*. 2005 Dec 1;50(12):1639-48.
15. Derom E, Van Weel C, Liistro G, Buffels J, Schermer T, Lammers E, Wouters E, Decramer M. Primary care spirometry. *European Respiratory Journal*. 2008 Jan 1;31(1):197-203.
16. Respiratory Function Testing During Endemic COVID-19. Association for Respiratory Technology & Physiology. May 2020.
<https://www.artp.org.uk/news/artp-guidance-respiratory-function-testing-and-sleep-services-during-endemic-covid-19>
17. Sakuraya M, Douno E, Iwata W, Takaba A, Hadama K, Kawamura N, Maezawa T, Iwamoto K, Yoshino Y, Yoshida K. Accuracy evaluation of mainstream and sidestream end-tidal carbon dioxide monitoring during noninvasive ventilation: a randomized crossover study (MASCAT-NIV study). *Journal of Intensive Care*. 2022 Dec;10(1):1-9.
18. Neville DM, Rupani H, Kalra PR, Adeniji K, Quint M, De Vos R, Begum S, Mottershaw M, Fogg C, Jones TL, Lanning E. Exploring the waveform characteristics of tidal breathing carbon dioxide, measured using

the N-Tidal C device in different breathing conditions (The General Breathing Record Study): protocol for an observational, longitudinal study. JMIR Research Protocols. 2018 May 24;7(5):e9767.

19. Diagnosing the problem: Right test, Right time. Asthma + Lung UK. August 2023.

<https://www.asthmaandlung.org.uk/diagnosing-problem-right-test-right-time-report>

20. Singh D, Stockley R, Anzueto A, et al. GOLD Science Committee recommendations for the use of pre- and post-bronchodilator spirometry for the diagnosis of COPD. Eur Respir J. 2025;65(2):2401603

23. APPENDIX A: SCHEDULE OF STUDY PROCEDURES

Procedures			
	Day 0	Day 1	At later date
	Screening	Visit	
Informed Consent	X		
Screening	X		
Eligibility Assessment	X		
Baseline	X		
Demographics	X	X	
Medical History	X	X	
N-Tidal		X	
Spirometry		X	
Acceptability score		X	
AE & SAE Reporting		X	X
Qualitative interview			X (Optional)
Notes review			X

24. APPENDIX B: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	V2.0 23Jan2026	19 Feb 2026	Charlotte Latimer-Bell	Minor change to study personnel Clarification of SAE definition Addition of AEs to be collected during study visit
2	V3.0 27Mar2026	30 Mar 2026	Charlotte Latimer-Bell	Extending recruitment period

3	V4.0 17Jul 2026		Susannah Fleming	Adjusting source of spirometry interpretation for analysis Adjusting definition of primary population to include pre-bronchodilator results in accordance with 2025 GOLD guidelines Additional co-investigator
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List details of all protocol amendments here whenever a new version of the protocol is produced