CLINICAL INVESTIGATION PLAN

Predict & Prevent AECOPD Clinical Investigation Plan

A phase III, 2 arm, multi-centre, open label, parallel-group randomised designed clinical investigation of the use of a personalised early warning decision support system with novel saliva bio-profiling to predict and prevent acute exacerbations of Chronic Obstructive Pulmonary Disease - 'Predict & Prevent AECOPD'

This Clinical Investigation Plan has regard for the HRA guidance and is compliant with SPIRIT

Version Number:	4.0
Version Date:	< **05-May-2020** >

Clinical Investigation Plan development

Clinical Investigation Plan Amendments				
The following amendments and/or administrative changes have been made to this Clinical Investigation Plan since the implementation of the first approved version.				
Amendment number	**Date of amendment**	**Clinical Investigation Plan version number**	**Type of amendment**	**Summary of amendment**

Funding and Support in Kind	
Funder (s) (Names and contact details of all organisations providing funding and/or support in kind for this clinical investigation)	**Financial and non-financial support given:**
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Clinical Investigation Plan Sign Off

CI Signature Page

The undersigned confirm that the following Clinical Investigation Plan has been agreed and accepted and that the Chief Investigator agrees to conduct the clinical investigation in compliance with the approved Clinical Investigation Plan.

I agree to ensure that the information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this Clinical Investigation Plan will be explained.

This Clinical Investigation Plan has been approved by:

Clinical investigation Name:	**Predict & Prevent Acute Exacerbations of Chronic Obstructive Pulmonary Disease Clinical investigation**
Clinical Investigation Plan Version Number:	Version: 4.0
Clinical Investigation Plan Version Date:	05-May-2020
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Sponsor statement:

As formally delegated by the, University of Birmingham, the sponsors confirm approval of this Clinical Investigation Plan.

Compliance statement:

This Clinical Investigation Plan describes the **Predict & Prevent AECOPD** clinical investigation only. The Clinical Investigation Plan should not be used as a guide for the treatment of participants not taking part in the **Predict & Prevent AECOPD** clinical investigation.

The clinical investigation will be conducted in compliance with the approved Clinical Investigation Plan, UK Policy Framework for Health and Social Care Research 2017, the Data Protection Act 2018, and the principals of Good Clinical Practice as defined by the European Good Clinical Practice (GCP) Directive. Every care has been taken in the drafting of this Clinical Investigation Plan, but future amendments may be necessary, which will receive the required approvals prior to implementation.

PI Signature Page

The undersigned confirm that the following Clinical Investigation Plan has been agreed and accepted and that the Principal Investigator agrees to conduct the clinical investigation in compliance with the approved Clinical Investigation Plan.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

This Clinical Investigation Plan has been approved by:

Clinical investigation Name:	**Predict & Prevent Acute Exacerbations of Chronic Obstructive Pulmonary Disease Clinical investigation**
Clinical Investigation Plan Version Number:	Version: 4.0
Clinical Investigation Plan Version Date:	05-May-2020
PI Name:	
Name of Site:	
Signature and date:	_____ __ __ / __ __ / __ __ __ __

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ABBREVIATIONS

Abbreviation	Term
A&E	Accident and Emergency Department of a hospital
AECOPD	Acute Exacerbation of Chronic Obstructive Pulmonary Disease
AI	Artificial Intelligence
App	Application
BCTU	Birmingham Clinical Trials Unit
CAT™	COPD Assessment Test
CI	Chief Investigator
CISC	Clinical Investigator Steering Committee
CIMG	Clinical Investigation Management Group
COPD	Chronic Obstructive Pulmonary Disorder
CRF	Case Report Form
CRP	C-reactive Protein
DMC	Data Monitoring Committee
EU	European Union
FEV_1	Forced Expiratory Volume
FVC	Forced Vital Capacity
GP	General Practitioner
HRA	Health Research Authority
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ISF	Investigator Site File
NHS	National Health Service
OWASP	Open Web Application Security Project
PI	Principal Investigator
PIS	Participant Information Sheet
POC	Point of Care
POCT	Point Of Care Testing
PPI	Patient & Public Involvement

PR	Pulmonary Rehabilitation
QA	Quality Assurance
RCT	Randomised Controlled Clinical investigation
REC	Research Ethics Committee
REST API	Representational State Transfer Application Program Interface
RM	Rescue Medication
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SSL	Secure Sockets Layer
SSMP	Standard Self-Management Plan
SUSAR	Suspected Unexpected Serious Adverse Reaction
UoB	University of Birmingham
UK	United Kingdom

DEFINITIONS

Term	Abbreviation	Description
Clinically diagnosed Chronic Obstructive Pulmonary Disease	COPD	confirmed by post-bronchodilator spirometry of FEV1/FVC<0.7 post and <lower limit of normal age post bronchodilator use, in the stable state
"Frequent" exacerbations		2 or more, or at least one hospital admission, in the preceding 12 months

CLINICAL INVESTIGATION SUMMARY

Title: A phase III, 2 arm, multi-centre, open label, parallel-group randomised clinical investigation investigating the use of a personalised early warning decision support system (COPDPredict™) to predict and prevent acute exacerbations of Chronic Obstructive Pulmonary Disease - 'Predict & Prevent AECOPD'

Objectives: Our overall ambition is clinical validation and commercialisation of the COPDPredict™ to guide and support chronic obstructive pulmonary disease (COPD) patients in identifying exacerbations early, leading to a reduction in total acute exacerbations of COPD (AECOPD)-induced hospital admissions in the 12 months following each patients randomisation. Using a multi-skills team approach, we aim to complete the trial over 27 months.
We aim to assess:

1) The clinical-effectiveness of COPDPredict™ (with regard to hospitalisation rate over the course of a year)
2) The cost- effectiveness of COPDPredict™ (in terms of whether patients use more or less health resources to manage their COPD)

Clinical investigation Design: A phase III, 2 arm, multi-centre, open label, parallel-group, individually randomised clinical investigation

Participant Population and Sample Size: 384 adult COPD patients who have had ≥2 AECOPD or ≥1 hospital admission for AECOPD in the previous year.

Setting: recruiting from at least four National Health Service (NHS) hospitals in the West Midlands

Eligibility Criteria:

Included patients will have:

- Clinically diagnosed COPD, confirmed by post-bronchodilator spirometry and defined as FEV1/FVC<0.7 and <lower limit of normal for age post bronchodilator use
- ≥2 AECOPD in the previous 12 months according to the patient and/or ≥1 hospital admission for AECOPD
- Exacerbation free for at least 6 weeks
- An age of at least 18 years
- Willing and able to comply with the data collection process out to 12 months from randomisation
- Ability to consent
- Ability to use intervention as judged by the investigator at screening, upon demonstration of the system to the patient

Exclusion criteria will be:

- Life expectancy < 12 months
- Patients with active infection, unstable co-morbidities at enrolment or very severe comorbidities such as grade IV heart failure, renal failure on haemodialysis or active neoplasia or significant cognitive impairment;

Interventions

Control Arm: a standard self-management plan (SSMP) involving the use of rescue medication (RM) containing 5 days of antibiotic and steroid treatment

Experimental Arm: supported self-management using the COPDPredict™ App, involving personalised alerts to both patients and the clinical care team

Outcome Measures

Primary Outcome: The number of hospital admissions up to t 12 months post randomisation, where the primary reason for admission is AECOPD

Secondary Outcomes:

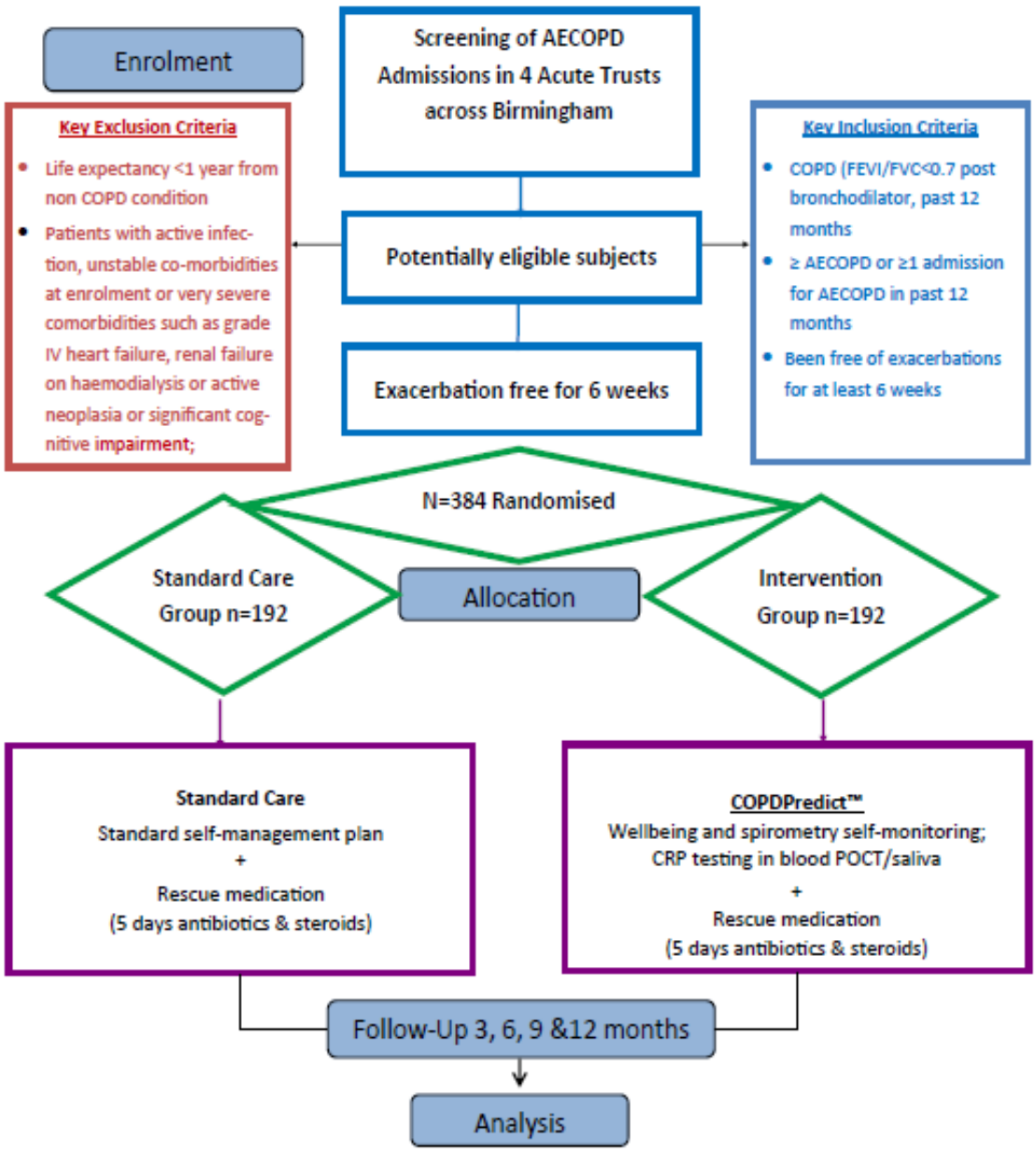
Over a 12 month period, following randomisation;

1) Total inpatient days
2) Number of patient defined exacerbations
3) Number of visits to Accident and Emergency (A&E)
4) Symptom control markers, specifically the amount of breathlessness and sputum (Anthonisen criteria)
5) End-user experience (technology acceptability usability/utility via questionnaires and interviews);
6) Health-related quality of life (COPD Assessment Test, CAT™ and EQ-5D-5L);
7) Lifestyle choices via App usage/questionnaires/interviews;
8) Blood and salivary C-Reactive Protein (CRP) levels

and,

9) FEV_1 at 12 months
10) social acceptability and practical responses to the intervention, including any implementation issues

Clinical Investigation Schema



Primary Outcome: The number of hospital admissions up to to 12 months post randomisation, where the primary reason for admission is AECOPD

Secondary Outcomes:

1) Total inpatient days
2) Number of patient-defined exacerbations,
3) Number of visits to Accident and Emergency (A&E)
4) Symptom control markers (Anthonisen criteria),
5) End-user experience (technology acceptability usability/utility via questionnaires and interviews)
6) Health-related quality of life (COPD Assessment Test, CAT™ and EQ-5D-5L)
7) Lifestyle choices via App usage/questionnaires/interviews
8) Blood and salivary CRP levels
9) FEV_1 at 12 months
10) Social acceptability and practical responses to the intervention, including any implementation issues

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1. BACKGROUND AND RATIONALE

1.1 Background

With 65 million cases globally, chronic obstructive pulmonary disease (COPD) is the 4th leading cause of death and imposes a heavy burden on patients' lives and healthcare resources worldwide (1). UK death rates are currently double the European Union (EU) average with over 30,000 people dying yearly and annual COPD-related NHS direct costs are over £800m (£1.3m/100,000 people). Patients can have acute exacerbations of their COPD (AECOPD), also called '*lung attacks*' by some clinicians, which cause distress, reduce quality of life, and lead to 140,000 emergency hospital admissions a year (2). Indeed, COPD exacerbations remain the 2nd commonest cause of emergency hospital admissions and 1 in 3 of these patients will be readmitted within 3 months(3, 4). Hospitalisation itself carries a poor prognosis with an increased mortality risk.

It is now widely accepted that each year around half of all patients with COPD have frequent AECOPD (≥2 per year (5)). For example in the UK 44-85% of patients with this AECOPD rate (≥2 per year) were hospitalised again within 12 months (6). Rapid readmissions are also common – the national COPD audit has shown that 43% of patients with COPD who were admitted are back in hospital within 90 days (7), and up to 71% by 12 months (8).

The average total annual admission cost per individual, excluding medications, is £3,396 (9), making COPD one of the costliest inpatient conditions (10). Furthermore, COPD prevents many working-age individuals from employment (11) with an estimated £3.8bn in lost revenue through reduced productivity from acute episodes and/or poor disease control (10) alongside a considerable burden in terms of disability-adjusted life years (12). An average UK district of 250,000 patients will have 14,200 General Practitioner (GP) consultations yearly for COPD (double the rate of consults for angina) (2). Socioeconomic impact is substantial, as summarised in a recent British Lung Foundation report, which estimated direct and indirect costs of COPD in the UK to be approximately £1.8bn and £61m respectively (10). These cost differentials make COPD extremely relevant to policymakers.

Enhancing care and outcomes for people with COPD is an understandable NHS priority:

1. Reducing premature mortality
2. Avoiding unnecessary hospitalisation
3. Improving quality of life

1.1.1. What is the evidence for patients self-managing AECOPD?

It is known that prompt exacerbation management optimises recovery and delays the time to the next acute episode (13), with NICE COPD guidelines highlighting a time window (prodrome) between an initial exacerbation's symptoms/signs and subsequent hospitalisation. Within this prodrome there is an opportunity to intervene (Predict & Prevent). Exacerbations impact significantly on COPD outcomes, causing significant lung function decline (14).
Current practice for COPD patients is that they are encouraged to recognise, via standard self-management plans (SSMPs), and treat, using rescue medication (RM), acute exacerbations of COPD

(AECOPD) but in many cases because of day-to-day variability in symptoms, the start of an exacerbation goes unrecognised and untreated. This inability/uncertainty to recognise and treat exacerbations in their early phase can lead to hospital admissions and long term decline.

Various treatments have potential to reduce COPD readmissions, or improve care, such as pulmonary rehabilitation (PR) (15). SSMPs help patients but have not really shown significant impact on A&E visits or hospital admissions as demonstrated by our systematic review of self-management strategies for COPD (16).

This study looks to address the problem by personalising and thus optimising effectiveness of AECOPD management. Intuitively early recognition and treatment of AECOPD would reduce exacerbation severity and duration, and improve prognosis; evidence for this is limited but supportive (17).

1.1.2. What would this study add?

COPDPredict™ consists of CE marked and MHRA registered software solution (1) App (iOS/Android) and (2) Clinician facing dashboard. The proprietary Early Warning Decision Support System (Predict&Prevent AECOPD) uses longitudinal home monitoring of relevant subjective and objective data (symptoms, spirometry, biomarkers) in real-time via the App which is connected to CE-marked Bluetooth-enabled sensor peripherals. These data are used to construct COPD-relevant individual profiles such that artificial intelligence (AI)-driven algorithms can then identify changes in health status to provide timely individualised alerts to patients and clinicians and sign-posting to action plans for patients.

COPDPredict™ also provides information around COPD self-management, pulmonary rehabilitation, inhaler technique and utilises gamification to help with adherence. Patients have full access to their results and can also directly message their clinical team. COPDPredict™ may signpost a patient to a self-management action plan for exacerbation management but clinical team supervision and oversight will remain throughout

Overall the system has been designed by/for patients living with COPD to help them assess/track their personal health, become educated on their condition and "sign-post" to action plans as and when required teaching them how to spot exacerbations early**.** Thus far, heterogeneity amongst COPD patients has hampered personalised AECOPD recognition.

The Clinician facing dashboard allows for "real-time" case management and the ability to remotely monitor the patients and facilitate interaction. Clinicians can choose to escalate treatments based on the results being transmitted by the patients.

A crucial dimension to this advanced system is that both blood and salivary biomarker measurements which inform an algorithm are incorporated to enhance accuracy. Saliva has measurable reproducible levels of target biomarkers e.g. C-reactive Protein (CRP) which complement wellbeing self-assessments and predict exacerbation onset (18-20). The measurement of CRP is to investigate the concept of inflammation as a driver and feature of COPD exacerbations (reported to be higher in frequent exacerbators) and poor prognosis in COPD (9, 21). Previous work has demonstrated significant correlation and agreement between saliva and serum CRP (22). Blood-based point of care (POC) analysers are already available for use with COPDPredict™ and these POC

analysers have been validated against hospital CRP machines. In addition, salivary point of care testing (POCT) development is fast advancing and a hand-held salivary CRP analyser is expected on the market in 2021 (*in-house privileged information*). An initial study in 90 patients showed that COPDPredict™ was accepted by patients and the number of admissions was markedly lower after using the system to aid their self-management (Appendix 1).

This clinical investigation asks if COPDPredict™ can be used by patients with COPD at home and the clinicians managing the patients to improve self-management and help them identify exacerbations, intervene promptly and avoid hospitalisation. The clinical investigation will randomise 384 patients, from 4 hospitals in the West Midlands, who have frequent AECOPD to use either the SSMP and RM (if needed according to the SSMP) or the COPDPredict App and RM (if needed according to the App self-management plan or clinician input).

1.2 Clinical Investigation Rationale

The clinical driver for this clinical investigation is a need to improve self-care in COPD, a common complex disease with debilitating breathlessness; mortality and reduced quality of life accelerated by frequent exacerbations.

Changes in dyspnoea, coughing and/or sputum production often precede exacerbations but as symptoms vary within-same day and across days, patients cannot easily judge the significance of such changes with the result that exacerbations remain unreported and untreated (23). Furthermore due to heterogeneity amongst COPD patients, predictions must be personalised to be clinically meaningful. Remote monitoring and POC systems have evolved rapidly but none have yet convincingly demonstrated the capability to predict exacerbations and stratify episode severity.

To address the above problem, COPDPredict™ has been created and developed. This System automatically processes information that is regularly sent by patients using COPDPredict™), which connects to peripheral monitors via Bluetooth and uses intelligent software to determine a patient's health through a combination of wellbeing scores, lung function and measurements of key biomarkers in blood and saliva. The clinical team has access to a secure web portal (dashboard) which allows them to monitor patient data, case manage and make informed decisions on clinical practice.

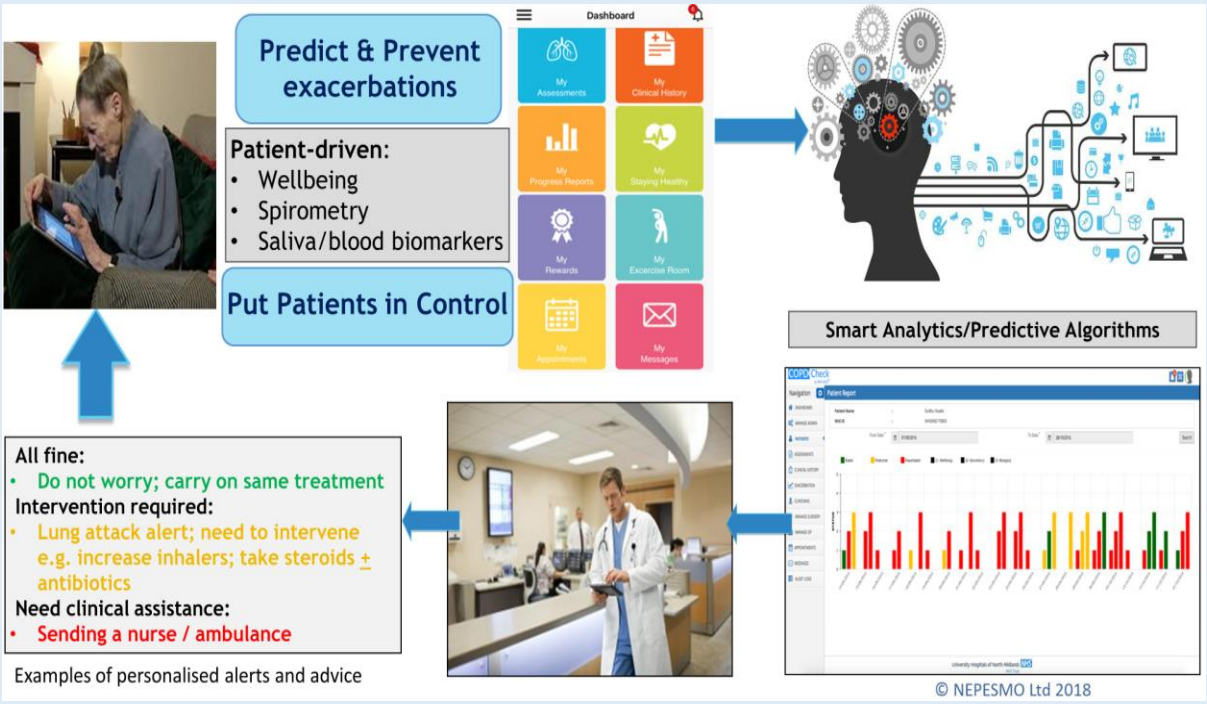
COPDPredict™ aims to prevent deterioration of a situation by assisting patients on the most appropriate course of action using built-in composite predictive models (8) that automatically process and integrate data received from each patient. Patients then transmit the data from their homes via bespoke COPDPredict™. In this way subjective and objective information combines to generate individualised profiles, with smart algorithms identifying changes in health status including the possibility of an imminent AECOPD.

Depending on the degree of change from a given patient's 'usual health', timely alerts are sent to the individual, with sign-posting to an action plan. Alerts are also sent to clinicians who support and advise patients via App's secure messaging facility. If patients fail to improve with self-treat plan or if

an episode triggers an 'at high risk alert' from the start, clinicians are prompted to be involved and intervene with escalated treatment: Figures 1, overleaf.

COPDPredict™ is anticipated to most benefit patients with frequent AECOPD who need predictive assistive tools at home to identify impending exacerbations and intervene accordingly, avoiding hospitalisation. As healthcare systems become more managed and leaner, interventions leading to simplification and decreased costs are welcomed so there is the potential for intuitive remote monitoring to remove many process steps, thereby reducing costs. Predict&Prevent AECOPD aims to support care shift for COPD frequent exacerbators from hospital to home, without decreasing quality of care, thereby enabling clinicians to work effectively with patients and improve personalised self-care plans (key National COPD Audit recommendation (24). Current, high 30-day readmission rates for AECOPD supports COPDPredict™ availability at hospital discharge to both improve the patient's quality of life and reduce financial penalties for readmissions.

Figure 1: Information flow via the COPDPredict™ system



This clinical investigation will test the clinical and cost benefits of COPDPredict™ on 384 patients who have frequent AECOPD. It will also examine the quality of the alerts and the efficiency of the clinical measurements through interviewing patients and healthcare professionals. Finally we will conduct an economic evaluation allied to the clinical investigation to inform whether it could be cost-effective in the NHS Overall, the aim is see if COPDPredict™ provides patients better personalised care and outcomes at lower costs than current practice.

1.2.1 Justification for participant population

This clinical investigation will test the clinical and cost benefits of COPDPredict™ compared to standard care on 384 patients (poct per arm) who are defined as frequent exacerbators (≥2 exacerbations per year and/or ≥1 hospitalisation). Although less than 20% of COPD patients are the frequent exacerbator phenotype, their treatment accounts for up to 75% of COPD-related costs in the NHS, mainly due to hospitalisations and increased medications. The clinical investigation is designed to show whether COPDPredict™ reduces the number of hospital admissions from AECOPD. We plan to enrol patients who have already been hospitalised at least once in the past 12 monthss for their COPD and/or have had at least 2 exacerbations, as this is the population at highest risk of readmission for COPD (4), hence within this cohort/population it will allow for an adequately powered study.

1.2.2 Justification for design

Randomised controlled clinical investigations are considered the "gold standard" for evidence-based medicine (25, 26). Because of the nature of the procedure it is not possible to conceal either the patients or the research team receiving the alerts from the allocation (see section 6.4 for details).

An important feature of this trial is that for the COPDPredict™ to be effective a personal baseline state must first be reached. For the purposes of this clinical investigation, a "personal baseline state" is defined as being free of exacerbations. Only once a personal baseline state is reached will a participant be randomised. Participants randomised to COPDPredict™ will then record data for 2 weeks as a measure of their personal baseline state.

1.2.3 Choice of intervention

There is currently no single definitive SSMP nationwide but some form of educational support for the patient is routinely given regarding when and how to initiate the use of the RM. As a pragmatic clinical investigation, the control arm will broadly follow the standard support offered at the recruiting centre, but we have standardised a trial-specific SSMP (in conjunction with patient and public involvement (PPI) input)in order to ensure that variance in efficacy of SSMP between centres does not impact on results. The intervention arm is using a COPDPredict™ to test its effectiveness in a real world situation and, as such, there is no viable alternative in this context.

2. AIMS AND OBJECTIVES

This clinical investigation asks if COPDPredict™, a personalised early warning decision support system with built-in composite predictive algorithms, used by patients with COPD and the clinicians managing the case- load, improves self-management and helps identification of exacerbations early, prompt and, thereby, avoid hospitalisation.

2.1. Pilot Stage Objectives

There is no internal pilot stage for this clinical investigation.

2.2. Main Clinical Investigation Objectives

2.2.1. Primary Clinical Objective

To test the hypothesis that COPDPredict™ can produce a reduction in AECOPD hospitalisations (where the primary reason for admission is AECOPD) in the 12 months post randomisation, when compared to SSMP.

2.2.2. Secondary Clinical Objectives

To compare, in the 12 months post-randomisation, in the two trial arms;

- symptom control markers, specifically the amount of breathlessness and sputum (Anthonisen criteria)
- Total inpatient days
- Number of visits to A&E
- Number of patient defined exacerbations *(from patient testimony or data entered on the App)*
- Health-related quality of life

To compare at 12 months post-randomisation, in the two trial arms:

- FEV_1 at 12 months

2.2.3. Secondary Cost Effective Objectives

The economic evaluation will assess the cost-effectiveness of the intervention versus standard care in patients with COPD. Hospital admission is the primary outcome of the clinical investigation, and therefore it is important to evaluate the cost-effectiveness of the intervention based on this outcome. The National Institute for Health and Care Excellence (NICE) recommend the use of quality adjusted life year (QALY) in economic evaluations to allow comparisons across different diseases and interventions. Therefore, the evaluation will take the form of

i) An incremental cost-effectiveness analysis to estimate cost per hospital admission avoided
ii) An incremental cost-utility analysis to estimate cost per quality adjusted life year (QALY)

Both analyses will be from an NHS perspective over 12 months follow-up using patient level data on costs and outcomes from the clinical investigation and will require the following data capture;

1) Length of in-hospital stay (days)
2) Number of patient defined exacerbations
3) Number of visits to Accident and Emergency (A&E)
4) Health-related quality of life (COPD Assessment Test, CAT™ and EQ-5D-5L);

2.2.4. Mechanistic Aims and Objectives

Blood and saliva samples will be taken to measure CRP levels, and saliva samples will be stored for future biomarker investigations (as per section 8.2.2.3). This trial will provide a significant number of matched saliva-blood samples for comparison to further validate these preliminary results. Alongside this, salivary CRP measurements will be performed in an accredited pathology laboratory (University Hospital of North Midlands) for comparison with blood CRP levels, but these data will not be part of the clinical investigation.

2.2.5. Qualitative Sub-study Aims and Objectives

Formal nested qualitative interviews will be conducted with a range of clinical and non-clinical staff (n≤30). The following data will be captured:

1. End-user experience (technology acceptability usability/utility via questionnaires and interviews)
2. Social acceptability and practical responses to the intervention, including any implementation issues

3. CLINICAL INVESTIGATION DESIGN AND SETTING

3.1. Clinical Investigation Design

A phase III, 2 arm parallel-group, multi-centre, open label, individually randomised clinical investigation of 384 patients in a 1:1 ratio, to receive either a standard self-management plan and rescue medication pack (standard arm) or the COPDPredict™ self-management system and rescue medication pack (intervention arm).

3.2. Clinical investigation Setting

Patients will be recruited from one of several participating hospitals in the West Midlands, UK, and monitored by a care team on discharge from the hospital back to the community. Data will be collected by the local research team and CRN nurses by a mixture of clinics, telephone follow-ups and home visits.

3.3. Identification of participants

Patients will be identified directly from adults attending participating hospitals in the West Midlands, UK, by members of their standard clinical care team. All patients will need to free from AECOPD for a minimum of 6 weeks prior to randomisation. They can be identified in three scenarios;

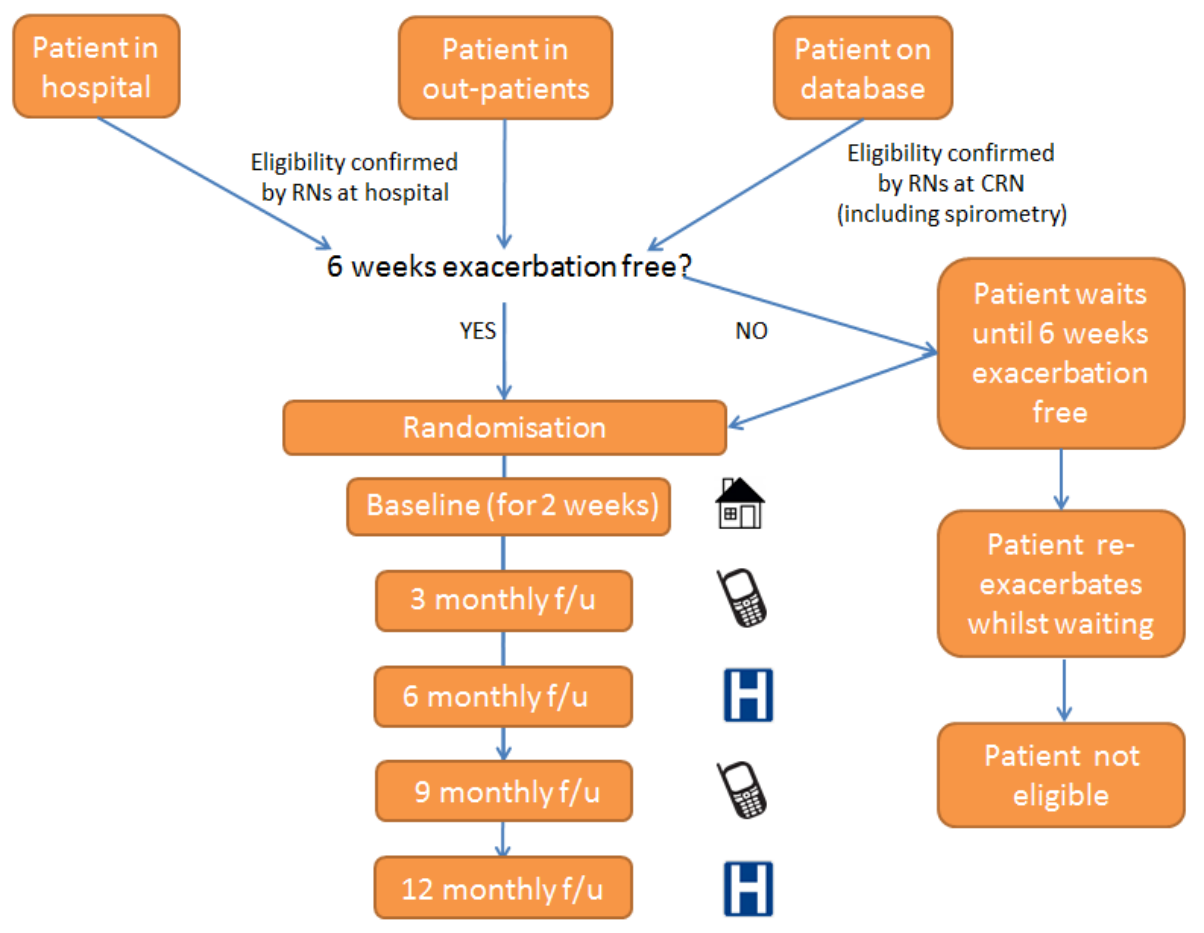
1) Patients who are currently hospitalised for an AECOPD
2) Patients with a known history of COPD who are attending routine outpatient appointments. Those who have been exacerbation free for at least 6 weeks can be randomised immediately following consent, those who have had an exacerbation in the last 6 weeks will have to wait until they have been exacerbation free for at least 6 weeks before randomisation
3) Via pre-established research databases in which patients have given prior consent to be being contacted by researchers for research purposes. These patients will be asked to attend an initial clinic appointment with a research nurse to confirm eligibility. Those who, at the time of appointment, have been exacerbation free for at least 6 weeks can be randomised immediately following consent and confirmation of eligibility; those who have had an exacerbation in the last 6 weeks will have to wait until they have been exacerbation free for at least 6 weeks before randomisation

Patients who appear to fulfil the inclusion criteria will be referred to the research team for confirmation by staff who have been identified on the Site Delegation Log as having this responsibility.

Clinical eligibility will be formally confirmed by the PI or delegate at the site. Once clinical eligibility is confirmed the patient will be approached by a suitable delegated member of the site team who will inform the patient of the trial

The identification of patients in relation to the Predict&Prevent AECOPD Clinical investigation is best illustrated via the following patient pathway.

Figure 2. The patient pathway for entry into Predict&Prevent AECOPD and the journey whilst on study.



3.4. Sub-studies

3.4.1. Qualitative sub-study

Approximately 30 patients will be selected for interview after enrolment, with follow-up interviews a few months later, splitting the sample equally between intervention and standard groups and ensuring diversity in the sample (age, gender, ethnicity etc. as far as possible). The topic guide will be developed drawing on existing literature and theories on attitudes to and practices around self-management of COPD, and in conjunction with our PPI group. Interviews will be audio recorded and transcribed verbatim, prior to qualitative analysis using the Framework method, as described in our previous work (27). This is a systematic approach well suited to interdisciplinary health research and to working with clinical and lay collaborator (27). Nested qualitative interviews will also be conducted with a range of clinical and non-clinical staff (n≤30).

3.5. Assessment of Risk

All clinical investigations can be considered to involve an element of risk and, in accordance with the guidance provided by the MHRA, this investigation is assessed as Class A (low risk), given that the device classification will be no higher than IIa. Instructions for use are not required for Class I and IIa devices if these devices can be used safely without any such instructions (Annex I Section 13.1. of Directive 93/42/EEC). This document forms the clinical investigation plan, not instructions on how to use the device itself.

4. ELIGIBILITY

4.1. Inclusion Criteria

- Clinically diagnosed COPD, confirmed by post-bronchodilator spirometry and defined as FEV1/FVC<0.7 and <lower limit of normal age post bronchodilator use, in the stable state
- ≥2 AECOPD in the previous 12 months according to the patient and/or ≥1 hospital admission for AECOPD
- Exacerbation free for at least 6 weeks
- An age of at least 18 years
- Willing and able to comply with the data collection process out to 12 months from randomisation
- Ability to consent
- Ability to use intervention as judged by the investigator at screening, upon demonstration of the system to the patient

4.2. Exclusion Criteria

- Life expectancy < 12 months
- Co-enrolment into any clinical trials of investigative medicinal product (CTIMPs)
- Patients with active infection, unstable co-morbidities at enrolment or very severe comorbidities such as grade IV heart failure, renal failure on haemodialysis or active neoplasia or significant cognitive impairment

4.3. Co-enrolment

Co-enrolment in non-interventional studies is allowed, such as cohort studies, but co-enrolment in interventional studies would have to be agreed in advance, on a case-by-case basis, with the Sponsor.

5. CONSENT

It will be the responsibility of the Investigator or delegate, who may be medically or non-medically qualified, provided they have appropriate skills to assess the patient (as decided by the local PI), to obtain written informed consent for each participant prior to performing any clinical investigation related procedure.

A Participant Information Sheet (PIS) which explains the different ways in which the patient may enter the clinical investigation will be provided to facilitate this process. Investigators or delegate(s) will

ensure that they adequately explain the aim, clinical investigation intervention, anticipated benefits and potential hazards of taking part in the clinical investigation to the participant. They will also stress that participation is voluntary and that the participant is free to refuse to take part and may withdraw from the clinical investigation at any time. The participant will be given sufficient time to read the PIS and to discuss their participation with others outside of the site research team. If the participant expresses an interest in participating in the clinical investigation they will be asked to sign and date the latest version of the Informed Consent Form (ICF). The participant must give explicit consent for the regulatory authorities, members of the research team and or representatives of the sponsor to be given direct access to the participant's medical records.

The Investigator or delegate(s) will then sign and date the ICF. A copy of the ICF will be given to the participant, a copy will be filed in the medical notes, and the original placed in the Investigator Site File (ISF). Once the participant is entered into the clinical investigation, the participant's clinical investigation number will be entered on the ICF maintained in the ISF. Since this data is entered only after randomisation, the person adding this information should initial and date next to the ID number. In addition, if the participant has given explicit consent, a copy of the signed ICF will be sent to the Birmingham Clinical Trials Unit (BCTU) clinical investigations team for review.

Details of the informed consent discussions will be recorded in the participant's medical notes. This will include date of discussion, the name of the clinical investigation, summary of discussion, version number of the PIS given to participant and version number of ICF signed and date consent received. Where consent is obtained on the same day that the clinical investigation related assessments are due to start, a note should be made in the medical notes as to what time the consent was obtained and what time the procedures started.

At each visit the participant's willingness to continue in the clinical investigation will be ascertained and documented in the medical notes. Throughout the clinical investigation the participant will have the opportunity to ask questions about the clinical investigation. Any new information that may be relevant to the participant's continued participation will be provided. Where new information becomes available which may affect the participants' decision to continue, participants will be given time to consider and if happy to continue will be re-consented. Re-consent will be documented in the medical notes. The participant's right to withdraw from the clinical investigation will remain.

Electronic copies of the PIS and ICF will be available from the Clinical investigations Office and will be printed or photocopied onto the headed paper of the local institution. Details of all participants approached about the clinical investigation will be recorded on a **Predict&Prevent AECOPD Participant Screening/Enrolment Log** and with the participant's prior consent, their General Practitioner (GP) will also be informed that they are taking part in the clinical investigation.

6. ENROLMENT AND RANDOMISATION

6.1. Enrolment & Screening

Patient identification can occur via 3 routes (see Section 3.3) and the subsequent pathways differ as follows;

1) Patients identified at the time of admission to hospital for an AECOPD

Such patients, following consent, but before randomisation, need to be exacerbation free for a minimum of 6 weeks in order to remain eligible.

2) Patients identified in out-patients

If free of exacerbations of COPD for at least 6 weeks these patients can be randomised and enter the baseline data phase of the clinical investigation immediately after consent. If they are not exacerbation free for 6 weeks they will have to return to clinic, once they are exacerbation free for 6 weeks, for randomisation.

3) Via a pre-established research database in which patients have given prior consent to be being contacted by researchers for research purposes. These patients should be sent the PIS in the post and requested to attend an appointment during which consent will be sought. Those who have been free of exacerbations for at least 6 weeks can enter the baseline data phase of the clinical investigation immediately following consent and confirmation of full eligibility. If they are not exacerbation free for 6 weeks they will have to return to clinic, once they are exacerbation free for 6 weeks, for randomisation.

Regardless of which of the above pathways has been followed to reach the randomisation point, all patients will then enter a 2 week baseline confirmation period during which those randomised to COPDPredict ™ will have their condition monitored to establish their personal baseline state.

Those patients randomised to the intervention (COPDPredict™) will record daily well-being scores on the patient-facing App and every other day will test their lung function via a Bluetooth spirometer linked directly to the App. During this 2 week period saliva will be collected by the patient and a finger-prick sample blood will be analysed POC at 2 time-points to measure biomarker (CRP) levels. Blood CRP levels will be inputted directly into the App at the time of testing by the research team. The solution will provide prompts to the patients via their tablet device to complete their daily wellbeing scores.

Those randomised to standard self-management will simply be asked at the end of the 2 weeks, via phone call, if they have had any exacerbations during this time.

Patients in either arm who do suffer an exacerbation during the 2 week baseline confirmation period, will then have to wait 6 weeks until they are exacerbation free before being asked to establish their personal baseline state again.

6.2. Randomisation

6.2.1. Randomisation Methodology

Participants will be randomised by computer/telephone at the level of the individual in a 1:1 ratio to either SSMP with RM (control arm) or COPDPredict™with RM (intervention arm).

A minimisation algorithm will be used within the online randomisation system to ensure balance in the treatment allocation over the following variables:

- centre
- age (<60, ≥60 years)
- severity of disease (FEV_1 <50% predicted, ≥ 50% predicted)

A 'random element' will be included in the minimisation algorithm, so that each participant has a probability (unspecified here), of being randomised to the opposite treatment that they would have otherwise received.

Full details of the randomisation specification will be stored in a confidential document at BCTU.

6.2.2. Randomisation Process

After informed consent has been received and full participant eligibility confirmed (including exacerbation free for 6 weeks), the participant can be randomised into the clinical investigation. Randomisation Notepads will be provided to investigators and may be used to collate the necessary information prior to randomisation. All questions and data items on the Randomisation Notepad must be answered before a Clinical investigation Number can be given. If data items are missing, randomisation will be suspended, but can be resumed once the information is available.

Randomisation will be provided by a secure online randomisation system at the Birmingham Clinical Clinical Trialss Unit (BCTU) (available at www.clinical investigations.bham.ac.uk/Predict & Prevent AECOPD). Unique log-in usernames and passwords will be provided to those who wish to use the online system and who have been delegated the role of randomising participants into the clinical investigation as detailed on the **Predict&Prevent AECOPD Clinical Investigation Signature and Delegation Log**. These unique log-in details must not be shared with other staff and in no circumstances should staff at sites access either the randomisation process or clinical investigation database using another person's login details. The online randomisation system will be available 24 hours a day, 7 days a week, apart from short periods of scheduled maintenance. A telephone toll-free randomisation service ((0044) 0800 953 0274) is available Monday to Friday, 09:00 to 17:00 UK time, except for bank holidays and University of Birmingham closed days.

6.2.3. Randomisation Records

Following randomisation, a confirmatory e-mail will be sent to the randomiser at site, local PI and research nurse.

Investigators will keep their own study file log which links participants with their allocated clinical investigation number in the **Predict&Prevent AECOPD Clinical investigation Participant Recruitment and Identification Log**. The Investigator must maintain this document, which is not for submission to the Clinical investigations Office. The Investigator will also keep and maintain the **Predict&Prevent**

AECOPD Clinical investigation Participant Screening/Enrolment Log which will be kept in the ISF, and should be available to be sent to the Clinical investigations Office upon request. The **Predict&Prevent AECOPD Clinical investigation Participant Recruitment and Identification Log** and **Predict&Prevent AECOPD Clinical investigation Participant Screening/Enrolment Log** should be held in strict confidence.

6.3. Informing Other Parties

This study is not a CTIMP but is a medical device clinical investigation, and as such it is important that the GP is informed of the participant's entry into the study.

If the participant has agreed, the participant's GP should be notified that they are in **Predict&Prevent AECOPD Clinical Investigation**, using the **Predict&Prevent AECOPD Clinical Investigation GP Letter.**

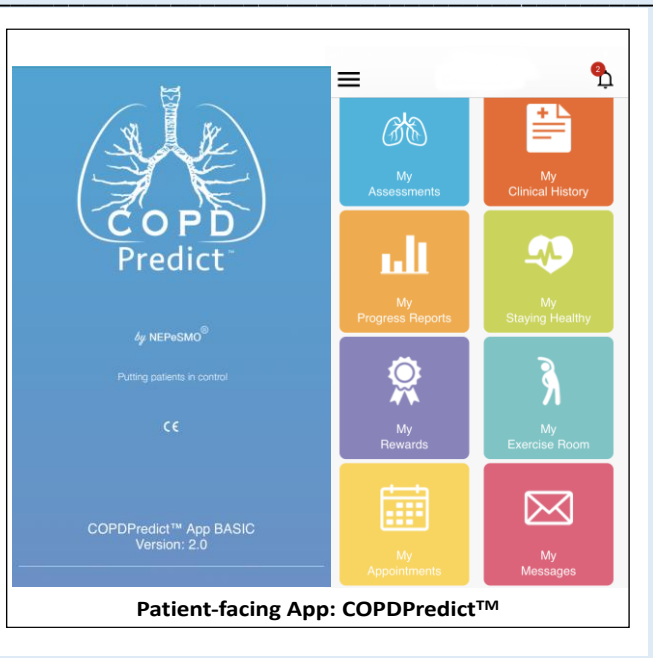
6.4. Blinding

This is an unblinded clinical investigation since it will be apparent to the participants whether they are in the standard or intervention arm. Similarly, clinicians will be able to see and review data as it arrives from the group using COPD Predict™, but will not have this data available from the standard care group, so clinicians too will be unblinded.

7. CLINICAL INVESTIGATION TREATMENT / INTERVENTION

7.1. Intervention(s) and Schedule

The intervention COPDPredict™is a CE marked Class I medical device, which comprises a patient-facing App and clinician-facing dashboard, CE-marked Bluetooth devices for assessment of physiology as well as CE-marked devices for collection of saliva. Analysis of capillary CRP will be performed by a nurse using finger-prick testing at POC either in the patients' homes or clinic. This is illustrated in the Figure below.



Patient-facing App: COPDPredict™

Figure 3. The patient interface to the COPDPredict™ System, Bluetooth spirometer, and saliva collection tubes.

The patient-facing App will be pre-installed onto a Tablet device (by the device manufacturer) which will be provided to participants randomised to this arm of the clinical investigation. The clinician facing dashboard is web-based and the website and login will be provided prior to commencement of the study. As the App and dashboard is one which will not be familiar to PIs at site a training pack explaining the use of COPDPredict™ will be issued to sites. A site initiation visit and investigator meeting will be used to ensure that staff understand its use.

Note: The App may signpost a patient to a self-management action plan. The App will not however make a decision to initiate treatment this is based on patient self-management and/or clinical oversight. The rescue medication pack itself is the standard of care for these patients and should be sourced locally in accordance with standard practice.

After 2-week baseline is set: Patients will be asked to complete their wellbeing diary daily and provide a sample of saliva perform spirometry weekly. The only derogation to this protocol is when the algorithm prompts extra testing i.e. wellbeing, spirometry or blood CRP. When blood CRP is

prompted a nurse will visit the patient home within 16 hours to take the test and input the results into the App.

Home visit assessments in response to exacerbation events should be performed on the day that initial alert occurs and within 16 hours of the site being aware of the potential exacerbation. If absolutely necessary (eg due to lack of 7 day working) a further 24 hours window is permissible (40hrs in total) but this extended window should be the last resort. We will monitor data on the timing of the visit and conduct analyses assessing the impact of delayed visits on outcomes. Hence, the time from the initial alert occurring to the time at which the visit the patient and take appropriate clinical measurements will be dichotomised (<=16 hours, >16 hours) and sensitivity analysis will be conducted.

At the time of testing, saliva will also be obtained from the patient to allow for matched samples. If the blood CRP indicated the possibility of an exacerbation of COPD advice will be provided by the clinical team. Saliva samples produced by the patient will be pre-labelled with all non-identifiable features however the patient will need to input the date and time. The patient will then need to contact the courier (CryoPDP) via either phone or text message to arrange for collection.

The standard care group will receive initial advice regarding self-management of their COPD and rescue medication but will not receive any of the additional equipment referred to above.

7.2. Intervention Modification

If the patient is unable to comply with the intervention, or fails to do so regularly enough to make it usable (it requires regular data to generate a personal baseline) then additional education will be given to the patient by the local team in the first instance. This will be facilitated by alerts to the local research team from within the App, namely in the first 2 weeks after randomisation if the patient is <75% compliant with symptom completion in the App, then both the local research team and clinical investigation manager will be informed via the software, and a telephone call will be made by the local research team to the patient to talk them through use of the device again. This will also trigger a push of an education module through to the patient via the App. If after the call, and the patient's review of the module, completion remains <75% for another 2 weeks then a face to face review with the patient will be arranged by the local research team (research nurse led appointment).

Patients in the standard arm will follow the standard, local, self-management advice and use their rescue medication, or not, accordingly.

7.3. Device accountability

Patients will be asked to sign a receipt for the hardware and device accountability will be undertaken at the each local site throughout the study for the reusable units and disposable sets (sterilisation/assembly batch number and disposable set number). The site will maintain a log of usage of the Tablet, spirometer and disposable set used throughout the study recording the lot number used against each subject (on an equipment log).

At the end of each participant's participation in the clinical investigation the Tablet, spirometers and any unused disposables will be removed from the patient's home and returned to the investigator centre.

7.4. Equipment Supply, Storage & Return of Equipment

Hardware for the intervention will be purchased on behalf of the Predict&Prevent AECOPD clinical investigation and provided to the patients. The hardware does not require any special storage conditions but should be handled with due care and in accordance with any instructions. Equipment failures will be replaced provided there is no evidence of inappropriate use or deliberate negligence, under which circumstances the Sponsor reserves the right not to re-supply the patient.

When patients have produced a sample of saliva in the Sal'Clenz collection devices, the vestibule containing the samples should be stored in the freezer pending collection.

7.5. Device labelling

All components of the COPDPredict™ system (Tablet computer installed with COPDPredict™ software, Spirometers and 15ml centrifuge/Sal'Clenz saliva collection tubes) will be labelled as "Exclusively for Clinical Investigation". Labelling will also include the Sponsor name, contact details and a unique trial identifier.

7.6. Device maintenance

Device cleaning and routine maintenance will be the responsibility of the participants. Full details for cleaning and routine maintenance required will be provided in a Patient Device Instruction Pack. The operating system on the tablet device will be maintained by the manufacturer of COPDPredict™ NEPeSMO.

7.7. Cessation of Intervention / Continuation after the Clinical investigation

Should completion still remain low after the face-to-face review described in section 7.2, then the participant will be withdrawn. Participants who withdraw from the study will not be able to continue the intervention and all hardware/software (Tablet computer installed with COPDPredict™ software, Spirometers and 15ml centrifuge/Sal'Clenz™ saliva collection tubes) will be retrieved from the participant and they will resort to standard care. Such patients will not crossover, in that they will not then be asked to complete follow up data. At the end of the study the App and dashboard will only remain available to participants if their local Trust has decided to support its use in this population.

7.8. Adherence Monitoring

This clinical investigation is comparing the effectiveness of two self-management strategies and, as such, adherence is built in to the intervention arm (Section 7.2). Adherence to the control arm will be measured in terms of the follow-up appointments attended/phone appointments responded to.

8. OUTCOME MEASURES AND STUDY PROCEDURES

8.1. Pilot Stage Outcomes

There is no pilot stage to this clinical investigation

8.2. Main Clinical investigation Outcomes

8.2.1. Primary Outcome

Number of hospital admissions at 12 months post randomisation where the primary reason for admission is AECOPD. This will be obtained from patient testimony and from centrally held (HES) records. Data from the 2 sources will be cross-referenced to remove double-counting. The total number of admissions will be the sum of unique admissions from the 2 sources of data

8.2.2. Secondary Outcomes

8.2.2.1. Clinical Outcomes

Over a 12 month period, following randomisation;

- Total inpatient days *(from patient testimony at 3, 6, 9 and 12 months, and from centrally held health records after 12 months)*
- Number of visits to A&E *(from patient testimony at 3, 6, 9 and 12 months, and from centrally held health records after 12 months)*
- Number of patient defined exacerbations *(from patient testimony at 3, 6, 9 and 12 months, and from centrally held health records after 12 months)*
- Association between symptom control markers, namely breathlessness and sputum (Anthonisen criteria – Appendix 2) and clinical judgement *(in the intervention arm:from data entered on the App throughout the 12 months the patient is on trial, in response to prompts. In the standard arm: at 3, 6, 9 and 12 months)*
- Health-related quality of life *(CAT)*

and,

- FEV_1 at 12 months post randomisation *(from spirometry obtained during hospital visit)*

8.2.2.2. Economic Outcomes

- Health-related quality of life at baseline and 3, 6, 9 and 12 months post randomisation *(EQ-5D-5L)*
- Healthcare utilisation at 3, 6, 9 and 12 months post randomisation *(as determined by a questionnaire that inquires on hospitalisations, GP attendances and medication usage)*

8.2.2.3. Qualitative sub-study

- End user experience (technology acceptability, integration into daily life, views on overall acceptability of intervention)
- Provider experience (attitudes to reducing antibiotic use using this intervention, ease of integrating additional monitoring into standard care, ease of understanding and explaining risk to patients)
- Lifestyle choices *(via App usage/questionnaires/interviews)*

8.3. Mechanistic Procedures

Capillary CRP levels will be measured during the 2 week baseline period at 2 timepoints, days 1and 14, theselevels will be measured in clinic. Subsequent to this, CRP will be measured when prompted by the algorithm (prodromal, exacerbation and recovery phases) or when the clinical team take the decision that a test is warranted. These measurements will generally be conducted at the patient's home and the data entered by the visiting healthcare worker.

Salivary CRP levels will be measured during the 2 week baseline phase on days 1, 7 (±2 days) and 14, with days 1 and 14 being collected in the clinic at the same time as the blood CRP and the midpoint saliva being taken by the patient, , in the patient's home. Subsequent to this, saliva samples will be measured weekly or when prompted by the algorithm (prodoromal, exacerbation and recovery phases). Saliva samples will be collected by CryoPDP medical couriers (within 72 hours) who will liaise directly with the study participants to transport said samples to Pathology Department, University Hospitals of North Midlands for processing and analysis.

(saliva samples will be biobanked, at -80^{o}C for future analysis)

8.4. Schedule of Assessments

Figure 4 Assessment schedule for Predict&Prevent AECOPD patients. All timings taken from randomisation

Visit	Hospital Discharge/ Initial appointment	Personal Baseline Day 1 after 6 weeks exacerbation free (in clinic)	Personal Baseline Day 7 (±2 days) (home visit)	End of Personal Baseline Period (Day 14) (in clinic)	Approximately 4 times during any exacerbation (home visit)	Weekly until Week 52	Week 13 Telephone follow Up +/-1 week	Week 26 Hospital follow Up +/-1 week	Week 39 Telephone follow Up +/-1 week	Week 52 Hospital follow Up +/- 2 weeks
Eligibility check	X									
Valid informed consent	X									
Randomisation		X								
Height and Weight	X									X
Concomitant medication	X									X
Baseline medical history taken[α]	X									
Request to GP for rescue medication	X						(X)	(X)	(X)	
Assessment of (S)AEs	X				(X)	X	X	X	X	X
Questionnaires (QoL and health utilisation)	X						X	X	X	X
Spirometry	X							X		X
Intervention only below this line					Intervention only below this line					
Provision of equipment & patient training		X								
Spirometry	X	X	X		(X)	X				
Symptom control markers	X	X	X	X	(X)	X	X	X	X	X
Saliva Collection		X	X	X	(X)	X				
Point of care blood test		X		X	(X)					

(X) denotes only when required. If rescue medication has not been used, fresh prescription requests will not be necessary

During the baseline period and any subsequent exacerbations patients will be entering well-being data on the App which will be related to lifestyle choices and the end-user experience. This data will not form part of the formal analysis of quality of life.

8.5. Participant Withdrawal and Changes of Status Within Clinical investigation

Informed consent is defined as the process of learning the key facts about a clinical investigation before deciding whether or not to participate. It is a continuous and dynamic process and participants should be asked about their ongoing willingness to continue participation.

Participants should be aware at the beginning that they can freely withdraw (discontinue participation) from the clinical investigation at any time. A participant who withdraws from the clinical investigation does so completely (i.e. from clinical investigation treatment and all follow up) and is not willing to have any of their data, including that already collected, to be used in any future clinical investigation analysis.

Patients will be withdrawn from the clinical investigation who:

in either arm

- suffer an exacerbation during the 2 week baseline period, wait a further 6 weeks to return to their personal baseline state again then suffer a further exacerbation during this new 2 week personal baseline period

in the intervention arm who

- fail to meet the data entry adherence threshold (75%) whilst establishing their personal baseline

A participant who wishes to cease to participate *in a particular aspect of the clinical investigation*, will be considered as having changed their status within the clinical investigation

The changes in status within clinical investigation are categorised in the following ways:

- No clinical investigation intervention: The participant would no longer like to receive the clinical investigation intervention, but is willing to be followed up in accordance with the schedule of assessments and if applicable using any central UK NHS bodies for long-term outcomes (i.e. the participant has agreed that data can be collected and used in the clinical investigation analysis)

- No clinical investigation related follow-up: The participant would no longer like to receive the clinical investigation intervention AND does not wish to attend clinical investigation visits in accordance with the schedule of assessments but is willing to be followed up at standard clinic visits and if applicable using any central UK NHS bodies for long-term outcomes (i.e. the participant has agreed that data can be collected at standard clinic visits and used in the clinical investigation analysis, including data collected as part of long-term outcomes)

- No further data use: The participant would no longer like to receive the clinical investigation intervention AND is not willing to be followed up in any way for the purposes of the clinical investigation AND does not wish for any further data to be collected (i.e. only data collected prior to the change of status can be used in the clinical investigation analysis)

The details of either withdrawal or change of status within clinical investigation (date, reason and category of status change) should be clearly documented in the source data. Patients subsequently found to be ineligible will still have their data analysed unless they explicitly withdraw consent.

9. ADVERSE EVENT REPORTING

9.1. Definitions

Adverse Event	AE	any untoward occurrence, unintended disease or injury or any untoward clinical sign, 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
Adverse Device Event	ADE	a device related adverse event
Serious Adverse Event	SAE	An adverse event that: a) led to a death, b) led to a serious deterioration in the health of the subject that c) resulted in a life-threatening illness or injury, d) resulted in a permanent impairment of a body structure or a body function, e) required in-patient hospitalization or prolongation of existing hospitalization, f) resulted in medical or surgical intervention to prevent permanent impairment to body structure or a body function, g) led to foetal distress, foetal death or a congenital abnormality or birth defect, h) any indirect harm as a consequence of an incorrect diagnostic test result or as a consequence of the use of a device when used within manufacturer´s instructions for use
Serious Adverse Device Effect	SADE	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune.
Unanticipated Serious Adverse Device Effects	USADE	Any serious adverse device effect which, by its nature, incidence, severity or outcome is unanticipated
Device Deficiency	DD	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Device

		deficiencies include malfunctions, use errors and inadequate labelling.
Use error	**UE**	Act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user. Use error includes slips, lapses and mistakes.
Severity definitions	**Mild** **Moderate** **Severe**	awareness of signs or symptoms, that does not interfere with the subject's usual activity or is transient that resolved without treatment and with no sequelae. a sign or symptom, which interferes with the subject's usual activity. incapacity with inability to do work or perform usual activities

NOTE : The above criteria encompass adverse incidents but it should be appreciated that not all adverse incidents lead to death or serious deterioration in health. It is sufficient that:

- an incident associated with a device happened, and
- the incident was such that, if it occurred again, it might lead to death or serious deterioration in health

9.2. Adverse Events (AE)

9.2.1. General *Recording* Requirements

The collection and reporting of Adverse Events (AEs) will be in accordance with the UK Policy Framework for Health and Social Care (2017) the Directive for Medical Devices (MDD), 93/42/EEC, and the requirements of the Health Research Authority (HRA). Definitions of different types of AEs are listed in the table of definitions in section 9.1.

All medical occurrences which meet the definition of an AE, Device Deficiencies and Adverse Device Effect (ADE) and User Errors, (see Section 9.1 for definitions) should be recorded, on discovery. It is routine practice to record adverse events in the patient's medical notes and it is also recommended that this includes the documentation of the assessment of severity and seriousness and also for causality (relatedness) in relation to the intervention(s) in accordance with the Clinical Investigation Plan. However, it may not be routine practice to record device deficiencies or user errors in the medical notes outside of the context of a clinical investigation, but must be so in this study, if discovered.
The assessment of causality associated with a given event should be made with regard to section 9.6 of this Clinical Investigation Plan.

9.2.2. Adverse Events *Reporting* Requirements in Predict&Prevent AECOPD Clinical investigation

Patients with chronic COPD can have high disease burden. It is expected that the clinical investigation population will be older, with co-morbidities such as osteoporosis (18), cardiovascular disease or raised cardiovascular risk (19, 20), along with associated complications and symptoms including abnormal lab results. A relatively high number of adverse events are anticipated as a result of the patients' existing disease history. However, this study is examining the role of increased patient surveillance and there are therefore few, if any, foreseeable risks of direct harm associated with the study intervention. AE reporting will therefore be limited to those events identified on the CRF, which are required for clinical investigation monitoring or outcome assessment. This does not negate the need for the research team at site to record any reported or observed adverse events in the participant's medical records, in line with routine medical practice.

9.3. Device Deficiencies, User Errors, Serious Adverse Advents (SAE) and Serious Adverse Device Effects (SADE) Reporting in the Predict&Prevent AECOPD Clinical Investigation

9.3.1. Serious Events that do not require reporting to the Clinical Investigation Office

All events which meet the definition of serious must be recorded in the participant notes, including the causality and severity, throughout the participant's time on trial, including follow-up, but for trial purposes these following events do not require reporting on the SAE Form. Such events are "safety reporting exempt".

- Planned hospitalisation for a pre-existing condition, or a procedure required by the trial Clinical Investigation Plan, without serious deterioration in health, is not considered a serious adverse event.
- An overnight stay in hospital that is due to transportation, organisational or accommodation problems, and without medical background

9.3.2. SAES *requiring expedited reporting*

Regulation 16(10)(a) of the Medical Devices Regulations 2002 (SI 618) and Annex X of the Medical Devices Directive 93/42 require manufacturers to report **all** serious adverse events occurring in all participating centres to the MHRA.

Any SAEs not referred to in section 9.3.1 will be reported to the clinical investigations office on an **SA(D)E Form** immediately, and within 24 hours of being made aware of the event.

All DDs and UEs, that;

1) led to an adverse event,
2) could have led to an adverse event if suitable action had not been taken, or intervention had not been made, or if circumstances had been less fortunate

will be collected and recorded in the participant notes and a **DD/UE Form** must also immediately, and within 24 hours of being made aware of the event, be reported to the Predict&Prevent AECOPD Clinical Investigation Office.

Any death occurring during the Clinical Investigation Plan defined follow up period (12 months), whether considered device-related or not, must be reported as an SAE within 24 hours of the local investigator becoming aware of the event.

Note: processes must be in place to make the clinical investigation team at the hospital aware of any SAEs, regardless which department first becomes aware of the event, in an expedited manner.

9.4. Reporting period

The reporting period will commence when the participant has been consented into the clinical investigation and ends 2 weeks after the participant completes their last EQ-5D-5L. Clinical investigation outcome and end point data, which includes some safety end points, should be reported for the full duration of the participant's clinical investigation participation.

9.5. Reporting procedure

9.5.1. Reporting Procedure for AEs

Targeted AEs, as requested on the CRF, should be reported on the CRF, in the same way and with the same timeframes as other CRF data. AEs will be identified at site by review of the participant's medical records and discussion with the participant at the study visits.

9.5.2. Reporting procedure for DDs, UEs and Serious Adverse (Device) Events by sites

On becoming aware that a participant has experienced a DD, UE or SA(D)E, the Investigator or delegate(s) should report it to their own Trust in accordance with local practice and to the BCTU clinical investigations office as per section 9.3, above.

To report a DD, UE or SA(D)E to the BCTU clinical investigations office the Investigator or delegate(s) (usually the PI but may be any suitably medically qualified person appearing on the delegation log) must complete, date and sign the **Predict&Prevent AECOPD DD, UE** or **SA(D)E form**. The completed form together with any other relevant, appropriately anonymised, data should be scanned and emailed to the **Predict&Prevent AECOPD** clinical investigations team using one of the numbers listed below and no later than 3 calendar days after first becoming aware of the event for expedited SAEs:.

To report a DD, UE SA(D)E, email the DD, UE or SA(D)E Form to:

Predictandprevent@trials.bham.ac.uk

Where a DD, UE or SA(D)E Form has been completed by someone other than the Investigator (or delegate), initially, the original DD, UE or SA(D)E form will need to be countersigned by the Investigator (or delegate) to confirm agreement with the causality and severity assessments.

When submitting DD, UE or SA(D)E forms via e-mail, care should be taken to anonymise the information. Trial forms and supporting information should not contain: patient name, patient address, discharge address, GP name, GP address, hospital number, or NHS number.

On receipt of a DD, UE or SA(D)E form, the **Predict&Prevent AECOPD Clinical investigation** team will allocate each DD, UE or SA(D)E a unique reference number and return this via email to the site as proof of receipt. The site and the **Predict&Prevent AECOPD Clinical investigation** team should ensure that the SAE reference number is quoted on all correspondence and follow-up reports regarding the DD, UE or SA(D)E and filed with the DD, UE or SA(D)E in the Site File.

If the site has not received confirmation of receipt of the DD, UE or SA(D)E from the **Predict&Prevent AECOPD Clinical investigation** team or if the DD, UE or SA(D)E has not been assigned a unique DD, UE or SA(D)E identification number within 1 working day, the site should contact the **Predict&Prevent AECOPD Clinical investigation** team.

9.5.3. Provision of follow-up information

Following reporting of an DD, UE or SA(D)E for a participant, the participants should be followed up until resolution or stabilisation of the event. Follow-up information should be provided using the DD, UE or SA(D)E reference number provided by the **Predict&Prevent AECOPD Clinical investigation** team. Once the DD, UE or SA(D)E has been resolved, all critical follow-up information has been received and the paperwork is complete, the final version or true copy of the original DD, UE or SA(D)E form completed at site must be returned to the **Predict&Prevent AECOPD Clinical investigation** office and a copy kept in the Site File.

9.6. Assessment of relatedness by the PI

When completing the DD, UE or SA(D)E form, the PI (or delegate) will be asked to define the causality (relatedness) and the severity of the DD, UE or SA(D)E. In defining the causality the PI (or delegate) must consider if any concomitant events or medications may have contributed to the event and, where this is so, these events or medications should be reported on the DD, UE or SA(D)E form. It is not necessary to report concomitant events or medications which do not contribute to the event.

Category	Definition	Causality
Definitely	the serious event is associated with the investigational device or with procedures beyond reasonable doubt when: - the event is a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has a temporal relationship with investigational device use/application or procedures; - the event involves a body-site or organ that o the investigational device or procedures are applied to; o the investigational device or procedures have an effect on; - the serious event follows a known response pattern to the medical device (if the response pattern is previously known); - the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible); - other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; - harm to the subject is due to error in use; - the event depends on a false result given by the investigational device used for diagnosis , when applicable; - In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.	Related
Probably	the relationship with the use of the investigational device seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained.	
Possibly	the relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.	

Unlikely	the relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.	
Not related	A relationship to the device or procedures can be excluded when: - the event is not a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has no temporal relationship with the use of the investigational device or the procedures; - the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; - the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event; - the event involves a body-site or an organ not expected to be affected by the device or procedure; - the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors); - the event does not depend on a false result given by the investigational device used for diagnosis , when applicable; - harms to the subject are not clearly due to use error; - In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.	Unrelated

On receipt of an DD, UE or SA(D)E Form the Clinical investigations Office will forward it, with the unique reference number, to the Chief Investigator (CI) or delegate(s) who will independently review the causality of the DD, UE or SA(D)E. An SAE judged by the PI or CI or delegate(s) to have a reasonable causal relationship with the intervention will be regarded as a related SADE . The causality assessment given by the PI will not be downgraded by the CI or delegate(s). If the CI or delegate(s) disagrees with the PI's causality assessment, the opinion of both parties will be documented, and where the event requires further reporting, the opinion will be provided with the report.

9.7. Assessment of Expectedness by the CI

9.7.1. Relevant Safety Information

This clinical investigation is using a non-invasive class I medical device which does not direct diagnosis. As such there are no known adverse events which can be expected as a result of the device itself, and SA(D)E events should be reported as unexpected as per section 9.7.2, below.

9.7.2. Criteria for Expectedness

CI or delegate(s) will also assess all related SAEs for expectedness with reference to the following criteria.

Category	Definition
Expected	An adverse event that is consistent with known information about the clinical investigation related procedures or that is clearly defined in the relevant safety information, above;
Unexpected	An adverse event that is not consistent with known information about the clinical investigation related procedures.

The CI will not overrule the severity or causality assessment given by the site Investigator but may add additional comment on these. If the event is unexpected (i.e. is not defined in the Clinical Investigation Plan as an expected event) it will be classified as an USADE.

9.8. Reporting DD and SA(D)Es to third parties

Details of all AEs will be reported to the MHRA on request.

The independent Data Monitoring Committee (DMC) may review any DD or SA(D)Es at their meetings.

In addition to notifying the appropriate regulatory agencies and RGT of all DD or SADE events that occur during this study will be reported to the manufacturer (for information only) by the Predict&Prevent AECOPD clinical investigation team, within 48 hours of the team becoming aware of the event.

All SA(D)Es regardless of causality or relatedness, excluding those listed in section 9.3.1, will be reported to the MHRA within 7 days of receipt from Site.

The Trials Office will report a minimal data set of all USADEs to the MHRA and main REC within 7 days. Detailed follow-up information will be provided as appropriate.

Additionally, within 30 days following the anniversary of the authorization date for the clinical investigation the Clinical Investigation Office will report details of all SADEs (including USADEs) to the MHRA and main REC an Annual Safety Report will be sent by the Chief Investigator to the MHRA and the Main Research Ethics Committee. A copy of the report will also be sent to RGT and the manufacturer (NEPESMO).

Details of all USADEs and any other safety issue which arises during the course of the trial will be reported to Principal Investigators. A copy of any such correspondence should be filed in the ISF.

9.9. Urgent Safety Measures

If any urgent safety measures are taken, the BCTU shall immediately, and in any event no later than 3 days from the date the measures are taken, give written notice to the REC, RGT and MHRA of the measures taken and the circumstances giving rise to those measures.

10. DATA HANDLING AND RECORD KEEPING

10.1. Source Data

Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical investigation necessary for the reconstruction and evaluation of the clinical investigation. In order to allow for the accurate reconstruction of the clinical investigation and clinical management of the subject, source data will be accessible and maintained.

Data	***Source***
Participant Reported Outcomes	*The original participant-completed CRF is the source. Patients on the intervention arm can enter data directly into the App. This will be exported to the Predict&Prevent Clinical Investigations Office at pre-defined times. Any CRFs completed by patients on the standard care arm will be kept with the participant's clinical investigation record at site, whilst copies will be provided to the Clinical investigations Office*
Point of care CRP results	*The original lab report (which may be electronic) is the source data and will be kept and maintained, in line with normal local practice. Information will be transcribed into the clinical screen of the COPDPredict™ App by the home care visitor*
Clinical event data	*The original clinical annotation is the source data. This may be found on clinical correspondence, or electronic or paper participant records. Clinical events reported by the participant, either in or out of clinic (e.g. phone calls), must be documented in the source data. However, patients may self-report clinical events for which they have not sought support by the research team via the App.*
Health Economics data	*Obtained by interview directly with the participant for transcription onto the CRF by the research team.*

Recruitment	*The original record of the randomisation is the source. It is held on BCTU servers as part of the randomisation and data entry system.*
Withdrawal or change of status	*Where a participant expresses a wish to withdraw, the conversation must be recorded in the medical record*

10.2. Case Report Form (CRF) Completion

A CRF is required and should be completed for each individual subject. The data held on the completed original CRFs should not be made available in any form to third parties except for authorised representatives or appropriate regulatory authorities without written permission from the sponsor. Appropriate data sharing requests will be considered by the Sponsor

It will be the responsibility of the investigator to ensure the accuracy of all data that are collected and entered in the CRFs by the research team, and confirm accordingly. The **Predict&Prevent AECOPD Clinical investigation Site Signature & Delegation Log** will identify all those personnel with responsibilities for data collection.

The CRFs will comprise (but will NOT be limited to) the following Forms *(Table 10.2):*

Table 10.2: Data Collection Forms

Form Name	***Schedule for submission***	***CRF Type***
Informed Consent Form	*At the point of randomisation*	*Paper by nurse and patient*
Randomisation CRF	*At the point of randomisation*	*Electronic by nurse*
Baseline CRF	*As soon as possible after the baseline assessment*	*Electronic by nurse*
Personal baseline data – intervention arm only	*In response to electronic reminders*	*Electronic by patient*
Home Visit CRF	*As soon as possible after days 1, 5, 9 and 14 of any exacerbation*	*Electronic by nurse*
Exacerbation details data – intervention arm only	*In response to electronic prompts*	*Electronic by patient*
Ongoing personal baseline monitoring - *Intervention arm only*	*In response to electronic reminders*	*Electronic by patient*
3, 6 9 and 12 monthly follow-up (times from randomisation)	*As soon as possible after each follow-up assessment*	*Electronic by nurse*

Serious Adverse (Device) Event CRF	*Emailed within 24hrs of research staff at site becoming aware of event*	*Paper*
Device Deficiency or User Error CRF	*Emailed within 24hrs of research staff at site becoming aware of event*	*Paper*
Change of status CRF	*At the point of withdrawal or death*	*Electronic*

Nurse-completed electronic CRFs will be completed online at

www.trials.bham.ac.uk/Predict&Prevent

from the source data. Authorised staff at sites (as delegated on the **Predict&Prevent Site Signature & Delegation Log**) will require an individual secure login username and password to access this online data entry system at BCTU. Unique passwords and usernames must not be shared.

Since data entry on the electronic CRFs are attributable by virtue of the user log-in, submission of data on the electronic form will be taken as 'sign-off' to attest the data entered is accurate. Any changes made on the electronic CRF are automatically tracked. A reason will be provided for changes. Changes can only be made to the electronic CRF by appropriately delegated staff at the correspondingly appropriate sites. Patient trial data cannot be changed by staff at BCTU or any other third party.

If information is not known, this must be clearly indicated on the CRF. Missing and ambiguous data will be queried in line with the **Predict&Prevent Data Management Plan**.

Investigators will keep their own study file logs which link patients with pseudoanonymised CRFs. The Investigator must maintain documents not for submission to the Clinical Investigation Office (e.g. **Predict&Prevent Patient Recruitment and Identification Logs**) in strict confidence.

CRFs may be amended by the **Predict&Prevent Clinical Investigation Office**, as appropriate, throughout the duration of the trial. Whilst this will not constitute a clinical investigation plan amendment, new versions of the CRFs must be implemented by participating sites immediately on receipt

Data reported on each form will be consistent with the source data and any discrepancies will be explained. All missing and ambiguous data will be queried by the Clinical Investigations Office via data clarification requests. Staff delegated to complete CRFs will be trained to adhere to the **Predict&Prevent CRF completion Guidelines**.

The following guidance applies to data and partial data:

Time format and unknown times – all times should be in accordance with the 24hr clock

Date format and partial dates – dates should be formatted DD/MON/YYYYY. If a precise day of the month is not known, then "15" can be used, and if the precise month of a year is not known, as may be the case for medical history, then "JUN" can be used.

Rounding conventions – rounding should be in the normal way

Clinical investigation-specific interpretation of data fields – where guidance is needed additional information will be supplied

Entry requirements for concomitant medications (generic or brand names) – generic names should be used where possible

Missing/incomplete data – should be clearly indicated – all blank fields will be queried by the clinical investigation office

Repeat laboratory tests – the data used to inform clinical decisions should always be supplied. If a test is repeated it is either to confirm or clarify a previous reading. Confirmatory tests should use the original test values.

Clinical Investigation Plan and GCP non-compliances should be reported to the Clinical investigations Office on discovery.

The brand name of concomitant medications is the preferred option but where concomitant medications are to be analysed, these will be assigned to appropriate drug classes.

The completed originals or true copy thereof will be submitted to the BCTU clinical investigations team and a copy filed in the Investigator Site File

Only CRFs approved by the Predict&Prevent Clinical Investigation Team must be used.

10.3. Participant completed Questionnaires

Participants will be ask to complete two types of questionnaire (CAT and EQ-5D-5L) at various timepoints as per the schedule of assessments in section 8.3. These questionnaires can be completed in several ways;

At baseline - in clinic by the patient, with the support of the nurse if required. Patients randomised to the intervention arm will be prompted by the App if data is missing but the system will permit the patient not to respond. Patients randomised to standard care will complete a paper questionnaire which will be checked by the nurse for completeness before entering data onto the online system.

During follow-up - by the patient, with the support of the nurse if required either over the phone or in clinic, as per the schedule of events. Since data is being entered electronically either by the patient (intervention arm) or by the nurse (standard arm) electronic prompts will occur for any missing data

The use of different data collection methods in the two arms means there is a risk of detection bias. Form return rates will be carefully monitored throughout. Multiple patient contacts will be made with patients to ensure high form return rates and consideration will be given to incentivising all patients for form returns if issues are noted.

10.4. Data Management

Processes will be employed to facilitate the accuracy of the data included in the final report. These processes will be detailed in the clinical investigation specific Data Management Plan. Coding and validation will be agreed between the clinical investigation team and the clinical investigation database will be signed off once the implementation of these has been assured. Missing and ambiguous data will be queried in line with the **Predict&Prevent Data Management Plan**, and will focus on data required for trial analysis and safety reporting. Data is coming from 2 principle sources:

1. Directly from the patient completed App – This data refers directly to the patients symptoms, well-being and experience. It is not possible to perform data clarifications on this data
2. From the site team – this data is entered onto the trial database via a web-portal and consists of transposed patient responses or data from medical records, such as hospitalisations and medical history. This data can be clarified via requests to the site staff and a transfer to site-unlock-resubmit data process

Single data entry with central monitoring will be employed. Staff at site (as delegated on the **Predict&Prevent Site Signature & Delegation Log**) will enter and submit data on an electronic CRF online at www.trials.bham.ac.uk/Predict&Prevent . The system will include data validations to improve data quality (e.g. to prevent nonsensical dates or numerical values). Changes to the data on the system will be documented and attributable, with a reason for the change documented. Changes to the data on the CRF will be made by site staff only. Staff at the Clinical Investigation Office will not have access to alter CRF data, but will have access to administrative aspects of the system.

To facilitate efficient data management the following self-evident corrections will be made without referral back to the site. In signing the protocol the PI has agreed to these instances of self-evident correction.

Contingent fields: When a response to a question determines, to a degree, the response required by a second question, then conflicts in the responses can be resolved by the data entry clerk. Eg. Has the person had procedure “x”? If yes, state type. If the response to the first question is “no”, yet the type of procedure is stated, it is self-evidently true that the initial response was incorrect.

Changes to administrative notes and reference numbers: when new information becomes available such that a reference number does not accurately reflect the sequence of CRFs received eg an in-patient form is received for an incident which occurred prior to an already reported incident, then it is appropriate to change the reference number provided no data clarifications have been raised using the original number. Similarly, any notes relating to the patient care which have an impact on the administration process, but not the datafields themselves, can be changed as appropriate by site staff with permissions to modify the administrative fields only.

10.5. Data Security

There are distinct phases during which data must be secured; prior to arrival at BCTU and post arrival.

10.5.1. COPDPredict™ Data Handling

All data captured on and held by the COPDPredict™ system will be in anonymised format and will hosted on dedicated servers within a secure data centre managed by Fasthosts Internet Limited (Company Registration Number 3656438) in Gloucester; the following physical security features are in place to guarantee the safety of the data:

- CCTV covering all areas of the data centre
- Highly experienced security guards on duty 24/7, 365 days a year
- Role-based access control swipe-card system across multiple secure areas to ensure absolutely no access by unauthorised personnel
- Only authorised people have access to the database and/or server and each event is logged to ensure full transparency

The COPDPredictTM system (patient-facing App and clinician-facing dashboard) will not hold any personal data. This data will then be transferred from the web host directly to BCTU at pre-specified intervals, "pushes", and will again be SSL encrypted during transfer. Data entered into the COPDPredictTM system has been tested for Open Web Application Security Project (OWASP) top 10 vulnerabilities as recommended by NHS data security and information toolkit, and has multiple layers of access security: standard MD5 (Message Digest algorithm, v5) login with u username and password, the patient-facing App also has a 4 digit pin which is setup on the first launch by the patient. On the patient-facing App, wellbeing, lung function and biomarker data is stored locally, on the tablet device, until there is availability of the internet. Once the device is connected to the internet the data is transferred to a secure server using 256 Bit Secure Socket Layer (SSL) encryption via Representational State Transfer Application Program Interfaces (REST APIs). The COPDPredictTM system is hosted on dedicated servers (described in A37) This state-of-the-art data centre is accredited with the ISO 27001 certification and periodic penetration testing is carried out to check for any vulnerabilities. ISO 27001 (formally known as ISO/IEC 27001:2005) is a specification for an information security management system (ISMS). An ISMS is a framework of policies and procedures that includes all legal, physical and technical controls involved in an organisation's information risk management processes.

10.5.2. Data Held at BCTU

The security of the System is governed by the policies of the University of Birmingham. The University's Data Protection Policy and the Conditions of Use of Computing and Network Facilities set out the security arrangements under which sensitive data should be processed and stored. All studies at the University of Birmingham have to be registered with the Data Protection Officer and data held in accordance with the Data Protection Act. The University will designate a Data Protection Officer upon registration of the study. The Study Centre has arrangements in place for the secure storage and processing of the study data which comply with the University of Birmingham policies.

The System incorporates the following security countermeasures:

Physical security measures: restricted access to the building, supervised onsite repairs and storages of back-up tapes/disks are stored in a fire-proof safe.

Logical measures for access control and privilege management: including restricted accessibility, access controlled servers, separate controls used non-identifiable data etc.

Network security measures: including site firewalls, antivirus software, separate secure network protected hosting etc.

System Management: the System shall be developed by the BCTU Programming Team and will be implemented and maintained by the BCTU Programming Team.

System Design: the system shall comprise of a database and a data entry application with firewalls, restricted access, encryption and role based security controls.

Operational Processes: the data will be processed and stored within the Study Centre (University of Birmingham).

Data processing: Statisticians will have access to anonymised data.

System Audit: The System shall benefit from the following internal/external audit arrangements:

Internal audit of the system

Periodic IT risk assessments

Data Protection Registration: The University of Birmingham has Data Protection Registration to cover the purposes of analysis and for the classes of data requested. The University's Data Protection Registration number is Z6195856.

10.6. Archiving

All records created by following clinical investigation procedures and all documents listed in guidance relating to the conduct of the clinical investigation must be retained and archived for the specified period.

It is the responsibility of the PI to ensure all essential clinical investigation documentation and source documents (e.g. signed ICFs, Investigator Site Files, participants' hospital notes, copies of CRFs etc.) at their site are securely retained for at least 25 years.

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1. Site Set-up and Initiation

All PIs will be asked to sign the necessary agreements including a **Predict&Prevent AECOPD Site Signature & Delegation Log** between the PI and the CTU and supply a current CV and GCP certificate to BCTU. All site staff who are performing clinical investigation specific tasks are required to sign the **Predict&Prevent AECOPD Site Signature & Delegation Log**, which details which tasks have been delegated to them by the PI.

Prior to commencing recruitment, each recruiting site will undergo a process of initiation, either a meeting or a teleconference, at which key members of the site research team are required to attend, covering aspects of the clinical investigation design, Clinical Investigation Plan procedures,

adverse event reporting, collection and reporting of data, use of the data entry dashboards in the intervention arm and record keeping. Sites will be provided with an Investigator Site File containing essential documentation, instructions, and other documentation required for the conduct of the clinical investigation. The **Predict&Prevent AECOPD Clinical Investigation Office** must be informed immediately of any change in the site research team.

11.2. Monitoring

The monitoring requirements for this clinical investigation have been developed following clinical investigation specific risk assessment by BCTU and as documented in the **Predict&Prevent AECOPD Clinical investigation Monitoring Plan**.

11.3. Onsite Monitoring

For this clinical investigation the BCTU trial team will monitor each of the participating recruiting centres within 90 days of recruitment of the first patient by that site. This is specifically to ensure that the eligibility criteria are being correctly employed and that the clinical investigation data is achievable. Any monitoring activities will be reported to the clinical investigations team and any issues noted will be followed up to resolution.

Additional on-site monitoring visits may be triggered, for example by poor CRF return, poor data quality, low SA(D)E reporting rates, excessive number of participant withdrawals or deviations (also defined in the monitoring plan). Investigators will allow the **Predict&Prevent AECOPD Clinical investigation** staff access to source documents as requested. The monitoring will be conducted by staff from BCTU.

11.4. Central Monitoring

Clinical investigations staff will be in regular contact with the site research team to check on progress and address any queries that they may have.

Clinical investigations staff will check incoming ICFs and CRFs for compliance with the Clinical Investigation Plan, data consistency, missing data and timing at a frequency and intensity determined by the Data Management Plan. Sites will be sent requests for missing data or clarification of inconsistencies or discrepancies.

For the intervention arm, data collected directly from patients will be checked via the relevant data screen on the web portal by the local research team and alerts provided to the research team if there is low compliance with submission or incomplete submissions so that patients can be contacted with a view to ascertaining if there any technical problems preventing compliance, or if it is by deliberate choice (see also section 7.7). Regular data monitoring reports will be provided to the BCTU Clinical Investigation Management Group.

11.5. Audit and Inspection

The Investigator will permit clinical investigation-related monitoring, audits, ethical review, and regulatory inspection(s) at their site, providing direct access to source data/documents. The investigator will comply with these visits and any required follow up. Sites are also requested to notify BCTU of any relevant inspections or local audits.

11.6. Notification of Serious Breaches

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the Clinical Investigation Plan and/or GCP, and/or poor recruitment. Any major problems identified may be reported to CIMG, CISG, MHRA and the REC. This includes reporting serious breaches of GCP and/or the clinical investigation Clinical Investigation Plan to the MHRA and REC.

The sponsor, in this case University of Birmingham, is responsible for notifying the MHRA and REC of any serious breach of the conditions and principles of GCP in connection with that clinical investigation or the Clinical Investigation Plan relating to that clinical investigation. Sites are therefore requested to notify the Clinical investigations Office of any suspected clinical investigation-related serious breach of GCP and/or the clinical investigation Clinical Investigation Plan. Where the Clinical investigations Office is investigating whether or not a serious breach has occurred sites are also requested to cooperate with the Clinical investigations Office in providing sufficient information to report the breach to the REC and MHRA where required and in undertaking any corrective and/or preventive action.

12. END OF CLINICAL INVESTIGATION DEFINITION

The end of clinical investigation will be 6 months after the last data capture. This will allow sufficient time for the completion of Clinical Investigation Plan procedures, data collection and data input. The BCTU clinical investigation team will notify the main REC, MHRA and RGT within 90 days of the end of clinical investigation. The Clinical investigations Office will provide them with a summary of the clinical investigation report within 12 months of the end of clinical investigation. Where the clinical investigation has terminated early, the Clinical investigations Office will inform REC and MHRA within 15 days of the end of clinical investigation.

A copy of the end of clinical investigation notification as well as the summary report will be sent to the MHRA and REC. The results of the clinical investigation will be shared with sites via links to the publications on the Predict&Prevent AECOPD webpage along with a lay summary for patients.

At the end of the study the App and dashboard will only remain available to participants if their local Trust has decided to support its use in this population, otherwise patients will receive the current standard of care.

13. STATISTICAL CONSIDERATIONS

13.1. Sample Size

The justification of the sample size is based on previous evidence (28) that had shown a mean estimate of 2.5 COPD admissions in the previous year in the control group.

To detect a difference of 1 admission in the mean number of admission between groups using the standard methods of difference between means and assuming standard deviation of 2.6 (28) with

90% power and a type I error rate of 5% (two-sided), 144 participants per group will need to be randomised, 288 in total. Assuming and adjusting for a 25% loss to follow-up/ drop-out rate, 384 participants will need to be recruited.

13.2. Analysis of Outcome Measures

A separate Statistical Analysis Plan (SAP) for the Predict&Prevent trial provides a detailed description of the planned statistical analyses. A brief outline of these analyses is given below.

The primary comparison groups will be composed of those randomised to the use of a personalised early warning decision support system with novel saliva bio-profiling and those randomised to the standard self-management plan (SSMP). All analyses will be based on the intention to treat principle, with all patients analysed in the treatment groups to which they were allocated irrespective of compliance with the randomised allocated treatment, and all patients will be included in the analyses. For all outcomes, summary statistics (e.g. mean differences, relative risks) will be reported and 95% confidence intervals will be constructed where appropriate. A p-value of <0.05 will be considered statistically significant, and there will be no adjustment for multiple comparisons.

13.2.1. Primary Outcome Measure

The primary analysis for this study will be to compare rates of hospital admission between the treatment groups (Predict&Prevent AECOPD versus Usual care) over 12 months, following randomisation, where the primary reason for admission is AECOPD. These hospital admissions per person will be analysed using Poisson regression models adjusting for treatment group and minimisation variables (Section 6.2). If there is over dispersion a negative binomial regression model adjusting for treatment group and the same minimisation variables will be taken into consideration. Point estimates (incidence rates) will be provided and accompanied with 95% confidence intervals and p-value.

13.2.2. Secondary Outcome Measures

Recorded observations taken over a 12 month period, following randomisation:

Total in-hospital days and FEV_1 – These variables will be summarised using basic descriptive statistics (Mean, SD)). We will also consider using a mixed linear regression model, to estimate differences between the intervention group supported with 95% CI adjusting for, baseline recording (key variables to be identified) and minimisation variables (listed under section 6.3.1) (centre will be included as a random effects variable).

Health-related quality of life questionnaires - EQ5D-5L and COPD Assessment Test (CAT)) will be converted into scores and analysed using mixed linear regression model, adjusting for the intervention group, baseline recording (if available) and minimisation variables (listed under section 6.3.1) (centre will be included as a random effects variable).

Number of A&E visits, patient defined exacerbations and healthcare utilisation - Where the patient experienced an episode the data during the 12 month from randomisation these will be analysed using mixed effects log-binomial regression techniques with presentation of relative risk and 95% confidence intervals. Furthermore sensitivity analysis based on patients' experience of multiple visits

to A&E and patient defined exacerbation will be analysed using Poisson regression techniques and relative risk supported with 95% CI will be calculated.

Symptom control marker association to clinical decision - The diagnostic accuracy of Predict&Prevent AECOPD and Usual care will be evaluated by calculating sensitivity, specificity, positive and negative predictive values and area under the receiver operating characteristic curves (AUC) together with 95% CI.

13.2.3. Subgroup Analyses

Subgroup analyses will be limited to the same variables used in the minimisation algorithm (see section 6.2), apart from centre. Tests for statistical heterogeneity (e.g. by including the treatment group by subgroup interaction parameter in the statistical model) will be performed prior to any examination of effect estimate within subgroups. The results of subgroup analyses will be treated with caution and will be used for the purposes of hypothesis generation only.

13.2.4. Missing Data and Sensitivity Analyses

Every attempt will be made to collect full follow-up data on all study participants; it is thus anticipated that missing data will be minimal. Participants with missing primary outcome data will not be included in the primary analysis in the first instance. This presents a risk of bias, and sensitivity analyses will be undertaken to assess the possible impact of the risk. This will consist of simulating the missing response using a multiple imputation approach. Parameters used to simulate the missing response will include the minimisation variables, intervention group and previous response. Full details will be included in the Statistical Analysis Plan.

13.3. Planned Interim Analysis

Interim analyses of safety and efficacy for presentation to the independent DMC will take place during the study. The committee will meet prior to study commencement to agree the manner and timing of such analyses but this is likely to include the analysis of the primary and major secondary outcomes and full assessment of safety (SAEs) at least at annual intervals. Criteria for stopping or modifying the study based on this information will be ratified by the DMC. Details of the agreed plan will be written into the Statistical Analysis Plan. Further details of DMC arrangements are given in section 14.5.

13.4. Planned Final Analyses

The primary analysis for the study will occur once all participants have completed the 12 months assessment and corresponding outcome data has been entered onto the study database and validated as being ready for analysis. This analysis will include data items up to and including the 12 months assessment and no further.

13.5. Health Economic Evaluation

The economic evaluation will assess the cost-effectiveness of the intervention versus standard care in patients with COPD. Hospital admission is the primary outcome of the clinical trial, and therefore it is important to evaluate the cost-effectiveness of the intervention based on this outcome. The National Institute for Health and Care Excellence (NICE) recommend the use of QALYs in economic

evaluations to allow comparisons across different diseases and interventions. Therefore, the evaluation will take the form of i) an incremental cost-effectiveness analysis to estimate cost per hospital admission avoided and ii) an incremental cost-utility analysis to estimate cost per quality adjusted life year (QALY). Both analyses will be from an NHS perspective over 12 months follow-up using patient level data on costs and outcomes from the trial. A secondary analysis will consider broader societal costs.

Data collection: Data on hospital admissions will be collected from patient testimony and centrally held healthcare records, as previously specified; the total number of medically confirmed AECOPD from these sources will be used in the economic evaluation. This is because self-reported data that does not result in a medically confirmed event or healthcare resource use (e.g. unreported AECOPD, reported events that the patient self-manages without new medication) will not be relevant for the economic evaluation. Resource use information will also be collected from patients on COPD-related primary care visits, visits to other health care professionals, prescribed medications, and hospital admissions (A&E, length and nature of inpatient admissions) at 3, 6, 9 and 12 months. Information will also be collected on private health care, out of pocket expenses, and time off work and other activities (leisure, caring responsibilities) to estimate broader societal costs.

The cost of the intervention will be calculated by undertaking a detailed cost analysis of Predict&Prevent to the NHS, considering costs of training, staff time, as aspects of the technology, consumables and equipment required for testing, but excluding protocol driven costs. ,. Unit costs from standard UK sources, for example NHS Reference costs will be sought for all health care resource use items. In order to calculate QALYs, the EQ-5D-5L questionnaire will be administered to patients at baseline, 3, 6, 9 and 12 months. The crosswalk value set will be applied to patient responses to obtain utility scores, in line with current NICE recommendations. The more recent English value set will be used in a sensitivity analysis.

Analysis: QALYs will be calculated using responses to the EQ-5D-5L, using the “area under the curve” approach. Unit costs will be applied to all health care resource use items, and mean resource use (for each category of health care usage) and mean total costs will be calculated for all trial participants. As cost data is likely to have a skewed distribution, the nature of the distribution of costs will be explored, and if the data is not normally distributed, a non-parametric comparison of means (using bootstrapping) will be undertaken. Multiple imputation will be used to impute all missing values for the EQ-5D and total cost estimates for non-responders.

A cost consequence analysis will initially be reported, describing all the important results relating to costs and consequences (across the full range of clinical outcomes). Incremental cost-effectiveness and cost-utility analyses will then be undertaken to estimate the incremental cost per hospital admission avoided and cost per QALY gained respectively, with adjustment for baseline covariates. The robustness of the results will be explored using sensitivity analysis. This will explore uncertainties in the trial based data itself, the methods employed to analyse the data and the generalisability of the results to other settings. Cost-effectiveness acceptability curves will also be produced to reflect the probability the intervention will be cost effective at different cost per QALY willingness to pay thresholds.

A Health Economic Analysis Plan (HEAP) will be developed which will describe this analysis in greater detail.

14. CLINICAL INVESTIGATION ORGANISATIONAL STRUCTURE

14.1. Sponsor

The University of Birmingham is the Sponsor for this Clinical Investigation.

14.2. Coordinating Centre

BCTU is the Coordinating Centre. Delegation of tasks to the BCTU, from the Sponsor, are documented in the **Predict&Prevent AECOPD Clinical investigations Task Delegation Log**.

14.3. Clinical Investigation Management Group

The Clinical Investigation Management Group (membership detailed in the Administrative Information section above) will monitor all aspects of the conduct and progress of the clinical investigation, ensure that the Clinical Investigation Plan is adhered to and take appropriate action to safeguard participants and the quality of the clinical investigation itself**.**

Meetings will be approximately monthly and may be face-to-face or via teleconference.

14.4. Clinical Investigation Steering Committee

A single CISC will be created for the **Predict&Prevent AECOPD Clinical investigation** and meet face-to-face or via teleconference at least once prior to recruitment of the first patient, then at least annually until the **Predict&Prevent AECOPD Clinical investigation** database is “hard locked”, and as required depending on the needs of the clinical investigation office.

Membership and duties/responsibilities are outlined in the CISC Charter. In summary, the CISC will: provide overall oversight of the clinical investigation, including the practical aspects of the study, as well as ensuring that the study is run in a way which is both safe for the participants and provides appropriate feasibility data to the sponsor and investigators.

14.5. Data Monitoring Committee

Data analyses will be supplied in confidence to an independent Data Monitoring Committee (DMC), which will be asked to give advice on whether the accumulated data from the clinical investigation, together with the results from other relevant research, justifies the continuing recruitment of further participants. The DMC will operate in accordance with a clinical investigation specific charter. The DMC will meet at least annually as agreed by the Committee and documented in the Charter. More frequent meetings may be required for a specific reason and will be recorded in minutes.

Additional meetings may be called if recruitment is much faster than anticipated and the DMC may, at their discretion, request to meet more frequently or continue to meet following completion of recruitment. An emergency meeting may also be convened if a safety issue is identified. The DMC may consider recommending the discontinuation of the clinical investigation if the recruitment rate or data quality are unacceptable or if any issues are identified which may compromise participant

safety. The clinical investigation will stop early if the interim analyses showed differences between interventions that were deemed to be convincing to the clinical community.

14.6. Finance

The National Institute for Health Research (NIHR) is funding this clinical investigation. Clinical Research Network (CRN) support will be sought, as appropriate. Excess cost for the study remains part of NHS costs while study resources outside routine care and not covered by the CRN will be supported in the form of per patient payments to a maximum of £300 per patient. Tablet devices will be centrally purchased by UoB and provided to patients for the duration of the study.

15. ETHICAL CONSIDERATIONS

The clinical investigation will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, 1964, amended by the 48th WMA General Assembly, Somerset West, Republic of South Africa, 1996 (website: http://www.wma.net/en/30publications/10policies/b3/index.html).

The clinical investigation will be conducted in accordance with the UK Policy Framework for Health and Social Care, the applicable UK Statutory Instruments, (which include the Data Protection Act 2018) and the Principles of GCP, the Human Tissue Act (2008), the Medical Devices Regulations (2002) (SI 618) and Annex X of the Medical Devices Directive 93/42 . The Clinical Investigation Plan will be submitted to and approved by the main REC prior to circulation.

Before any participants are enrolled into the clinical investigation, the PI at each site will obtain local R&D approval/assurance. Sites will not be permitted to enrol participants until written confirmation of R&D approval/assurance is received by the BCTU clinical investigations team.

It is the responsibility of the PI to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual participants.

16. CONFIDENTIALITY AND DATA PROTECTION

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act 2018.

Participants will always be identified using their unique clinical investigation identification number, date of birth and initials via the App and on any Case Report Forms as well as correspondence within the BCTU. Participants will give their explicit consent for the movement of their consent form, giving permission for BCTU to be sent a copy. This will be used to perform in-house monitoring of the consent process.

The Investigator must maintain documents not for submission to BCTU (e.g. Participant Identification Logs) in strict confidence. In the case of specific issues and/or queries from the

regulatory authorities, it will be necessary to have access to the complete clinical investigation records, provided that participant confidentiality is protected.

BCTU will maintain the confidentiality of all participant's data and will not disclose information by which participants may be identified to any third party other than those directly involved in the treatment of the participant and organisations for which the participant has given explicit consent for data transfer. Representatives of the **Predict&Prevent AECOPD Clinical investigation** team and sponsor may be required to have access to participant's notes for quality assurance purposes but participants should be reassured that their confidentiality will be respected at all times.

17. FINANCIAL AND OTHER COMPETING INTERESTS

The CI does not have any relevant direct financial disclosures, nor do members of the TMG with the exception of Neil Patel, who is a founder, director and share-holder of NEPESMO, who own the intervention.

The CI has grants from pharmaceutical companies working in the area of COPD (Chiesi, AstraZeneca) and has conducted advisory work for such (Boehringer, CSL Behring) but not in the area of medical devices or admission prevention. Neither has she worked for, or received monies from, any company working on admission prevention in the last 3 years.

18. INSURANCE AND INDEMNITY

The University of Birmingham has in place Clinical investigations indemnity coverage for this clinical investigation which provides cover to the University for harm which comes about through the University's, or its staff's, negligence in relation to the design or management of the clinical investigation and may alternatively, and at the University's discretion, provide cover for non-negligent harm to participants.

With respect to the conduct of the clinical investigation at Site and other clinical care of the participant, responsibility for the care of the participants remains with the NHS organisation responsible for the Clinical Site and is therefore indemnified through the NHS Litigation Authority.

The University of Birmingham is independent of any pharmaceutical company, and as such it is not covered by the Association of the British Pharmaceutical Industry (ABPI) guidelines for participant compensation.

19. POST-CLINICAL INVESTIGATION CARE

Participants and clinicians who want to continue to use the system at the end of the clinical investigation would only be able to do so if the system is to be procured by the relevant trust. In these circumstances it may be possible to negotiate with the owners (NEPESMO) several months prior to the end of the study to ensure there is no gap in the continuity of care.

20. PUBLICATION POLICY

Results of this clinical investigation will be submitted for publication in a peer reviewed journal. The manuscript will be prepared by the **Predict&Prevent AECOPD CIMG** and authorship will be determined by the clinical investigation publication policy.

Any secondary publications and presentations prepared by Investigators must be reviewed and approved by the CISC. Manuscripts must be submitted to the CISC in a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues. Authors must acknowledge that the clinical investigation was performed with the support of University of Birmingham. Intellectual property rights will be addressed in the Clinical Investigation Site Agreement between Sponsor and site.

21. ACCESS TO FINAL DATA SET

Biological samples and the associated clinical Research Data will be owned by University Hospitals of North Midlands NHS Trust [UHNM]. As part of the Collaboration Agreement between UHNM, the University of Birmingham and NEPESMO Ltd, all Parties will have unrestricted access to and the right to use the collected Research Data from the current study for patient benefit, research, publications and teaching. Trial Data is owned by the University of Birmingham.

22. APPENDICES

22.1. Appendix 1 - COPDPredict™.

A pilot study recruited 90 patients with an established diagnosis of chronic obstructive pulmonary disease (COPD) and who had a history of frequent exacerbations (that is 2 or more acute exacerbations per year) were evaluated using COPDPredict™ in clinical feasibility studies. The studies were conducted following research ethics approval from the North West - Greater Manchester Central Research Ethics Committee [reference numbers 15/NW/0638 and 12/NW/0623].

The demographics of the patients taking part are shown in Table 22.1

Table 22.1 Characteristics of the Study Population at Baseline (n = 90).

Demographics	(n = 90)
Age, [a]years	68.7 ± 8.2
Gender, Male (Female)	45 (45)
Duration of COPD, [a]years	9.0 ± 6.9
FEV_1, [a] (% predicted)	49.9 ± 19.6

FVC, [a] (% predicted)	**76.3 ± 15.5**
BMI, [a](kg/m^2)	**27.0 ± 5.4**
MRC Score, [b] n	**3.00, 2.00**
Exacerbations in the last 1 year, [a]n	**4.0 ± 2.3**
Co-morbidities	
None	**20**
Cardiovascular	**38**
Type 2 Diabetes Mellitus	**14**
Gum Disease	**1**
Other	**23**
COPD Treatment	
β_2-Agonists, Short Acting, (Long Acting)	**88, (79)**
Anticholinergic, Short Acting, Long Acing)	**7, (67)**
Inhaled Steroid	**78**
Oral Theophyllines	**17**

The total duration of all COPDPredict™ was mean ± standard weeks per patient. For COPD patients were two cohorts: 80 experienced their trial period "exacerbators") and 10 stable throughout the exacerbators"). The further sub-divided into exacerbators (n = 28). participation for the exacerbator cohort (n = weeks and for the non-10) was 21.7 ± 12.0 COPD patients utilising 1342.29 weeks with a deviation of 14.9 ± 9.0 data analysis, the 90 further sub-divided into patients who exacerbations during (termed patients who remained trial (termed "non-exacerbator cohort was single (n = 52) and re-The length of study COPD patients in the 80) was 14.8 ± 7.9 exacerbator cohort (n = weeks.

Subject Characteristics and Study Design

From November 2012 to July 2014 and June 2016 to February 2018, individuals were recruited consecutively from University Hospitals of North Midlands (UHNM) NHS Trust research and outpatient clinic databases; their history satisfied inclusion criteria of: (i) established COPD confirmed by spirometry according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria; (ii) known frequent exacerbations with two or more documented COPD episodes a year; and (iii) ex-smokers for one year with a minimum 20 pack year history. Individuals with other respiratory disorders were excluded. All participants were accustomed to self-managing their disease and had 'rescue' medication of a 7-day course of antibiotics [amoxicillin 500mg three times a day or doxycycline 200mg on first day followed by 100mg daily for 6 days] and steroids [prednisolone 30mg daily] which they normally used if they felt they had an acute exacerbation.

At enrolment, participants had to be clinically stable and exacerbation-free for at least six weeks prior to the study. The study was community-based, and participants were monitored in their homes from enrolment at stable baseline through their exacerbation period and two weeks' post-exacerbation recovery. Exacerbation length was defined as the period between the date on which an exacerbation was confirmed and the date on which the participants reported a return to their normal breathing and completed treatment. Those participants who felt a further deterioration of their COPD and need for recommencing treatment during the 14 days post-their index episode [defined as a re-exacerbation], continued to be monitored until they reported a return to their usual self. During the study period, treatment could also be initiated if a clinical deterioration was noted by the research team. In this way exacerbations and recovery were patient and/or clinician defined.

At visit 1, participants were provided with a tablet computer pre-installed with COPDPredict™ App and a unique user-login identification number. A hand-held portable spirometer: Smart Lung Monitor (Vitalograph, Ireland) was also provided to allow spirometric volumes (FEV_1) to be independently measured by participants. This device was paired to COPDPredict™ to permit synchronisation of the data between the spirometer and the App. Demographic details were recorded including, clinical history, duration of COPD diagnosis, smoking history, modified Medical Research Council (MRC) dyspnoea score, childhood and other respiratory diseases, co-morbidities and medications; participants with any infection or unstable illness in the preceding 6 weeks were excluded. Unstimulated whole saliva collected (2ml) and blood sampling was also undertaken. Each participant then received a "walk-through" on how to use COPDPredict™ including how to complete and submit their wellbeing scores alongside spirometry.

Following visit 1, participants entered a 2 week "run-in" phase with daily wellbeing self-assessment and alternate day spirometry and saliva/blood sampling for biomarker (C-Reactive protein: CRP) levels. This established their baseline levels for the 3 metrics. Subsequent to this, participants completed the wellbeing diary daily, spirometry and saliva sample weekly and blood samples were obtained at key time-points (stable, prodromal, exacerbation, post-exacerbation recovery). Patients were followed up weekly in their own home to obtain a sample of saliva/blood and update the clinical history. In-between scheduled visits, participants were informed that their metrics would be remotely monitored daily and that a change in symptoms/spirometry (algorithm), and/or diary non-completion would trigger a notification and/or visit from the research team. At this visit the research team would perform a clinical check-up, spirometry and saliva/blood sampling.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics Version 21 (IBM, USA). Parametric data were expressed as mean ± standard deviation, and non-parametric as median, interquartile range. For parametric data between-group comparison was performed using a paired t-test. The output from the algorithm was compared to the patient/clinician reported health status to identify the sensitivity and specificity of the algorithm to identify acute exacerbations. A Bonferroni correction was applied in cases of multiple comparison testing. A p-value of less than 0.05 was considered statistically significant.

Results

Pre COPDPredict™ exacerbation and hospitalisation rates compared to the period in which the system was used. Across the whole group there were a total of 109 exacerbations; 106 treated with antibiotics, 93 with steroids and 14 escalated to nebulised salbutamol. In brief the results showed that number of hospitalisations was reduced from 90 to 3 in the group, representing a greater than 95% reduction in admissions ($p<0.001$). Hospitalisation rate was 1/year in the period prior to COPDPredict™ and 0.16/year in the COPDPredict™ period. There were no significant App related adverse events and App failure rate (defined as significant App dysfunction which resulted in corrupted data) did not occur.

Algorithm Data

In total 3257 unique time-points of patient/clinician reported health status were compared to the reported health status from the constructed algorithms to determine sensitivity and specificity.

Wellbeing score + Spirometry

Sensitivity = 77%, Specificity = 65%

Wellbeing score + Spirometry + CRP

Sensitivity = 98%, Specificity = 84%

End-users' experience of using COPDPredict™

A formal qualitative study by an independent clinical psychologist explored patients' attitudes to using COPDPredict™ in their everyday management of their COPD at home. One to one interviews were held with patients.

Extracted quotes from the interviews include:

- "One of the things that I found most useful was to see the results of my daily diary, my spirometer tests in graphic form, so easy to see";
- "… I'm more confident about my self-management";
- "… it gives you more confidence and direction";
- "… before I didn't even look at the colour of my sputum or think about how I feel but I do now."
- "… straightforward… I'm not brilliant with electronics but yes I found it very easy."
- "… I like to share my progress with my family …it gives them greater understanding of my condition".

Economic Evaluation.

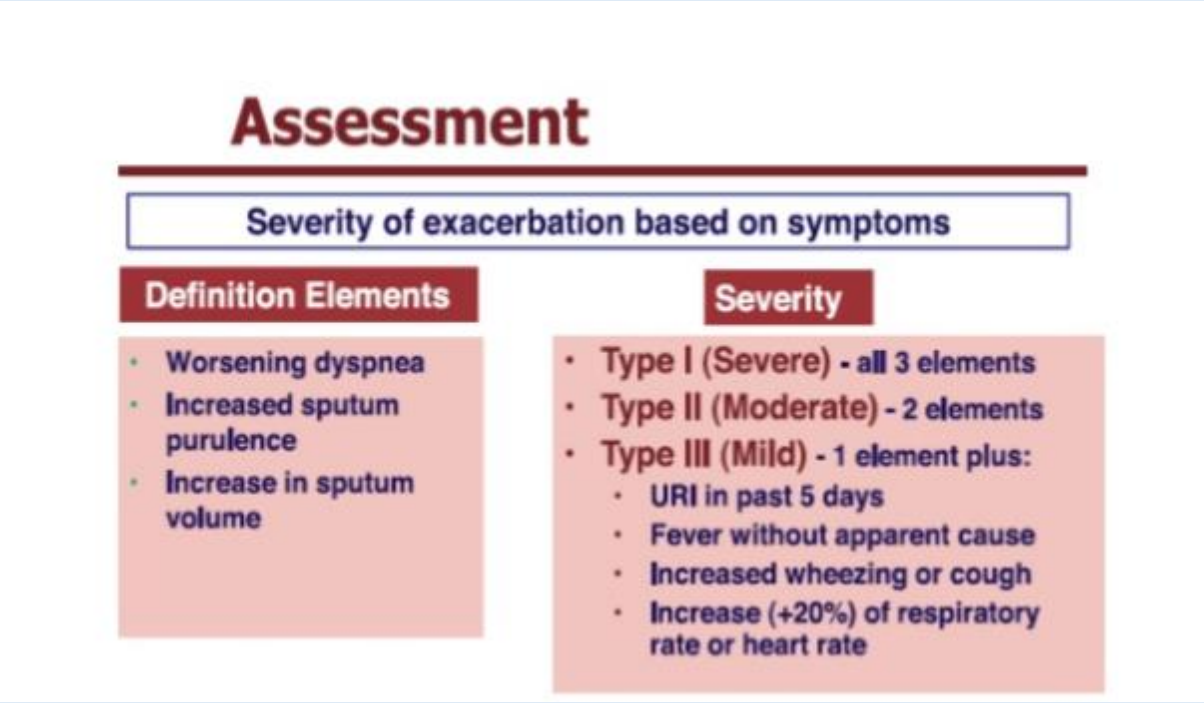
Within the 90-participant population:

Pre - COPDPredict™
90 hospital admissions costing £3.76K, per patient.
90 patients' mean length of stay: 5days
Monitoring Costs - £0 per patient.
Total Cost - £338.4K
Total Bed Days - 450

With - COPDPredict™
3 hospital admissions - £2.0K per patient
2 patients mean length of stay: 1 day
Monitoring Costs £500 per patient per annum
Total Cost £51.0K
Total Bed Days - 2

COPDPredict™ Economic Impact
Cost Savings: £287.4K
Bed Days Released: 448.

22.2. Appendix 2 – Anthonisen Criteria



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