**Maximizing Adherence and Gaining New Information For Your Chronic Obstructive Pulmonary Disease (MAGNIFY COPD): Study Protocol for the Pragmatic, Cluster Randomized Trial Evaluating the Impact of Dual Bronchodilator with Add-on Sensor and Electronic Monitoring on Clinical Outcomes**

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**SUPPLEMENTARY FILES**

* **Supplementary file S1:** InterventionPackage
* **Supplementary file S2:** Data Analysis
* **Supplementary file S3:** Statistical Analysis
* **Supplementary file S4:** Ethics Approval and Data Dissemination

**Supplementary file S1**

**Intervention package**

The intervention package consists of the dual bronchodilator indacaterol/glycopyrronium Breezhaler® with an add-on inhaler sensor device and connected mobile application, developed and manufactured by Propeller Health (Wisconsin, US).

1. Indacaterol/glycopyrroniumBreezhaler®

* Indacaterol/glycopyrronium Breezhaler® is available in the United Kingdom (UK), but patients on other treatments can also be included in the study if their primary care practitioner initiates them on indacaterol/glycopyrronium based on their medical discretion and aligned with current clinical guidance.
* The study will not assess the impact of the technology alone, but rather the combined impact of a package that includes
  + identifying and inviting patients with poor outcomes and poor adherence to current treatment
  + initiating on indacaterol/glycopyrronium Breezhaler® (if not previously prescribed)
  + adopting the adherence technology, and
* discussions with the healthcare professionals (HCPs) who are instructing the patients on use of this technology

1. Add-on sensor

* The add-on sensor device is a customisable class I medical device certified with a Conformité Européene (CE) mark. The device is developed for the indacaterol/glycopyrronium inhaler by Propeller Health (Wisconsin, US). The add-on sensor device includes a microchip, a microphone, Bluetooth capabilities, an antenna and a battery.
* The additional electronics do not alter the drug delivery characteristics of the inhaler, but produce a recording of each administered dose and a date and time stamp whenever the patient inhales a dose from the device.27
* These data can then be interpreted and specific appropriate feedback to the patient is provided via the app. Based on the patient’s medication usage, patients are presented with personalised content in the app, such as educational information about their inputted medication usage trends, to help them better self-manage their COPD.

1. Application

The patient application requires a standard smartphone running on one of the latest two versions of an iOS or Android operating system and require an internet connection. The intended use of the application is to monitor adherence to COPD maintenance therapy medication delivered through the indacaterol/glycopyrronium inhaler. Functionalities of the app include the following:

* Initial setup
* Connecting and pairing with the indacaterol/glycopyrronium add-on device
* Receiving information from a paired indacaterol/glycopyrronium add-on device
* Providing ‘Did You Know Cards’ (share useful or interesting general tips or facts)
* Displaying dose reminders and daily schedules (tracks when and whether or not the patient has taken each dose for the day)
* Displaying of statistics (graphic presentations of overall adherence to “on time” and missed doses)
* Changing of settings and sync reminders
* Performing COPD Assessment Test (CAT; patients can be reminded to take the CAT once per month. These notifications can also come as an email or SMS message)
* Providing a weekly COPD digest (patients can receive a weekly summary of their medication use via email)
* The add-on device will record the date and time each time the patient inhales via the connected indacaterol/glycopyrronium inhaler. The information will be transmitted to the patient’s application on the patient’s smartphone. If patients do not inhale their medication once daily as prescribed, the application will deliver reminders to the patients to inhale their medication. Each puff/inhalation that the patient takes is recorded. If there are multiple puffs taken within a two-minute window, this would be counted as one "event". The adherence calculation is puff-based.

**Web-based HCP portal**

* The portal for HCPs shares information on patient medication usage data collected from the patient app through the sensor and also self-reported usage. HCPs at the adherence support arm sites will be provided with information about, and access to the provider portal for patient monitoring and outreach during the study. HCPs at participating sites randomised to the adherence support arm will receive training from Propeller Health or the sponsor on the use and functionalities of the provider portal and can determine how to integrate this information into their patient care workflow.
* In order to set up the patient on the portal, the HCP will create a patient account and indicate what sensor was provided for their indacaterol/glycopyrronium Breezhaler®. Providers can then log into the provider portal at any time to see their patients’ maintenance medication adherence data and additional details, such as most recent CAT results, medication schedule, and contact and sensor information.
* The HCPs on all sites, which are randomised to the adherence support cluster arm, will receive training from Propeller Health on the use of the add-on device and app. This training will also cover how the technology can be utilised by HCPs in their ongoing patient management, ie, to monitor adherence and COPD control via the provider portal, or through reviewing data recorded on the patient’s device at routine appointments. At the end of the study, each site will be asked whether they had used the provider portal and/or checked device data at routine appointments on a regular basis.

**Supplementary file S2**

**Data analysis**

* All participating practices must be able and willing to share their electronic health records with Optimum Patient Care (OPC) or another organisation specialized in primary care data extraction. Obtaining data in this manner permits data capture without burdening the practice or patients.
* All practices (adherence support and control) will be asked to use a specific read code for technology-accepting patients that will be used by data managers and statisticians to identify patients for distinguishing their data from patients suitable for technology.
* Post-one year, data extractions will be conducted to obtain clinical event data for the year before and the year after the practice randomization; the last recorded values for demographic and patient characterisation data (weight, height, smoking status etc.) will also be obtained (**Figure**).

**Figure: COPD study data flow and sources**



**Supplementary file S3**

**Statistical Analysis**

***Primary analyses***

* For primary analysis, time-to-treatment failure will be determined at the individual patient level, with standard errors adjusted for clustering of patients within the same practice. The primary comparison of study arms will be based on the intention-to-treat principle including all patients identified as suitable and accepting of new technology.
* A time-to-event analysis will be performed to analyse the association between intervention and time-to-first outcome event (treatment failure) with censoring at the time of death or loss to follow-up. Kaplan-Meier curves will be used to describe event-free survival over time and comparisons. Cox regression, with random effects for the practice and fixed effects for the stratification factors used in the randomisation algorithm, will be performed with time-to- first event as the outcome variable to estimate hazard ratios with 95% confidence intervals of the treatment effect.
* The proportional hazard assumption will be evaluated visually by means of a log-log plot of survival. If the assumptions of proportional hazards are not met then the results will be presented using the restricted mean survival time at an appropriate time point.
* Negative binomial regression will be used to compare count outcomes, and logistic regression will be used to compare binary outcomes. Both will include random effects for the practice and fixed effects for the stratification factors used in the randomization algorithm. Key outcome predictors (ie smoking status, age, exacerbation history) will also be included in the primary analysis model as pre-specified covariates. No imputing will be performed.

***Exploratory and sensitivity analyses***

For respiratory-related healthcare resource utilization and costs, we will use the cluster-adjusted independent student’s t-test to compare the parameters between the two arms. In the event of severe imbalance in important risk factors between the arms, we would use the random effect linear regression model to analyze the data. Analysis will be performed on intention-to-treat basis.

To assess potential sources of bias, the following sensitivity analyses will be conducted:

* Analysis of the primary endpoint using the date of first prescription for COPD therapy post-practice randomization as the index date in the control group
* Analysis of the primary endpoint using the date of first primary care practitioner consultation (any clinical consultation) after practice randomisation as the index date in the control group
* Analysis of the primary endpoint using a modified definition of treatment failure, where prescription of any additional inhaled maintenance therapy (addition of inhaled corticosteroids [ICS], long-acting β2 agonists [LABA] or long-acting muscarinic antagonists [LAMA]) is considered treatment failure, ie, treatment failure is defined as:
* Moderate/severe COPD exacerbation, or
* Prescription of any additional inhaled maintenance therapy (addition of ICS, LABA or LAMA), or
* Prescription of additional chronic therapy, or
* Respiratory-related death

**Supplementary file S4**

**Ethics Approval and Data Dissemination**

* The staff at participating sites must comply with the NHS Confidentiality Code of Practice at all times, to protect the privacy of their patients. Optimum Patient Care Research Database (OPCRD) is fully compliant with the EU General Data Protection Regulation and does not include any personally identifiable information. The study will be submitted for adoption into the National Institute for Health Research Clinical Research Network Portfolio and registered with European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. Written informed consent from patients is not required, as extracted data is completely anonymized.
* In order to disseminate our research outputs to a wider audience, we will make presentations at international congresses and local workshops, and all publications from this study will report results in accordance with the current “Uniform Requirements for Manuscripts Submitted to Biomedical Journals” as established by the International Committee of Medical Journal Editors (ICMJE; www.ICMJE.org). Authorship will be determined in accordance with ICMJE guidelines and any other contributors will be acknowledged. We will engage with policymakers by participating in organized events where we can showcase the study findings and publications, and interact with policymakers and the general public.