Study Protocol

Study Protocol Number	MS202559_0001
Title	A study to investigate the association of real-world sensor-derived biometric data with clinical parameters and patient-reported outcomes for monitoring disease activity in patients with COPD
Protocol version identifier	3.0
Protocol Date/Version	01 MAR 2023 / 3.0
Replaces Version	Not applicable
Product reference	Not applicable. No medical device or medicinal product is investigated in this study.
Sponsor	Merck Healthcare KGaA an affiliate of Merck KGaA, Darmstadt, Germany Frankfurter Str. 250 Darmstadt, Germany
Research question and objectives	**Primary Objectives:** 1. To describe the distribution of sensor collected data on physical activity, heart rate, heart rate variability, temperature, respiration rate, cough frequency, and sleep pattern, by severity of COPD exacerbations. 2. To predict moderate or severe COPD exacerbations by building a statistical model employing sensor-derived data and demographic and medical covariates. **Secondary Objectives:** 3. To evaluate the correlation of sensor collected data with a) patients' self-assessed health status and symptoms (CAT) at baseline and study end, b) lung function and lab values at baseline and study end, c) and with history of mild, moderate and severe exacerbations at study end. 4. Sensor derived data may be related to the CAT score, therefore, an additional objective is to investigate whether changes physical activity, heart rate, heart rate variability, temperature, respiration rate, cough frequency, and sleep pattern in the 3-month observation period, are associated with changes of the patient self-assessed symptoms (CAT). 5. To predict the CAT score and changes thereof by building a statistical model employing sensor-

	derived data and demographic and medical covariates.
Country(-ies) of study	Germany
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2 List of Abbreviations

AE	Adverse Event
AECOPD	Acute Exacerbation of COPD
BfArM	Bundesinstitut for Arzneimittel und Medizinprodukte
BGA	Blood Gas Analysis
CAT	COPD Assessment Test
CBC	Complete Blood Count
CDB	Clinical Database
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CRO	Contract Research Organization
eCRF	Electronic Case Report Form
CRP	C-Reactive Protein
ECG	Electrocardiogram
EDC	Electronic Data Capture
FEV1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
IAP	Integrated Analysis Plan
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LOCF	Last Observation Carried Forward
LTE	Long Term Evolution (Phone)
MCID	Minimal Clinically Important Difference
MDR	Medical Device Regulation
MPDG	Medizinprodukterecht-Durchführungsgesetz
PRO	Patient Reported Outcomes
RPM	Remote Patient Monitoring

SADE	Serious Adverse Device Effects
SAE	Serious Adverse Event
SoA	Schedule of Assessments

3 Responsible Parties

Responsible Parties	**Contact Details**
Coordinating Investigator	Univ.-PPD D-69126 Heidelberg, Germany
Protocol Lead	PPD Merck Healthcare KGaA Frankfurter Str. 250 64293, Darmstadt, Germany
Clinical Research Organization (CRO)	palleos healthcare GmbH Taunusstraße 5a 65183 Wiesbaden, Germany

3.1 Responsibilities of the Investigator

The Investigator is responsible for the conduct of the study at his/her site. He/She will ensure that the study is performed in accordance with the protocol and will ensure the quality and integrity of data, following all applicable international and national guidelines.

This study will not interfere with any treatment or any prescription by Investigators. Accordingly, the Investigator will decide in advance the best therapeutic strategy as well as monitoring of the underlying disease for each patient according to current practice, regardless of the potential participation of this patient in the study. Subsequently, the Investigator will consider the possibility of including the patient in the study.

The Investigator is responsible for adverse reaction and/or laboratory abnormalities recording and reporting, as specified in Section 11.

4 Abstract

Title	A study to investigate the association of real-world sensor-derived biometric data with clinical parameters and patient-reported outcomes for monitoring disease activity in patients
Rationale and background	Remote patient monitoring (RPM) using wearable sensors has the potential to improve Chronic Obstructive Pulmonary Disease (COPD) patients' treatment and outcome by providing patients and physicians with early actionable insights, therefore reducing, or preventing exacerbations and increasing the quality of life. Previous published studies on sensor-based remote patient monitoring in patients with COPD suggest that such an approach is scientifically feasible and clinically promising, especially for decreasing the number of hospitalizations associated with exacerbations and improving overall outcome. The purpose of this study (designated as "Sonstige Klinische Prüfung" (other clinical study) as per Art. 82 Regulation (EU) 2017/745 /§3 No. 4 MPDG) is to generate biometric sensor-derived data, correlate them to clinical parameters and patient reported outcomes and develop predictive models for COPD exacerbations and patients' disease status as a basis for a future RPM solution for patients with COPD.
Research question and objectives	**Primary Objectives:** 1. To describe the distribution of sensor collected data on physical activity, heart rate, heart rate variability, temperature, respiration rate, cough frequency, and sleep pattern, by severity of COPD exacerbations. 2. To predict moderate or severe COPD exacerbations by building a statistical model employing sensor-derived data and demographic and medical covariates. **Secondary Objectives:** 3. To evaluate the correlation of sensor collected data with a) patients' self-assessed health status and symptoms (CAT) at baseline and study end, b) lung function and lab values at baseline and study end, c) and with history of mild, moderate and severe exacerbations at study end. 4. Sensor derived data may be related to the CAT score, therefore, an additional objective is to investigate whether changes in physical activity, heart rate, heart rate variability, temperature, respiration rate, cough frequency, and sleep pattern in the 3-month observation period, are associated with changes of the patient self-assessed symptoms (CAT). 5. To predict the CAT score and changes thereof by building a statistical model employing sensor-derived data and demographic and medical covariates.

Study Design	This multicenter, prospective cohort study will be conducted at 11 sites in Germany, a cohort of participants with COPD GOLD stage II-IV will be followed for 3 months. During the Baseline visit each enrolled participant will be provided with a wearable device which records ECG, temperature and movement via an accelerometer and a connected smartphone and trained on the use of these devices. A study digital application is provided with the smartphone for the participants to fill in a daily COPD symptoms' questionnaire (CAT), label activities or events relevant for the interpretation of sensor signals, and receive notifications/reminders. During the 3-month observation period the participants will attend visits at sites as per routine clinical practice in case of exacerbations or regular COPD check-ups. At all visits at the study sites, assessments will be performed as per physician's judgement and routine clinical practice. At the end of the 3-month observation period, the participants will return the devices to the site during a regular COPD related visit scheduled at 3 months (± 14 days) after the baseline visit (Day 0). Additionally, a calibration cohort of non-COPD participants will be enrolled in an internal medicine center in Germany. The participants will use the wearable device during a 2-week observation period.
Population	**Key Inclusion criteria:** For participants with COPD: • Participants ≥40 and ≤80 years at baseline • Diagnosis of COPD stage II to IV (documented post-bronchodilator Forced Expiratory Volume in 1 second (FEV1)/ Forced Vital Capacity (FVC) < 0.7 and FEV1 < 80% predicted) • History of moderate or severe exacerbations (≥2 moderate exacerbations or ≥1 severe exacerbations in any 12-month time window during last 3 years prior to inclusion and ≥1 moderate or severe exacerbations in the last 12 months prior to inclusion, considering that the last 12 months may reflect lower exacerbation rate due to Covid-19 measures) For participants in the calibration cohort: • Participants ≥40 and ≤80 years at baseline **Key Exclusion criteria:** For participants with COPD: • Participants with a cardiac pacemaker, defibrillators, or other implanted electronic devices • Participants with known allergies or sensitivity to silicon or hydrogel • Less than 6 weeks since previous moderate/severe exacerbation

	For participants in the calibration cohort: • Participants with a cardiac pacemaker, defibrillators, or other implanted electronic devices • Participants with known allergies or sensitivity to silicon or hydrogel • Diagnosis of pulmonary disease including, but not limited to COPD, asthma, pulmonary fibrosis, with impact on the lung function and exercise capacity
Outcomes	The **primary outcome**, COPD exacerbations during observation period will be defined as follows: • For moderate/severe exacerbation requiring a physician's intervention, emergency room visit or hospitalization, the severity, date of the exacerbation, and the duration of the exacerbation will be recorded via eCRF. • For mild exacerbations: self-reported; treated by the participant without intervention by a physician will be documented in the patient application labeling section (days with added treatment). **Secondary outcomes** will be defined as follows: • Patients' health status and symptoms at baseline (Day 0) and study end will be measured as the summary score across items of the CAT questionnaire that consists of 8-items in which participants can choose a score from 0 to 5, for each visit. • Lung function will be assessed using plethysmography and lab values including complete blood count (CBC) with differential, blood gas analyses (BGA), procalcitonin and CRP will be assessed as per standard practice at baseline (Day 0) and at study end. • Number, date of onset and duration of mild, moderate, and severe exacerbations, respectively, during the observation period. • During the observation period the CAT score will be obtained on a daily basis. Daily summary score across items of the CAT questionnaire will be computed. • Patients' health status and symptoms at baseline (Day 0) will be measured as the summary score across items of the CAT questionnaire that consists of 8-items in which participants can choose a score from 0 to 5. During the observation period the CAT score will be obtained via a digital application on a daily basis.
Key Variables	Variables measured with the Vivalink wearable device (including, but not limited to): • Physical activity • Heart rate • Temperature • Respiration rate Self-measured Variables: • Data on Self-reported COPD symptoms will be collected via the CAT questionnaires using the participant app

	• Self-reported activities (e.g., coughing, sports, sleeping) as collected by the participant app • Self-reported satisfaction to the study, collected via end of study questionnaire Covariates will be collected from patient records (status at the time of Day 0, closest record prior to): • Demographics, Body mass index, Smoking status • Relevant medical history, comorbidities, current medication including COPD treatment at baseline • Date of diagnosis of COPD and COPD severity (GOLD stage) • Number of moderate or severe exacerbations prior to baseline visit (at Day 0, moderate/severe exacerbation visit and End of study visit): • Current body plethysmography parameters • Current (capillary) pO2, O2 saturation and pCO2 Several biomarkers at the time of baseline depending on availability
Data Sources	The data source used for this study will consist of patients charts from 11 sites (mainly pulmonology private practices) in Germany as well as from a device, which will get handed out to the participant. The data informing this study will be extracted from patient medical records using eCRF directly in an electronic data capture system. In addition, a patient reported outcomes (PRO) questionnaire (COPD assessment tool [CAT], filled in by the participant electronically), and a wearable device (adhesive patch device with sensors) will be used for data collection.
Study Size	Sample size required to show a sensitivity of ≥0.85 for a model predicting moderate to severe COPD exacerbations was estimated to be 67 participants including a drop-out rate of 10%. The study will also observe 10 participants in the calibration cohort for 2 weeks. The number of participants for this cohort is chosen on an exploratory basis.
Data Analysis	Sensor collected data on physical activity, heart rate, heart rate variability, temperature, respiration rate, cough frequency, sleep pattern, at baseline, and shortly prior (14 days prior to, 7 days prior) to, during an exacerbation and after an exacerbation (8 to 14 days after, 2 weeks after, 3 weeks after, up to 4 weeks after an exacerbation) will be reported as mean (SD) and/or median (Interquartile Range) for continuous variables and counts and frequency (%) for categorical variables. A statistical model employing sensor collected data to predict COPD exacerbations will be built as follows: As input to the model a number of algorithms (e.g. self-learning algorithms) for obtaining derived parameters such as cough frequency, physical activities and sleep pattern will be developed first using the label dataset obtained via the app.

	Different machine learning algorithms will be evaluated, and their performance will be assessed by estimating their accuracy, specificity, sensitivity, and area under ROC metrics.

5 Amendments and Updates

The following amendments and updates to the protocol were implemented.

Protocol Number	Date	Section of Study Protocol	Amendment or update	Reason
3.0	01 MAR 2023	throughout	Changed the number of study centers from “up to 10” to “11”.	To achieve enrolment more than anticipated study centers need to be activated.
2.0	21 OCT 2022	9.2.1	Added capability of giving signed informed consent to in-/exclusion criteria.	EC request
		9.2.4	“Data collection via App (labeling events and activities)” added to Table 5: Planned Assessments Calibration Cohort	Correction of oversight.
		9.10.1	Addition of Section 9.10.1 Ethical Conduct of the Study	EC request to add a statement of compliance
		9.10.6	Addition of Section 9.10.6 Medical Device Supply, Accountability and Handling	EC request to add a description on the accountability of the device.
		10.1	Deleted possibility to delegate patient informed consent taking	EC request to clarify that informed consent is given exclusively by investigators.
		throughout	Correction of typos and spelling of units	Correction of oversights.

6 Milestones

Not applicable as no existing databases are used.

7 Rationale and Background

Chronic Obstructive Pulmonary Disease (COPD) is a progressive life-threatening lung disease with no curative treatment available (Christenson 2022). According to the World Health Organization (WHO), COPD is currently the fourth, and will soon become the third, most frequent cause of death worldwide (WHO 2022; Quaderi 2018). It is also associated with high costs for treating and managing patients (Sullivan 2000). The Global Burden of Disease Study reports a prevalence of 251 million cases of COPD globally in 2016.

COPD exacerbations are defined as an acute worsening of respiratory symptoms that result in additional therapy (GOLD 2022). Exacerbations usually cause further damage to the lungs, lead to more rapid progression, and carry a substantial mortality risk (Rhodes 2022). Hence, frequency of exacerbations is an important efficacy endpoint in COPD clinical studies and pharmacological therapy of COPD is used to reduce frequency and severity of exacerbations. Exacerbations are classified by severity into severe, moderate and mild. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) consortium defines these as severe if they require hospitalization, moderate if they require added drug treatment from the group of systemic corticosteroids and antibiotics which requires a physician’s interaction, and mild if they can be treated by the patient by an additional (inhaled) drug without intervention of a physician (Vogelmeier 2017). The main target

of all therapeutic approaches are the severe and moderate exacerbations. Limited knowledge exists on the importance of mild exacerbations.

Most patients with COPD experience chronic respiratory symptoms and limitations to their daily lives such as chest tightness and shortness of breath, chronic cough and excessive mucus, activity and exercise limitations and impaired physical functioning (Kessler 2011; Landis 2014). The COPD Assessment Test (CAT) was developed according to the Food and Drug Administration's (FDA) patient reported outcome development guidance, and it is a short digital or paper tool that can be used to assess the symptoms of COPD (Jones 2013).

Since its launch in 2009, CAT has been used globally, with >90 approved and linguistically validated translations. Furthermore, clinical and observational studies, as well as randomized controlled trials, have used CAT as a measure of health-related quality of life (HRQoL) and clinical efficacy, respectively (Müllerová 2019).

The CAT has also been incorporated in the GOLD combined assessment to establish a threshold at which patients become symptomatic to justify and guide in the selection of treatment (Jones 2013) and is used in routine clinical practice. The score is higher in people with more frequent exacerbation and it changes with the onset and recovery from an exacerbation (Al Rajeh 2020, Zimmermann 2020). The 8 items of the CAT questionnaire provide a scoring range of 0 to 40. A 2-point change in the CAT score has been established as the Minimally Clinically Important Difference (MCID, Kon 2014). Importantly, the CAT closely reflects the functional status of patients with COPD (Gulart 2017).

Remote patient monitoring using wearable sensors has the potential to improve treatment and outcomes of patients with COPD by providing patients and physicians with early actionable insights, therefore reducing, or preventing exacerbations and increasing the quality of life. Previous published studies on sensor-based remote patient monitoring in patients with COPD suggest that such an approach is scientifically feasible and clinically promising, especially for decreasing the number of hospitalizations associated with exacerbations and improving overall outcome (Pedone 2013; McLean 2011; Isaranuwatchai 2018).

The purpose of this study (designated as "Sonstige Klinische Prüfung" [other clinical study] as per Art. 82 Regulation [EU] 2017/745 /§3 No. 4 Medizinprodukterecht-Durchführungsgesetz [MPDG]) is to generate biometric sensor-derived data, evaluate their correlation to clinical parameters and patient reported outcomes (PRO) and develop a predictive model for COPD exacerbations as well as for monitoring current disease status and changes thereof. In the this study the participants will receive a wearable device (Vivalink) with sensors that will measure heart rate, heart rate variability, respiration patterns, temperature, and physical activity. The analysis of this data will help to understand the utility of remote patient monitoring using a multimodal sensor approach and contribute to the development of a future remote patient monitoring solution. The purpose of this study is not to evaluate, validate, nor register the device itself, the device merely serves as a means for collecting the targeted sensor-derived data.

Specifically, this study aims at predicting 2 target outcomes: acute exacerbations of COPD (AECOPDs) as defined by the GOLD initiative, and the CAT score as a proxy for patients' disease status. The start of an exacerbation within a patient, regardless of how many exacerbations the patient may have experienced before, will be predicted based on sensor data preceding the

exacerbation, and using basic covariates as well. For type of exacerbations, the severe and moderate exacerbations are considered as our main target as these are linked to the need of urgent medical intervention and will predict those as a group, but also separately (distinguish by type), if possible. Mild exacerbations, the relevance of which is currently a subject of investigation in the field, will also be explored.

For the CAT score, the aim is to predict the total score (max = 40) from the sensor data, and changes in the CAT score of ≥ 2 based on the MCID. With this approach, it is aimed to use the model built on sensor data as an objective means to reflect patients' disease status. While for the prediction of exacerbations the aim is to predict them as early as possible, i.e. days before an exacerbation, for the CAT/disease status prediction the aim is to reflect the daily status.

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This study is exploratory in nature and any predictive models will need to be validated in future studies. A future remote patient montoring (RPM) solution for patients with COPD built on these models will have 2 prime utilities: First, ameliorating or preventing exacerbations and their negative sequelae by early treatment intervention and second, to provide physicians and patients with a highly granular and precise view on the current disease status and past changes. Such information can be used by the treating physician to optimize therapeutic regimens and by the patients to accompany and optimize lifestyle changes. By using a multimodal sensor approach we intend to increase the accuracy of our predictive models beyond what has been described in the literature and thereby increase their clinical utility.

8 Research Question and Objectives

The aim of the study is to investigate the correlation of real-world sensor-derived biometric data obtained via a wearable device with clinical parameters and PROs for monitoring disease activity and predicting exacerbations for patients with COPD.

Participants with COPD and participants in the calibration cohort will receive a wearable device to measure physiological parameters during normal daily activities and sleep and will use a digital application to daily record symptoms, events, and/or activities. The sensor-collected data will be statistically explored, and algorithms derived for a.) predicting exacerbations b.) assessing the health status and changes in the health status of the participant.

8.1 Primary Objectives

1. To describe the distribution of sensor collected data on physical activity, heart rate, heart rate variability, temperature, respiration rate, cough frequency, and sleep pattern, by severity of COPD exacerbations.
2. To predict moderate or severe COPD exacerbations by building a statistical model employing sensor-derived data and demographic and medical covariates.

8.2 Secondary Objectives

3. To evaluate the correlation of sensor collected data with

   a) patients' self-assessed health status and symptoms (CAT) at baseline and study end,

   b) lung function and lab values at baseline and study end,

   c) and with history of mild, moderate and severe exacerbations at study end.

4. Sensor derived data may be related to the CAT score, therefore, an additional objective is to investigate whether changes in physical activity, heart rate, heart rate variability, temperature, respiration rate, cough frequency, and sleep pattern in the 3-month observation period, are associated with changes of the patient self-assessed symptoms (CAT).

5. To predict the CAT score and changes thereof by building a statistical model employing sensor-derived data and demographic and medical covariates.

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9 Research Methods

9.1 Study Design

9.1.1 Design Overview

This is a multicenter, prospective cohort study classified as "Sonstige Klinische Prüfung" (other clinical study) as per Art. 82 Regulation (EU) 2017/745 /§3 No. 4 MPDG. The study will be conducted at 11 sites in Germany, a cohort of participants with COPD stage II-IV will be followed for 3 months.

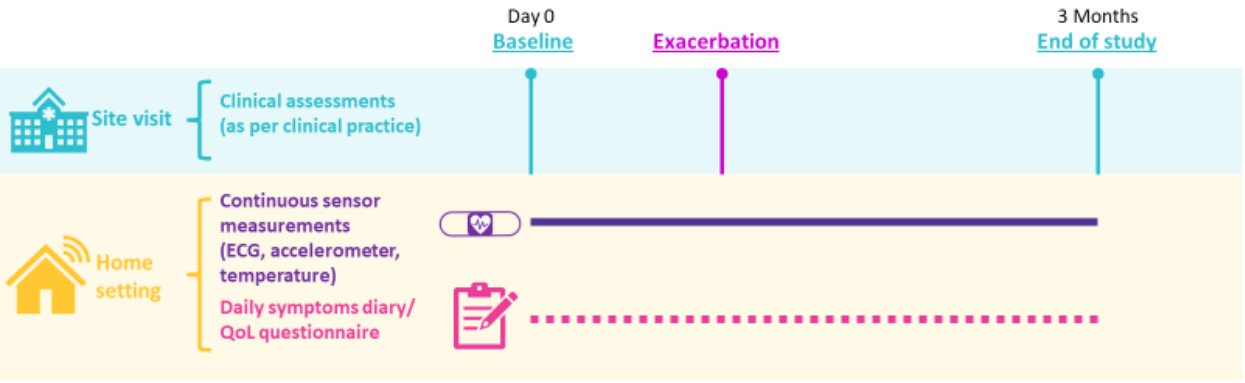
The device used in this study is a CE marked device modified to add a temperature measurement algorithm in addition to ECG and respiratory rate measurements (a modification solely regarding the software). This modification has not yet been evaluated by the Notified Body. The device will be utilized to collect physiologic data for analysis only. The data will not be communicated to the physicians or study participants during the study; therefore, this data cannot and will not be used to prevent, monitor, predict or diagnose disease or in any other way impact the treatment of the study participants. Data will be collected as close to the usual clinical practice as possible without applying burdensome or invasive procedures. The therapeutic strategy is not decided in advance

by the study protocol but will be determined as per normal clinical practice, and decision to prescribe a particular medication is fully independent from the decision to enroll the participant in the study. No medication or other therapeutic measure will be provided to the participants as part of the study.

A calibration cohort with non-COPD participants will be included and followed for 2 weeks.

See Figure 1 for a graphical design overview.

Figure 1 **Design Overview for COPD Cohort**



Note: Exacerbation visit(s) could take place at any time point during the observation period, based on the occurrence of exacerbations.

COPD Cohort

Participants will be enrolled consecutively, in pulmonology practices and/or outpatient hospital settings during the regular scheduled clinical visits. The Baseline visit (Day 0) can take place once the participant provides written informed consent to participate in the study. Enrolled participants with COPD will be followed for a 3-month observation period.

During the Baseline visit each enrolled participant will be provided with a Vivalink wearable device and a connected phone and trained on the how to use these devices. The participants should wear the Vivalink device continuously, day and night (except for charging times and situations described in the instructions for use), during the observation period to ensure recording of ECG, accelerometer, and temperature data.

A study digital application is installed on the phone provided with the Vivalink wearable device for the participants to fill in the CAT questionnaire, label activities or events relevant for the interpretation of sensor signals, receive notifications/reminders and visualize their progress with study related activities.

The CAT questionnaire will be filled in by each participant at home, once per day, every day during the observation period electronically using the study digital application. The validated translation of the CAT questionnaire in German will be incorporated as an electronic questionnaire in the software application for the study participants. The participants will be trained during the baseline visit how to use the study application to fill in the CAT questionnaire.

The study digital application will be used also for the labeling of activities relevant for interpretation of data collected with the wearable device. The application will contain a predefined list of options: coughing, coughing with sputum production, spray use, non-scheduled spray use, eating, going to bed, waking up, walking, climbing stairs, and physical exercise that can be easily selected to indicate when such an event/activity occurs. The participants will be trained to use the application to correctly label events and activities. Participants will be requested to label at least 5 events per day, every day during the observation period.

The digital study application will also provide participants automated notifications/reminders related to the Vivalink device (e.g. to charge or to wear the device), to fill in the CAT questionnaire, and to input labeling information. Participants will be encouraged to fulfill these daily tasks by reminders and notifications triggered once data is not entered as requested. A dashboard with compliance data will be provided to the participants allowing them to have an overview of outstanding tasks and their performance to fill out questionnaires, wear the device, and label events to encourage them to be compliant.

A help line will be set up to assist participants in case of questions or issues regarding use of the Vivalink device or the digital application.

During the 3-month observation period the participants will attend visits at sites as per routine clinical practice in case of exacerbations, regular COPD check-ups, or other medical issues or events. At all visits at the study sites, assessments will be performed as per physician's judgement and documented as part of the routine clinical practice.

At the end of the 3-month observation period the participants will return the devices to the site during a regular COPD related visit scheduled at 3 months (± 14 days) after the baseline visit (Day 0). This will be the End of Study and assessments will be performed as per clinical practice.

In cases, when the End of Study does not align with an intended COPD related visit as per routine clinical practice, an End of Study visit will be scheduled at 3 months (± 14 days) after the baseline visit (Day 0) for the return of the devices. The assessments performed at this visit should be aligned with the clinical practice for a regular COPD related visit and costs shall be covered by the sponsor of the study.

In cases when the End of Study visit cannot be performed on site, the participants will be contacted via phone and provided with instructions to return the devices.

Death also defines End of Study. Although data from an End of Study visit will not be available, data from the patient will be used for analyses.

Calibration Participants Cohort

Participants will be enrolled in an internal medicine center in Germany. No additional procedures are required for establishing eligibility except for physician's judgement as described in the inclusion criteria (see Section 9.2.1). The Baseline visit (Day 0) can take place once the participants provided written consent to participate in the study. During the Baseline visit the enrolled participants will receive the following: the Vivalink wearable device (adhesive patch device with

ECG, accelerometer, temperature sensor), a connected phone, and training on how to use these devices.

The participants should wear the Vivalink device continuously, day and night, during a 2-week observation period in order to ensure recording of ECG, accelerometer and temperature data.

A study digital application is provided on the phone provided with the Vivalink device for the participants to label activities or events relevant for the interpretation of sensor signals and receive notifications/reminders. The application will contain a predefined list of options. The participants will be trained to use the application to correctly label as many such events as possible during the observation period.

At the end of the observation period, the participants will return the devices to the site. In case the participants are not able to visit the site, they will be provided with instructions on how to return the devices.

9.1.2 Outcomes

A complete mapping of objectives, outcomes and variables is available in Section 14.1.2.

9.1.2.1 Primary Outcomes

The primary objective is to 1) describe the distribution of sensor collected data with COPD exacerbations, as well as 2) to predict COPD exacerbations by building a statistical model.

Severity of acute exacerbations of COPD (AECOPD) are defined using the GOLD definitions based on treatment consequences (event-based) (Vogelmeier 2017): AECOPDs are defined as "an acute worsening of respiratory symptoms that results in additional therapy". Exacerbations are classified as 1) **mild** if they are treated with short-acting bronchodilators only; 2) **moderate** if they are treated with short-acting bronchodilators plus antibiotics and/or oral corticosteroids; or 3) **severe** if the patient visits the emergency room or requires hospitalization because of an exacerbation.

The occurrence of exacerbations during the observation period will be defined as follows:

- For moderate/severe exacerbation requiring a physician's intervention, emergency room visit or hospitalization, the severity, date of the exacerbation, and the duration of the exacerbation will be recorded via an eCRF.
- For mild exacerbations: self-reported; treated by the participant without intervention by a physician will be documented in the patient application labeling section (days with added treatment).

The duration of exacerbations during the observation period will be defined as follows:

The duration of a severe/ moderate exacerbation will be derived from the duration of added medication from the group of systemic corticosteroids and/or antibiotics which define moderate exacerbations by GOLD. Days in-hospital for severe exacerbations will also be captured.

The duration of mild exacerbations will be derived from the event "additional relieve medication taken" noted in the labelling section of the patient facing applicaton (which defines mild exacerbations). Duration and start / stop will be derived from these patient entries.

9.1.2.2 Secondary Outcomes

The outcomes defined to meet secondary study objectives are described in Table 1.

Table 1 Outcomes to Achieve Secondary Objectives

Secondary objective	Outcome definition	Number of objective
To evaluate the correlation of sensor collected data with a) patients´ self-assessed health status and symptoms (CAT) at baseline and study end, b) lung function and lab values at baseline and study end, c) and with history of mild, moderate and severe exacerbations at study end.	a) Patients' health status and symptoms at baseline (Day 0) and study end will be measured as the summary score across items of the CAT questionnaire that consists of 8-items in which participants can choose a score from 0 to 5, for each visit b) Lung function will be assessed using plethysmography and lab values including complete blood count (CBC) with differential, blood gas analyses (BGA), procalcitonin and CRP will be assessed as per standard practice at baseline (Day 0) and at study end (for details see Section 9.3) c) number, date of onset and duration of mild, moderate, and severe exacerbations, respectively, during the observation period	3
Sensor derived data may be related to the CAT score, therefore, an additional objective is to investigate whether changes in physical activity, heart rate, heart rate variability, temperature, respiration rate, cough frequency, and sleep pattern in the 3-month observation period, are associated with changes of the patient self-assessed symptoms (CAT).	Please see above (3a) During the observation period the CAT score will be obtained on a daily basis. Daily summary score across items of the CAT questionnaire will be computed.	4
To build a model for predicting patient self-assessed symptoms (CAT) score on daily basis and change in the CAT score (and change of CAT score by 2 points or more considered as MCID) employing sensor collected data on physical activity, heart rate, heart rate variability, temperature, respiration pattern, cough frequency, and/or sleep pattern.	Patients' health status and symptoms at baseline (Day 0) will be measured as the summary score across items of the CAT questionnaire that consists of 8-items in which participants can choose a score from 0 to 5. During the observation period the CAT score will be obtained via a digital application on a daily basis.	5

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[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	Self-reported satisfaction assessed via questionnaire.	9

9.2 Setting

This study will comprise of a population enrolled at internal medicine and pulmonology centers in Germany.

9.2.1 Study Population

The study population will be identified according to the below inclusion and exclusion criteria. For inclusion in the study, all of the following inclusion criteria must be fulfilled:

For participants with COPD:

1. Participants capable of giving signed informed consent, as described in Section 10.1, which includes compliance with the requirements and restrictions listed in the ICF and this protocol
2. Participants ≥40 and ≤80 years at baseline
3. Diagnosis of COPD stage II to IV (documented post-bronchodilator Forced Expiratory Volume in 1 second (FEV1)/ Forced Vital Capacity (FVC) < 0.7 and FEV1 < 80% predicted)
4. History of moderate or severe exacerbations (≥2 moderate exacerbations or ≥1 severe exacerbations in any 12-month time window during last 3 years prior to inclusion and ≥1 moderate or severe exacerbations in the last 12 months prior to inclusion, considering that the last 12 months may reflect lower exacerbation rate due to Covid-19 measures)

For participants in the calibration cohort:

1. Participants capable of giving signed informed consent, as described in Section 10.1, which includes compliance with the requirements and restrictions listed in the ICF and this protocol
2. Participants ≥40 and ≤80 years at baseline

Participants are not eligible for this study if they fulfill any of the following exclusion criteria:
For participants with COPD:

1. Participants who, at the discretion of the Investigator, are unlikely to complete the study or will not be able to provide reliable information for the study
2. Clinically relevant and/or serious concurrent medical conditions including, but not limited to visual problems, severe mental illness or cognitive impairment, musculoskeletal or movement disorders, cardiac disease (e.g., heart failure, arrythmia [esp. atrial fibrillation and conduction blocks]), lung cancer (currently treated) that in the opinion of the Investigator, would interfere with participant's ability to participate in the study or draw meaningful conclusions from the study
3. Participants with a cardiac pacemaker, defibrillators, or other implanted electronic devices
4. Participants with known allergies or sensitivity to silicon or hydrogel
5. Less than 6 weeks since previous moderate/severe exacerbation

For participants in the calibration cohort:

1. Participants who, at the discretion of the Investigator, are unlikely to complete the study or will not be able to provide reliable information for the study
2. Clinically relevant and/or serious concurrent medical conditions including, but not limited to visual problems, severe mental illness or cognitive impairment, musculo-skeletal or movement disorders, cardiac disease (e.g., heart failure, arrythmia [esp. atrial fibrillation and conduction blocks]), lung cancer (currently treated) that in the opinion of the Investigator, would interfere with participant's ability to participate in the study or draw meaningful conclusions from the study
3. Participants with a cardiac pacemaker, defibrillators, or other implanted electronic devices
4. Participants with known allergies or sensitivity to silicon or hydrogel
5. Diagnosis of pulmonary disease including, but not limited to COPD, asthma, pulmonary fibrosis, with impact on the lung function and exercise capacity

9.2.2 Definition of Study Cohorts and Description of Devices

Cohorts

A cohort of participants with COPD will be established. This cohort will consist of all eligible patients (based on all inclusion criteria and none of the exclusion criteria, see section 9.2.1) at Day 0 visit. Participants will be enrolled consecutively, based on the scheduled visits occurring in 11 health centers in Germany.

In addition, for device calibration purposes a cohort of non-COPD participants will be established. These participants will be recruited at 1 internal medicine center in Germany.

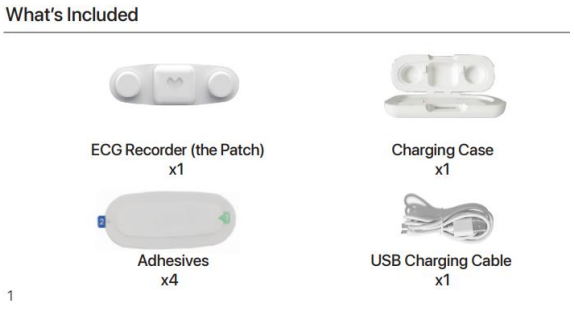
At the Baseline visit (Day 0), the eligible participants (all inclusion and none of the exclusion criteria) of both cohorts will receive a set of devices (adhesive patch device with sensors and phone).

Devices

The Vivalink wearable device will be used to collect data on physical activity, heart rate, heart rate variability, temperature, respiration pattern, cough frequency and sleep pattern. The model of the Vivalink wearable device that will be used in the study is the same as the CE marked model VV-330 with the addition of temperature monitoring. The new model inclusive of temperature monitoring has not yet received the CE mark. Details of the device are presented in Table 3.

Table 3 Vivalink Wearable Device.

Text in blue italics comes direct from the manufacturer or manufacturer's literature.

Device photo including accessories	
Brand Name	Medical Wearable Platform SDK-01
Manufacturer	VivaLNK, Inc.
Name or number of the model(s)/type(s)	Model: VV-330 + temperature monitor
Software version	*Planned special release for Merck KGaA,*
Accessories	Charging Case, Adhesives (hold the ECG recorder in place during recording), USB Charging Cable + USB electrical outlet adapter
Intended purpose	Below in italics is the intended purpose of the CE marked Model VV-330 as supplied by VivaLNK. The device to be used in the study, includes a temperature monitoring algorithm not covered by the CE marked device described below. *"Medical Wearable Platform SDK-01 is intended to record, store and transfer electrocardiogram (ECG) and accelerometer data. The platform has the capability to provide Heart Rate, Respiratory Rate and R-R Interval using the ECG rhythm. The ECG recorder patch is an ambulatory, continuous recording patch, intended for at-home or hospital, by clinicians or health professionals who intend to monitor their patient's physiological and health conditions for an extended period of time. The device is not intended for patients under 18 years old. This Instructions for Use is only limited to the use of the hardware and the Software Development Kit (SDK). It does not include any information about the mobile application or user interfacing device as that is outside the scope of the system."*
The period of validity of CE certificate for model VV-330.	Issue date: 2019-11-08 Expiry Date: 2024-05-26

NOTE: the model to be used in the study has been modified from the CE marked device to add an temperature monitoring algorithm (a software only change).	
Statement of deviation from the CE marked device	The device used in the study will be the same as the CE marked model VV-330 with the addition of temperature monitoring capabilities. A temperature sensor already present in the model VV-330 has been "activated" by the addition of an algorithm. The temperature sensor was already physically present in the wearable patch at the time of the CE mark, but was not turned on, tested or evaluated by the Notified Body for the current CE mark status.
Description of device materials in contact with body tissues	*Body-contacting materials are on the Adhesive, which includes proprietary textile and medical-grade adhesive layers with hydrogel conductive contacts.*
Statement that this device does not include any medicinal substances, human or animal tissues or their derivatives, or other biological active substances	"*Our device does **not** include any medicinal substances, human or animal tissues or their derivatives, or other biological active substances.*"
Reference to the compliance of applicable national regulations	VV-330 complies with the EU Medical Device Regulation (MDR) 2017/745 and meets the requirements in Annex1 General Safety and Performance Requirements. The addition of the temperature monitoring algorithm has not yet been evaluated by the Notified Body for conformance.
Describe the necessary training and experience required for the use of the MD.	VV-330 + temperature monitor is intended to be used by adult patients (18 or older) and their health care providers. No special training outside of familiarization of the general instructions from the approved labelling is needed.

LTE Phone (EDGE Device)

An EDGE device serves as a data transmission route from the Vivalink adhesive patch to the clinical database. The EDGE device is a Long-Term Evolution (LTE) phone which functionality is limited to data transfer and to the study software application that includes a questionnaire and the possibility to label events (see above). On this EDGE device a daily CAT questionnaire will be presented to the participant (see Section 9.1.1).

9.2.3 Observation Period

Participants will be followed-up for 3 months (until End of Study visit) or until premature discontinuation from study, whichever occurs first.

Participants in the calibration cohort will be followed-up for 2 weeks.

9.2.4 Frequency of Assessments

An overview of the planned assessments is provided in Table 4 and Table 5.

COPD cohort

The participants will visit the sites as per routine practice and the timing of the visits and assessments performed will be as per the treating physician judgment. Results of the assessments will be collected upon availability.

Table 4 Planned Assessments: COPD Cohort

Assessments	Baseline Visit Day 0	Exacerbation Visits (moderate and severe)	End of Study 3 Months ± 14 days	Comments
Participant Informed consent	X			
Inclusion/Exclusion criteria	X			
Demographics	X			
Medical history	X			
Physical examination	X	X	X	
COPD history	X			
Baseline Medication	X			
Record changes in medication (COPD and other)		X	X	Changes in medication means changes of medication at the time of the current visit (including newly prescribed medication) as compared to the baseline visit (Day 0)
Comorbidities	X			
Smoking status	X			
Exacerbation history	X			
Moderate and severe exacerbations during observation period		X	X	Moderate and severe exacerbations should be recorded that occurred between Day 0 and the current visit (including exacerbations at the time of the visit)
Lung function (Plethysmography)	X	X	X	For the Baseline visit (Day 0), data from the past 2 weeks are acceptable.
End of study satisfaction questionnaire			X	
(S)AE recording	→	→	→	Continuous recording
Serious Adverse Device Effects (SADE) and Device Deficiency (DD) reporting	→	→	→	Continuous reporting
CAT collection via App	Daily at home			
Data collection via App (labeling events and activities)	Daily at home			Includes medication data used to identify mild exacerbations

Laboratory values (if available from clinical practice)				For the Baseline visit (Day 0), data from the past 2 weeks are acceptable.
C-reactive protein (CRP)	X	X	X	
Procalcitonin	X	X	X	
Blood count (including eosinophiles, neutrophiles, Hb)	X	X	X	
Capillary blood gas analysis: pO2 and pCO2; SpO2	X	X	X	

Table 5 Planned Assessments Calibration Cohort

Assessments	Day 0	End of Study 2 Weeks	Comments
Participant informed consent	X		
Inclusion/Exclusion criteria	X		Assessed by Investigator by review of medical history and/or participant reported medical history
Demographics	X		
Medical history	X		
Comorbidities	X		
Medication	X	X	
End of Study satisfaction questionnaire		X	
(S)AE recording	→		Continuous recording
SADE and DD reporting	→		Continuous reporting
Data collection via App (labeling events and activities)	Daily at home		

9.2.5 Withdrawal from the Study

Participants are free to discontinue the study at any time without giving their reasons. Participants will be withdrawn from study participation for any of the following reasons:

- Informed consent withdrawal
- Participant is unable to handle the devices and has proven to not provide reliable data
- The study is prematurely stopped by the sponsor

9.3 Variables

The following variables will be collected for this study (pending availability):

Several biometric parameters will be measured in a time-dependent manner using the Vivalink wearable device. Values measured from day 8 to 14 will be used as baseline data (e.g. for determining parameter changes during the observation period or as co-factor in model building) unless this time period is within a 2-week distance of an exacerbation. In this case the next 7-day period with a distance of 4 weeks from an exacerbation will be considered the baseline in this context.

Variables measured with the Vivalink wearable device (including, but not limited to):

- Physical activity including stair climbing, (calculated based on continuous accelerometer measurement) [daily average] (derived parameter)
- Heart rate as beats per minute [daily average] (derived parameter)
- Resting heart rate (resting state as determined by accelerometer, beats per minute) [daily average] (derived parameter)
- Heart rate variability reflecting differences in time intervals between 2 R-waves in the ECG (milliseconds) [daily average (where applicable) of the following parameters: SDRR (standard deviation of RR intervals), SDNN (standard deviation of NN intervals), SDNNI (Mean of the standard deviations of all the NN intervals for each 5 min segment of a 24 h HRV recording), RMSSD (Root Mean Sum of Squared Distance), ln(RMSSD) (natural logarithm of RMSSD), pNN50 (percentage of successive RR intervals that differ by more than 50 ms) SI (stress index), LF power (low frequency fraction of HRV, 0.04 – 0.15 Hz), HF power (high frequency portion of HRV, 0.15 – 0.40 Hz), LF/HF (ratio of LF-to-HF power); for details of calculation check see Shaffer 2017] (derived parameters).
- Temperature [daily average, minimum -maximum values]
- Respiration rate (breath per minute) [daily average, minimum -maximum values] (derived parameter)
- Ratio of inspiration vs expiration time [daily average min-max] (derived parameter)
- Cough frequency (derived parameter)
- Sleep pattern (derived parameter)

Self-measured Variables:

- Self-reported COPD symptoms via the CAT questionnaire
- Self-reported activities (coughing, coughing with sputum production, spray use, non scheduled spray use, eating, going to bed, waking up, walking, climbing stairs, and physical exercise) as collected by the participant app
- Self-reported satisfaction with the study, collected via end of study questionnaire

Covariates (status at the time of Day 0, closest record prior to):

- Demographics data at baseline: (sex, age, height, and weight, race and ethnicity)
- Body mass index will be calculated based on height and weight
- Smoking status (current, ex-, non-smoker)
- Medical history at baseline
    - Date of diagnosis of COPD
    - Number of moderate or severe exacerbations prior to baseline visit (preceding 36 months, in case available)
- Comorbidities at baseline
- Current medication including COPD treatment at baseline
- COPD severity (GOLD stage)

Lung Function and Laboratory variables
(at Day 0, moderate/severe exacerbation visit and End of study visit)

- Body plethysmography parameters: FEV1 [L], FVC [L], FEV1/FVC, TLC [L] (total lung capacity), RV [L] (residual volume), FRC_{pleth} [L] (functional reserve capacity), IC [L] (inspiratory capacity), R_{aw} [kPa s L^{-1}] (=ratio of sRaw to FRC_{pleth}; airway resistance), sR_{aw} [kPa s] (specific airway resistance), VT [L] (mean tidal volume), ERV [L] (expiratory reserve volume), IRV [L] (inspiratory reserve volume). For definitions see Criée 2011.
- Blood gas analysis:(capillary) pO2 [mmHg], O2 saturation [%] and pCO2 [mmHg],
- Serum CRP [mg/l] and serum procalcitonin levels [ng/ml]
- Blood count (CBC with differential); only values that are available with routine blood counts: Hb [g/dL], Hct [%], Erythrocyte count [10^6/µL], MCV [fL], MCH [pg], MCHC [g/dL], Reticulocytes [x10^3/µL] [‰ (of erythrocytes)], RDW [], platelet count [10^3/µL], WBC count [x10^3/µL], Lymphocytes [x10^3/µL] [%], Monocytes [x10^3/µL] [%], Neutrophils [x10^3/µL] [%], Eosinophils [x10^3/µL] [%], Basophils [x10^3/µL] [%]

Derived and transformed data needed for the analysis are described in Section 9.7.1.1.

A complete mapping of objectives, outcomes and variables is available in Section 14.1.2.

9.4 Data Source

The data source used for this study will consist of patient charts from 11 centers (e.g. academic, referral, community) in Germany as well as from a device, which will get handed out to the participant.

The data informing this study will be extracted from patient medical records by the site personnel by means of an electronic Case Report Form (eCRF) directly in an electronic data capture system. In addition, a PRO questionnaire (CAT, filled in by the participant home electronically), and wearable devices (adhesive patch device with sensors) will be used for data collection. The data recorded in the eCRF should be consistent with the relevant source documents. Further details are provided in Section 9.6.

9.5 Study Size

Sample size calculation is based on the second part of the primary objective, especially on predicting exacerbations of a severe or moderate type as outcome.

Assuming a desirable sensitivity and specificity of 0.85 for our algorithm and requiring that the lower 95% confidence limit should be at least 0.50 (with a probability of 0.95) for this exploratory approach, the number of observed exacerbation events needed is 18 (Flahault 2005).

Assuming that patients with COPD within our eligibility criteria (GOLD stage II-IV with a history of at least 2 moderate and/or severe exacerbations within any 12 month period within the last 3 years and at least 1 moderate or severe exacerbation within the last 12 months) show a frequency of 2 moderate or severe exacerbations per year, participants with COPD will have 0.5 events in 3 months (the in-study time). Further assuming that event occurrence over 3 months for every individual participant follows a Poisson distribution with parameter $\lambda = 0.5$, the number of events in the overall study population is also Poisson distributed and the corresponding parameter is the sum of individual parameters λ. Calculations show that a λ of 30 is needed to reach an upper cumulative distribution probability of 0.99 for observing at least 18 exacerbations. Therefore, 60 participants are needed to observe at least 18 exacerbation events within the 3-month observation period.

The events of interest in the context of the present study are COPD exacerbations (severe or moderate), exactly the onset of an exacerbation. For building the binary classifier predictive models we also require “no exacerbation” events. We will sample such events randomly from periods with no exacerbations, avoiding 2 weeks before and after an exacerbation.

Considering a drop-out rate of 10%, the estimated number is 67 participants with COPD that need to be included in this study.

This recruitment number is also in good agreement with published studies with regards to the ability to build predictive models for exacerbations. Studies with similar recruitment numbers (Yañez 2012) have been able to predict exacerbations based on single parameters studied. Strong features can compensate for low numbers in COPD machine learning model building as shown in

Al Rajeh 2020, and using several features improves the accuracy of predictive models as seen in Jensen 2012.

The study will also observe 10 participants in a calibration cohort for a limited time (2 weeks). This calibration cohort is intended to obtain sensor parameter ranges for individuals who are not suffering from COPD or other pulmonary diseases. These parameter ranges will be used to calculate distance measures of parameters (e.g. physical activity) for participants with COPD, and obtain additional sensitivity measures for the sensors used with regards to distinguish COPD symptoms from a calibration population. The number of participants for these secondary objectives is chosen on an exploratory basis, no sample size calculation has been conducted here. As we expect no major perturbations (e.g. exacerbations) within the calibration population, we deem a time period of 2 weeks sufficient for generating a representative sample of the participants sensor data.

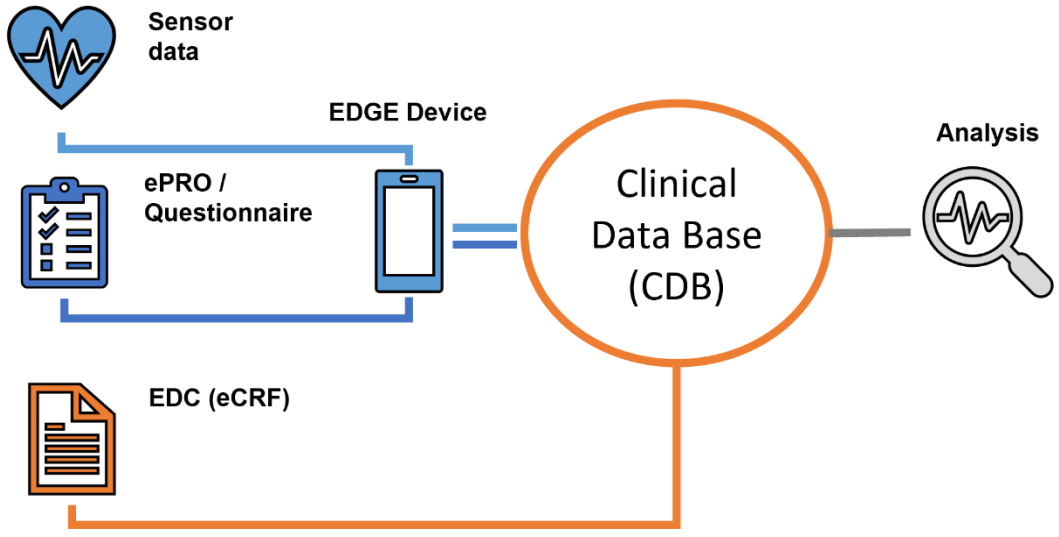
9.6 Data Management

9.6.1 Data Collection

The data collection in this study consists of different components, which are outlined in Figure 2 below. Those components encompass different methods and tools:

- Clinical Data: A cloud-based **Electronic Data Capture (EDC)** System. The purpose of the EDC system is the setup, collection, and review of study data entered by the site personnel. The data is entered through electronical case report forms (eCRF) by qualified and trained site staff.
- Patient Reported Data**: Electronic Questionnaire** through an EDGE device provided to the participants as part of the study.
- Medical Device Data: A wearable **device (ECG, accelerometer, temperature)** for the participants. The device is linked with the study EDGE device.

Figure 2 Schema of the Data Collection



Data from all described sources will be processed, evaluated, and stored in pseudonymized form in accordance with applicable data protection regulations. The Investigator must ensure that the eCRFs and any other associated documents forwarded to the Sponsor or its designated organization contain no mention of any participant names. The data from all sources will be transferred into a validated Clinical Database (CDB). The CRO or its designee will be responsible for data processing, in accordance with the CRO's data management procedures. Database lock will occur once quality control and quality assurance procedures (including Serious Adverse Events [SAE]/SADE reconciliation) and coding activities have been completed. PDF files of the (e)CRFs will be provided to the Investigators at the completion of the study.

9.6.2 Data Collection Systems

The main purpose of the CDB is to process and aggregate data from several sources for further central processes, like data validation, analysis, and data submissions. The CDB serves as data repository and is used to run quality control measures throughout the study.

Clinical Data

The Vault EDC system of Veeva Inc. is used for documentation of all relevant study data collected by the Investigator via eCRF. The main purpose of the eCRF is to obtain data required by the study protocol in a complete, accurate, legible, and timely manner. The data in the eCRF should be consistent with the relevant source documents. The Investigator or designee is responsible for ensuring that the data collected during the course of this study is accurate and documented appropriately on all applicable forms. eCRF data collection is following the study design. The software is accessed through a login with password secured web-interface.

Patient Reported Data

For the patient reported data collection, a Smartphone (a so-called EDGE device) with study specific functionality will be provided to the study participants. The main purpose of the device is to transmit data from the study participant to the CDB. It will contain the following software to collect data from participants:

- A daily PRO questionnaire (CAT questionnaire)
- Further information from the label section of the patient application with the following items: coughing, coughing with sputum production, spray use, nonscheduled spray use, eating, going to bed, waking up, walking, climbing stairs, and physical exercise
- In addition, but outside of the app, the participants will be asked to fill in an end of study questionnaire on user satisfaction with the study, device and application.

Medical Device Data

All device data will be collected via the Vivalink wearable patch and an associated LTE smartphone. Participants and site physicians do not receive feedback or diagnostic data based on collected device data to not intervene with the regular treatment.

The Vivalink device contains 3 physical sensors for temperature, ECG, and a 3-axis accelerometer. The following parameters are therefore the primary (raw) outputs of the device:

- ECG in an approximate Einthoven I configuration
- Temperature
- Movement data in the 3 axes of the accelerometer

Vivalink will provide the following derived data:

- Heart Rate
- Physical activity
- Respiratory Rate

Using the raw data and participant labelling information, a number of further derived data will be generated by Merck as listed under variables.

Participants in the COPD and calibration cohorts will receive their devices at study inclusion, be instructed on use and return the devices at study end. Data will be collected continuously during the study.

Security of data transmission and storage

Data transmission and storage will comply to EU-General Data Protection Regulation (EU-GDPR) and to the German "Bundesdatenschutzgesetz" BDSG. Data from the medical device will be transmitted in encrypted and pseudonymized way. Servers for data storage will be located in Europe, and data stored in a secure encrypted format.

9.6.3 Query Management

If entries in the eCRF are incorrect or incomplete, queries will be created. Queries are inquiries about the entries in the eCRF. Queries may be automated or manually entered. Manual queries may only be submitted by the CRO. In case entries in the eCRF must be changed, those changes are documented within an audit trail. The time of the data change, the person making the change, the clear attribution of participants and variables, the old and the new value and, if necessary, the reason for the change are stored.

9.7 Data Analysis

Further details will be provided in an integrated Analysis Plan (IAP) that will be finalized prior to study start (inclusion of first participant).

9.7.1 Analysis Sets

Two Analysis Sets will be defined:

1. Participants with COPD including all patients with COPD included in the study, i.e, all patients with COPD fulfilling all of the inclusion criteria and none of the exclusion criteria (see Section 9.2.2).
2. Participants in the calibration cohort included in the study (see Section 9.2.2).

9.7.1.1 Derived and Transformed Data

Variable	Original data	Description of derived data
Body mass index (BMI [kg/m^2])	Measured height and weight. (Demographics data at baseline)	Weight (kg) / (Height [cm]/100)^2
Physical activity, including stair climbing	Continuous accelerometer measurement, self-reported activities	Classification algorithm, similar to the one described in Fadel 2019
Heart rate	ECG	Beats per minute.
Resting heart rate	Accelerometer, ECG	Resting state as determined by accelerometer, Beats per minute extracted from ECG
Heart rate variability reflecting differences in time intervals between 2 R-waves in the ECG (milliseconds) SDRR , SDNN, SDNNI, RMSSD, ln(RMSSD), pNN50, SI, LF power, HF power, LF/HF	ECG	For details of calculation check see Shaffer 2017
Respiration rate	ECG	Measure of R-R peaks, and application of algorithms as the ones described in Varon 2020
Ratio of in- vs. expiration time	ECG	Measure of R-R peaks, and application of algorithms as the ones described in Varon 2020
Cough frequency	Accelerometer, ECG, self-reported activities	Predictive algorithm similar to the one described in Georgescu 2019
Sleep pattern	Accelerometer, self-reported activities	Self reported going to bed and waking up, combined with accelerometer data to improve accuracy of sleeping time, plus accelerometer analysis to infer sleep quality.

9.7.1.2 Missing Data

For variables obtained only at the baseline visit, missing values will not be replaced.

For the self-reported satisfaction questionnaire items, collected at the end of study visit, missing values will not be replaced. For variables measured daily during the observation period such as sensor-generated data, CAT score, and labelling information, missing data will not be imputed for all descriptive statistical analyses performed. The CAT score and derived sensor variables may be imputed for the purpose of building machine learning models if needed to avoid loss of instances

using a suitable imputation method (e.g. LOCF, forward filling, multiple imputation [MI]). Sensitivity analyses will be conducted to assess the impact of imputation.

For variables with values collected at baseline, at the exacerbation visit and at end of study visit, missing values will not be imputed for all descriptive statistical analyses. Lung function parameters and laboratory values may be imputed for the purpose of building machine learning models if needed to avoid loss of instances by LOCF method if the last (previous) available value is recorded within 2 weeks before the date of the visit of interest. In cases where no value for a variable is available for a participant, imputation strategies across instances may be used (e.g. median imputation or iterative imputation methods). Sensitivity analyses will be conducted to assess the impact of imputation.

9.7.2 Statistical Methods

Descriptive statistics will include:

- For continuous variables: mean, SD, median, first and third quartiles, minimum and maximum values, and number of missing values.
- For categorical variables: counts and percentages. Percentage will be calculated with the denominator being the total number of participants with non-missing values for the variable of interest in the cohort at the corresponding time point.

9.7.2.1 Primary Objectives

Primary objective 1): To describe the distribution of sensor collected data on physical activity, heart rate, heart rate variability, temperature, respiration rate, cough frequency, and sleep pattern, by severity of COPD exacerbations.

This analysis will be performed on the COPD participants set.

- Sensor collected data on physical activity, heart rate, heart rate variability, temperature, respiration rate, cough frequency, sleep pattern, at baseline (Day 0), in the period Day 8 to Day 14, and shortly prior (14 days prior to, 7 days prior) to, during an exacerbation and after an exacerbation (8 to 14 days after, 2 weeks after, 3 weeks after, up to 4 weeks after an exacerbation) will be reported as mean (SD) and/or median (Interquartile Range) for continuous variables and counts and frequency (%) for categorical variables. The analysis will be done on the group of severe or moderate exacerbations and on exacerbations by type.

Primary objective 2): To predict moderate or severe COPD exacerbations by building a statistical model employing sensor-derived data and demographic and medical covariates.

This objective aims at predicting the occurrence of a severe or moderate exacerbation, in other words, predicting an event out of the combined group of severe and moderate exacerbations. It is desirable to predict an AECOPD as early as possible, therefore dependency of model metrics on the time period before exacerbation will be explored.

As input to the model a number of algorithms (e.g. self-learning algorithms) for obtaining derived parameters such as cough frequency, physical activities and sleep pattern, heart rate variability, temperature, respiration pattern, cough frequency, or sleep pattern will be developed first using the labeling of activities dataset obtained via the app. Said derived features will help to understand the importance of different raw data patterns, so that explanatory models can be built on top of the machine learning algorithms (Molnar 2022), as a way to support rationalization for physicians and regulatory organizations.

Different machine learning algorithms (e.g. gradient boosting, SVMs, K-nn) will be evaluated, and their performance will be assessed by estimating their accuracy, specificity, sensitivity, and area under ROC metrics.

This analysis will be performed on the COPD participants set.

Based on previous analysis of clinical data, both in literature and internally, methods that are known to be useful on data where some features are strongly correlated with the desired outcome will be used, in order to create unbiased models. The following methods will be used:

- Logistic regression
- Random Forest
- K-nearest neighbors
- Boosting methods (e.g. Gradient boosting machine, GBM)
- Support vector machines (SVM)

Other methods may be tested.

9.7.2.2 Secondary Objectives

Secondary Objective 3):

To evaluate the correlation of sensor collected data with

a) patients´ self-assessed health status and symptoms (CAT) at baseline and study end,

b) lung function and lab values at baseline and study end,

c) and with history of moderate and severe exacerbations at study end

This analysis will be performed on the COPD participants set.

Coefficients of correlation with 95% CI of sensor collected data on physical activity, heart rate, heart rate variability, temperature, respiration rate, cough frequency, sleep pattern with patients' health status (CAT) at baseline (Day 0) and study end, lung function (e.g. FEV1) at baseline

(Day 0) and study end, laboratory values at baseline (Day 0) and study end and with moderate and severe exacerbations throughout the observation period.

- **Secondary Objective 4):** Sensor derived data may be related to the CAT score, therefore, an additional objective is to investigate whether changes in physical activity, heart rate, heart rate variability, temperature, respiration rate, cough frequency, and sleep pattern in the 3-month observation period, are associated with changes of the patient self-assessed symptoms (CAT).

This analysis will be performed on the COPD participants set using correlation maps and linear models as appropriate.

Secondary Objective 5): To predict the CAT score and changes thereof by building a statistical model employing sensor-derived data and demographic and medical covariates.

To build a model based on sensor-derived data, demographic and medical covariates to predict:

- patient self-assessed symptoms (CAT score measured on a daily basis)
- change of CAT score by 2 points or more (considered as MCID).

This analysis will be performed on the COPD participants set.

Different machine learning algorithms will be evaluated, and their performance will be assessed by estimating their accuracy, specificity, sensitivity, and area under receiver operator curve (ROC) metrics.

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[redacted]

[redacted]

Data analyses will employ SAS (Version 9.4 or higher), JMP (Version 16.2 or higher), R (Version 4.2 or higher) and Python (Version 3.8 or higher).

9.7.3 Sequence of Analyses

No formal interim analyses are planned. Sensor-derived data will be constantly observed and analyzed during study conduct in order to monitor data quality and taking actions to improve the data quality from the Vivalink device.

9.8 Quality Control

The quality and the integrity of the data will be controlled by means of monitoring. The monitoring contains source data verification as well as check on primary outcomes. For further information refer to the monitoring plan.

In compliance with regulatory requirements, the Sponsor, a third party on behalf of the Sponsor, regulatory agencies, or Independent Ethics Committees (IECs) may conduct quality assurance audits/inspections at any time during or following a study. The Investigator must agree to allow auditors/inspectors direct access to all study-related documents, including source documents, and must agree to allocate his or her time and the time of his or her study staff to the auditors/inspectors in order to discuss findings and issues.

The study protocol, each step of the data capture procedure, and the handling of the data, as well as the eventual study report, may be subject to independent Clinical Quality Assurance. Audits may be conducted at any time during or after the study to ensure the validity and integrity of the study data.

For key statistical results, the validation of statistical programming will use a risk-based approach according to Good Automation Manufacturing Practices (GAMP)-5 principles.

A self-validation approach will be used for other results, where the quality control process involves a code review where critical errors will be identified, using the following checks:

- Adherence to requirements and specifications as per the protocol have been respected
- Adherence to standards, e.g. program header, comments, Good Programming Practice Guideline
- Review of the statistical outputs:
    - for consistency of populations sizes
    - minimum and maximum values
    - overall relevance of results
    - consistency with the tables and figures templates

All programs and analysis datasets will be stored in a centralized electronic data warehouse on secure, password-protected and validated, GxP compliant servers. These secure servers are accessible only from the Merck and CRO intranet where access is restricted to relevant employees and computers which access these servers must have approved usage rights and training certifications to use the system.

The results reported in the result section of the final report will be reviewed by the scientist to ensure an accurate transcription of results.

9.9 Limitations of the Research Methods

- The data is collected from a very limited number of study sites in Germany. Hence the study population may not be representative of the population of patients with COPD. In addition, the fact that participation in the study requires cognitive capabilities to use applications and devices used for data collection in the study may cause selection bias towards a younger age group.
- Daily averages will be calculated to represent continuous measurements each day. There may be additional information encoded in smaller time periods (hour by hour or minute by minute) data or through defining bouts of activity.
- Some of the outcomes are based on subjective self-assessment e.g. COPD symptoms and health status will be assessed by the CAT score. In validation studies, the CAT score has been shown to be a valid and reliable tool to assess perceived health status (Jones 2013), though validity of the online version remains to be proven.
- The number of observed exacerbations will be low, and predictive models will need to be refined and validated in a larger population.

- Severe and moderate AECOPDs will likely be encountered in only ~40% of the participants with COPD. This may impact the generalizability of predictive models for AECOPDs.
- This study is a national study in Germany and will only recruit patients with sufficient proficiency in the German language. It is therefore impossible to assess potential bias in the gathered data and conclusions with regards to language, ethnicity, cultural background, country of origin, and social factors not encountered in the study population. This refers both to PROs and the interpretation of sensor data. Future studies will need to study these potential biases in a multinational setting.
- Mild exacerbations are captured via the labelling section in the patient facing application as "additional medication used" (self-reporting). Therefore, the capture of mild exacerbations depends on patients' adherence to the intended application use and daily reporting. Mild exacerbations may therefore be under-reported (but also over-reported in case of erroneous entries).
- Participants may not adhere to the intended constant wearing or charging regimens of the device and therefore available data may have too many gaps to allow meaningful interpretation.
- Participants may wear the device not at the intended location or in the intended orientation. This may introduce errors into the interpretation of sensor derived data. Participants may enter wrong data into both the CAT questionnaire and the labelling section leading to difficulties in model building and conclusions from the study.
- The device may have undetected technical errors that introduce errors into the sensor data leading to difficulties in model building and conclusions from the study.

9.10 Other Aspects

9.10.1 Ethical Conduct of the Study

This study will be conducted in accordance with the clinical trial protocol, the current version of the Declaration of Helsinki , ISO14155, ICH-GCP (as applicable), and all national legal and regulatory requirements.

9.10.2 Independent Ethics Committee or Institutional Review Board

This multicenter, prospective cohort study with a medical device is classified as "Sonstige Klinische Prüfung" (other clinical study) as per Article 82 Regulation (EU) 2017/745 /§3 No. 4 MPDG. The medical device used in this study for physiological monitoring will be used modified to its CE marking with the addition of temperature monitoring capabilities. Prior to commencement of the study at a given site, the protocol will be submitted together with its associated documents to the responsible Independent Ethics Committee (IEC)/Institutional Review Board (IRB) for its opinion.

The study must not start at a site before the Sponsor has obtained written confirmation of a favorable opinion from the concerned IEC/IRB in accordance to §47 (2) No. 1 and §52 Section 1 MPDG.

The written evidence of the favorable opinion from the concerned IEC/IRB will be filed in the trial master file and a copy will be sent to the Investigator. The written evidence should clearly identify the study, the protocol version, and the Informed Consent Form version reviewed. In addition, the IEC/IRB will be asked to provide documentation of the date of the meeting at which the study was discussed, and of the members and voting members present at the meeting.

In accordance with § 54 MPDG, all changes to the protocol and any applicable documentation will be notified to the responsible IEC/IRB immediately. In case of substantial changes, the responsible IEC/IRB will be asked for favorable opinion in accordance with § 55 MPDG. Substantial changes will only be implemented, if the responsible IEC/IRB issues a favorable opinion or if the responsible IEC/IRB issues no rejection notice within 38 days after confirmation of a formally complete application.

In case of temporary suspension or premature termination of the study, the responsible IRB/IEC will be notified within 15 days with indications of the reasons. If the temporary suspension or premature termination are performed out of security reasons, the responsible IRB/IEC will be notified within 24 hours in accordance with §64 MPDG.

9.10.3 Monitoring

A CRO will perform monitoring according to the study's Monitoring Plan. Investigators need to ensure that the Monitor has access to relevant documents during monitoring visits and that they and/or relevant site staff members are available to discuss any issues that may arise.

Recruitment rates and exacerbation frequency in the COPD study population will be reviewed in 2-week intervals to compare against assumptions and allow for timely adjustments of the study protocol and conducting sites to reach the projected minimum number of moderate or severe exacerbations (n=18). Participants will be instructed to inform any physician outside of this study of their participation in this study and the need to inform the respective PI on relevant medical events and exacerbations.

The study monitor will send monitoring reports to the Sponsor.

9.10.4 Health Authorities

The study must not start at a site before the protocol and any applicable documentation has been notified to the German Federal Institute for Drugs and Medical Devices (BfArM) in accordance with the § 47 (2) No. 2 and § 53 Section 1 MPDG.

In accordance with § 54 MPDG, all changes to the protocol and any applicable documentation will be notified to BfArM immediately.

In case of temporary suspension or premature termination of the study BfArM will be notified within 15 days with indications of the reasons. If the temporary suspension or premature termination are performed out of security reasons, the BfArM will be notified within 24 hours in accordance with §64 MPDG.

9.10.5 Quality Assurance

In compliance with regulatory requirements, the Sponsor, a third party on behalf of the Sponsor, competent authorities, or IRB/IECs may conduct quality assurance audits/inspections at any time during or following a study. The Investigator must agree to allow auditors/inspectors direct access to all study-related documents, including source documents, and must agree to allocate his or her time and the time of his or her study staff to the auditors/inspectors in order to discuss findings and issues.

The protocol, each step of the data capture procedure, and the handling of the data, as well as the study report, may be subject to independent Clinical Quality Assurance. Audits may be conducted at any time during or after the study to ensure the validity and integrity of the study data.

9.10.6 Medical Device Supply, Accountability and Handling

The Medical Device will be shipped by the manufacturer to the CRO and subjected to a receiving inspection. After successful receiving inspection the Medical Devices will be equipped with an ID, tracked and stored at the CRO in a restricted area. Only designated personnel involved in the supply chain of the Medical Devices will have access. The Medical Devices will be prepared for shipment to the sites by the CRO and tracked after handover to the logistic company.

The site will confirm the intact receipt of the Medical Device shipment in writing to the CRO. All Medical Devices must be stored in accordance with the manufacturer instructions. The investigator is responsible for assurance of adequate storage. The Device must be stored in a lockable room or locker, so that only investigator and specifically designated study personnel can have access. Only participants enrolled in the study may receive the devices and only authorized site staff may supply the device.

At the end of the study, all Medical Devices will be returned by the participants and checked for completeness at the site. Those devices and unused devices are returned to the CRO. The CRO will check, store and return the Medical Devices to the manufacturer.

Storage, dispensing and return of Medical Devices must be documented by the site and the CRO.

In case of reported device deficiencies, including malfunction, usability issues, or inadequacy in the information supplied by the manufacturer including labelling, the devices will be returned to the CRO, if already supplied, and the sponsor will be informed. Poorly performing devices will be replaced during the study and returned to the CRO by the site.

The study team at the CRO and site staff involved in the supply chain will be trained on the process.

9.10.7 Archiving

The archive should be maintained for the period specified by local regulations (10 years in Germany) (MPDG/appendix XV EU-MDR). All original participant files (medical records) must be stored at the site (hospital, research institute, or practice) for the longest possible time permitted

by the applicable regulations. In any case, the Investigator should ensure that no destruction of medical records is performed without the written approval of the Sponsor.

10 Protection of Human Participants

The sponsor will use safeguards to comply with national and European Union requirements for protecting the well-being and rights of human participants. To ensure the protection of privacy of participants, the sponsor is using data which have been pre anonymized and have had all protected health information removed. The sponsor will have no access to these data and will be unable to link these data to or identify the participants of the study. The sponsor will also restrict the access to the data to ensure that only those study personnel who have been appropriately trained and are in compliance with all of Merck's Codes of Ethics can examine the data.

10.1 Participant Information and Informed Consent

An unconditional prerequisite for a participation in the study is a written informed consent. The participants written informed consent must be given before any study-related activities are carried out.

Adequate information must therefore be given to the participant by the Investigator before informed consent is obtained. A participant information sheet in the local language (German) will be provided by the Sponsor for the purpose of obtaining informed consent. In addition to providing this written information to a potential participant, the Investigator will inform the participant verbally of all pertinent aspects of the study (the language used in doing so must be chosen so that the information can be fully and readily understood by laypersons).

The Informed Consent Form must be signed and personally dated by the participant and the Investigator. The signed and dated declaration of informed consent will remain at the Investigator's site and must be safely archived by the Investigator. A copy of the signed and dated information and consent form should be provided to the participant prior to participation.

Whenever important new information becomes available that may be relevant to the participant's consent, the written participant information sheet and any other written information provided to participants will be revised by the Sponsor and be submitted again to the IEC/IRB for review and favorable opinion. The agreed, revised information will be forwarded to each participant in the study. The Investigator will explain the changes to the previous version.

10.2 Participant Identification and Privacy

A unique participant number will be assigned to each participant at inclusion. This number will serve as the participant identifier in the study as well in the study database.

The Investigator must ensure that the participants' anonymity is maintained. On the eCRFs or other documents submitted to the Sponsor, participants should not be identified by their names, but by their assigned identification numbers. If participant names are included on copies of documents submitted to the Sponsor, the names (except for initials) must be obliterated and the assigned participant numbers added to the documents.

The Investigator should keep a separate log of participants' identification numbers, names, addresses, telephone numbers and hospital numbers (if applicable). Documents not for submission to the Sponsor, such as signed Informed Consent Forms, should be maintained in strict confidence by the Investigator.

Only authorized persons will have access to identifiable personal details, if required for data verification. The participant's original medical data that are reviewed at the site during source data verification by the Monitor, audits, and Health Authority inspections will be kept strictly confidential. The Investigator agrees to provide direct access to these documents to the Sponsor and to Health Authority representatives. The Investigator is responsible for retrieving information from personal medical records.

Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing participant data. Participants will be informed accordingly and will be requested to give their consent on data handling procedures in accordance with national regulations.

11 Management and Reporting of Adverse Events and Device Deficiencies

11.1 Definition of (Serious) Adverse Events and other safety related events

Adverse Event (AE) (Art. 2 [57] MDR)

Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in participants, users, or other persons whether or not related to the medical device.

Note: medical conditions presented and documented at study start, that do not worsen in severity or frequency during the study are defined as Baseline Medical Conditions and elective procedures, and NOT to be considered adverse events.

Serious Adverse Event (SAE) (Art. 2 [58] MDR)

Any adverse event that led to any of the following:

(a) death,

(b) serious deterioration in the health of the participant that resulted in any of the following:

(i) life-threatening illness or injury,

(ii) permanent impairment of a body structure or a body function,

(iii) hospitalization or prolongation of patient hospitalization,

(iv) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

(v) chronic disease,

(c) fetal distress, fetal death or a congenital physical or mental impairment or birth defect.

Note: planned hospitalization for pre-existing condition, or a procedure required by the study protocol, without a serious deterioration of the health status of the participant, is not considered an SAE.

Device deficiency (Art. 2 [59] MDR)

Inadequacy of the medical device with respect to its identity, quality, durability, reliability, safety, or performance, including malfunction, user errors and inadequate information supplied by the manufacturer.

Malfunction (ISO14155)

Failure of a medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or the study protocol.

Device deficiency with Serious Adverse Device Effect (SADE) potential (Art. 80 [1c] MDR)

Any device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.

Adverse Device Effect (ADE) (ISO14155)

Adverse events possibly, probably, or causally related to the use of a medical device or procedures.

This includes any adverse event resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, operation, or any malfunction of the medical device used in the study. This includes any event that is a result of a use error or intentional misuse.

Serious Adverse Device Effect (SADE) (ISO14155)

Adverse device effect (ADE) that has resulted in any of the consequences characteristic of a serious adverse event.

Unanticipated Serious Adverse Device Effect (USADE) (ISO14155)

SADE which by its nature, incidence, severity, or outcome has not been identified in the current risk assessment.

Adverse events categorization

The adverse events are categorized by the PI and the Sponsor or authorized designee using the following algorithm:

Does the AE meet the seriousness criteria?

- No, it is not serious
  - Is the relationship to the device or the procedure possible, probable, or causal?
    - No: non-related AE
    - Yes: ADE
- Yes, it is serious: SAE
  - Is the relationship to the device or the procedure possible, probable, or causal?
    - No: non-related SAE
    - Yes: SADE
      - Is it anticipated (within expected type, severity, and frequency of the complications)?
        - No: unanticipated SADE (USADE)
        - Yes: anticipated SADE (ASADE)

Events Not to be considered as AEs

Medical conditions presented and documented at study start that do not worsen in severity or frequency during the study are defined as Baseline Medical Conditions and elective procedures and are NOT to be considered adverse events.

11.2 Severity of Adverse Events

Investigators should assess the severity/intensity of any AE as follows:

Mild: The participant is aware of the event or symptom, but the event or symptom is easily tolerated.

Moderate: The participant experiences sufficient discomfort to interfere with or reduce his or her usual level of activity.

Severe: Significant impairment of functioning: the participant is unable to carry out usual activities.

11.3 Causality Assessment

A causal relationship towards the device(s) used in the study or the procedure of the investigation should be rated by the Investigator as follows (MDCG 2020-10/1):

- Not related: The relationship to the device or procedures can be excluded.
- Possible: The relationship with the use of the device is weak but cannot be ruled out completely. Alternative causes are also possible.
- Probable: The relationship with the use of the device seems relevant and/or the event cannot reasonably be explained by another cause.

- Causal relationship: The serious event is associated with the device or with procedures beyond reasonable doubt.

The Investigator will use clinical judgment to determine the relationship.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to the device used or study procedures will be considered and investigated.

The Investigator will also consult the Vivalink device instructions for use and/or the Vivalink device current risk assessment, when applicable, in his/her assessment.

For each AE/SAE, the Investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations in which an SADE has occurred, and the Investigator has minimal information to include in the initial report to the CRO. However, it is very important that the Investigator always makes an assessment of causality for every event before the initial transmission of the SADE data to the CRO.

The Investigator may change his/her opinion of causality in light of follow-up information and create a SADE follow-up report with the updated causality assessment.

11.4 Recording of Adverse Events

The recording period for (S)AEs/DDs begins when the participant is initially included in the study (date of signature of first informed consent) and continues until the last study protocol-specific procedure.

During the conduct of the study, the Investigator must fully record all the following:

- any AE;
- any SAE;
- any DD that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate;
- any new findings in relation to any event referred to in the previous points.

AEs/DDs must be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative) to the Investigator during visits defined in the SoA of the study protocol. The Investigator must record all directly observed events and all spontaneously reported events by the study participant. In addition, each study participant will be questioned about AEs/DDs.

All safety data AEs/SAEs, as specified above, occurring during the study, must be documented and recorded in the Case Report Form (CRF) by the Investigator, including its description, seriousness, severity (grading), duration (onset and resolution dates), causal relationship, any other potential causal factors, actions taken with the device, required treatment and outcome of the AE.

All SADEs and DDs must be also documented and recorded in the SADE Report Form and the DD Report Form, respectively, by the Investigator within 24 hours of awareness.

All AEs must be recorded in the participant's medical record and on the AE form in the eCRF. Investigators should use correct medical terminology/concepts when recording AEs on the AE form in the eCRF and avoid colloquialisms and abbreviations. Only 1 AE term should be recorded in the event field on the AE form in the eCRF. All AE terms will be coded with the most recent MedDRA version by the sponsor.

AE without resolution between participant evaluation time points should only be recorded once in the eCRF. In case there is an increase in severity and/or seriousness of the event, a new AE with the new severity and/or seriousness must be recorded as a separate event on the AE form in the eCRF.

A recurrent AE is one that occurs and resolves between participant evaluation time points and subsequently recurs. Each recurrence of an AE should be recorded as a separate event on the AE form in the eCRF.

11.5 Safety Data Collection for Reporting

Safety data collection forms:

The following safety data collection forms are used in this study:

- SADE Report Form.
- DD Report Form.

Reportable events:

The following events are reportable to the Safety Department of the CRO palleos healthcare GmbH within 24 hours of awareness:

- any SAE that has a causal relationship with the non-CE marked device used in the study or the investigation procedure or where such causal relationship is reasonably possible (SADE).
- any DD that might have led to an SAE/SADE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.

Procedure for Safety Data Reporting (completion and forwarding):

For all defined reportable events the Investigator must immediately (within 24 hours after becoming aware of the event) send a written SADE/DD Report Form by email or fax to the CRO. The Investigator must respond to any request by the CRO for follow-up information. The sponsor or authorized designee has to meet strict regulatory timelines associated with expedited safety reporting obligations (see Section 11.6).

CRO Safety Department:

- Email: CCI [redacted]

- Fax: CCI [redacted]

The data entered on the SADE Report Forms must be consistent with the information recorded in the eCRF. If some data are missing, the form should be completed with the available data and a follow-up report will be sent as soon as possible. The minimum information to be included in the initial SADE/DD report is the following:

- Investigator name and contact details
- Participant identification (e.g. ID number, sex, age)
- Medical device lot and/or serial number
- Description of the event

The SADE report should also contain causality and seriousness information, and the DD report must be assessed regarding their potential to lead to a SADE. Both reports must be signed off by the Investigator.

The CRO executes a second assessment of the SADEs concerning seriousness, relatedness and expectedness on all initial reports and relevant follow-up information to a known case. The CRO also reviews all DDs regarding their potential to lead to a SADE.

The CRO forwards each SADE and DD Report to Global Patient Safety of Merck Healthcare KGaA and to the manufacturer of the medical device as soon as possible but not later than 72 hours after becoming aware of the event.

CCI [redacted]

The Investigator must promptly respond to any request by the CRO for follow-up information or questions from the Sponsor or delegate. Such requests will be sent to the Investigator via the CRO. AEs and SAEs occurring during the study must be monitored and followed up by the Investigator until stabilization or until the outcome is known unless the participant has a fatal outcome or is lost to follow-up. All events that are still ongoing at the end of the observation period will continue to be documented as such.

The Investigator will ensure any necessary additional therapeutic measures and follow-up procedures are recorded and reported via a follow-up SADE/DD Report Form. Reasonable attempts to obtain follow-up information must be made and documented.

Reporting of any new information on a previously reported event (follow-up) will follow the procedures and timelines of the original report.

The CRO must forward the follow-up information within 72 hours to Global Patient Safety and to the manufacturer of the medical device, as noted above for initial reports.

11.6 Safety Reporting to the Competent Authorities and IEC/IRBs.

The Sponsor or authorized designee reports to the Competent Authorities (CA) any reportable event defined in Section 11.5.

The period for reporting must take account of the severity of the event:

- For all reportable events which indicate an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients, users or other persons or a new finding to it: Immediately, but not later than 2 calendar days after awareness by the Sponsor or authorized designee of a new reportable event or of new information in relation with an already reported event.
- This includes events that are of significant and unexpected nature such that they become alarming as a potential public health hazard. It also includes the possibility of multiple deaths occurring at short intervals.
- Any other reportable events or a new finding/update to it: Immediately, but not later than 7 calendar days following the date of awareness by the Sponsor or authorized designee of the new reportable event or of new information in relation with an already reported event.

Where necessary to ensure timely reporting, the sponsor or authorized designee may submit an initial report that is incomplete followed up by a complete report.

The reporting to the IECs/IRBs follows the requirements of the local ethics committees in Germany.

The Sponsor or authorized designee provides the CA and the IEC/IRB with the documentation defined in Section 11.4 at their request.

Periodic safety reporting

The Sponsor or authorized designee sends to the CA a quarterly summary evaluation with the information of all reportable SADEs and DDs occurred during the conduct of the study.

12 Plans for Disseminating and Communicating Study Results

12.1 Study Report

The study will be summarized in a final report that accurately and completely presents the study objectives, methods, results, limitations of the study, and interpretation of the findings in accordance with Annex XV Chapter I Section 2.8 and Chapter II Section 7 of Regulation (EU) 2017/745. In accordance with §64 MPDG, 12 months after completion of the study, the final report

will be submitted to BfArM; in case of premature termination or temporary suspension of the study, the study report will be submitted within 3 months.

12.2 Publication

Findings from this study will be shared in scientific meetings/congresses and described in one or more manuscripts submitted to relevant peer-reviewed medical journal(s), after the approval of the final study report. Authorship will follow the guidelines proposed by the International Committee of Medical Journal Editors (ICMJE). Authors will adhere to the ICMJE guidelines, specifically, all authors will have (1) made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) participated in drafting the article or revising it critically for important intellectual content; (3) approved the version to be published, and (4) agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. In addition, any potential conflicts of interest will be disclosed.

The Investigator will inform the Sponsor in advance about any plans to publish or present data from the study, and a publication plan will be agreed in advance between the Investigator and the Sponsor. Any publications and presentations of the results (abstracts in journals or newspapers, oral presentations, etc.), either in whole or in part, by the Investigator or representatives will require pre-submission review by the Sponsor. The Sponsor will ensure that the internal pre-submission review will take place within a reasonable timing (i.e. a month) and will not suppress or veto publications but maintains the right to delay publication in order to protect intellectual property rights.

13 References

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14 Appendices

14.1 Additional Information

14.1.1 End of the Study Questionnaire

English Wording:

1) The study app was easy to use
   1. Fully agree 2. Agree 3. Disagree 4. Fully disagree

2) The written instruction I received at the beginning of the study was easy to understand
   1. Fully agree 2. Agree 3. Disagree 4. Fully disagree

3) The verbal instruction I received at the beginning of the study was easy to understand
   1. Fully agree 2. Agree 3. Disagree 4. Fully disagree

4) Answering the questionnaire daily was acceptable for me
   1. Fully agree 2. Agree 3. Disagree 4. Fully disagree

5) Regularly labeling events was acceptable for me
   1. Fully agree 2. Agree 3. Disagree 4. Fully disagree

6) Regularly recharging the devices was acceptable for me
   1. Fully agree 2. Agree 3. Disagree 4. Fully disagree

7) I am satisfied with the support received during the study from the site
   1. Fully agree 2. Agree 3. Disagree 4. Fully disagree

8) I am satisfied with the support received during the study from the help center
   1. Fully agree 2. Agree 3. Disagree 4. Fully disagree 5. I did not need support from the help center

9) I am interested to have access to health-related data (e.g., activity level)
   1. Fully agree 2. Agree 3. Disagree 4. Fully disagree

10) I would give my physician access to real-time health related data (e.g., heart rate, respiratory rate, temperature) for the benefit of my treatment
   1. very likely 2. Maybe 3. very unlikely

11) I am using my own smartphone (not the one in the study) daily
   1. agree 2. Disagree 3. I don't have a smartphone

German Wording:

1) Die App für die Studie war einfach zu bedienen
   1: stimme voll zu 2: stimme eher zu 3: stimme eher nicht zu
   4: stimme überhaupt nicht zu

2) Die schriftliche Einweisung, die ich vor der Studie erhalten habe, war leicht verständlich
   1: stimme voll zu 2: stimme eher zu 3: stimme eher nicht zu
   4: stimme überhaupt nicht zu

3) Die mündliche Einweisung, die ich vor der Studie erhalten habe, war leicht verständlich
   1: stimme voll zu 2: stimme eher zu 3: stimme eher nicht zu
   4: stimme überhaupt nicht zu

4) Es war für mich akzeptabel, den Fragebogen täglich auszufüllen
   1: stimme voll zu 2: stimme eher zu 3: stimme eher nicht zu
   4: stimme überhaupt nicht zu

5) Es war für mich akzeptabel, regelmäßig Aktivitäten (z.B. Treppensteigen) zu kennzeichnen
   1: stimme voll zu 2: stimme eher zu 3: stimme eher nicht zu
   4: stimme überhaupt nicht zu

6) Es war für mich akzeptabel, die Geräte regelmäßig aufzuladen
   1: stimme voll zu 2: stimme eher zu 3: stimme eher nicht zu
   4: stimme überhaupt nicht zu

7) Ich bin mit der Unterstützung zufrieden, die ich während der Studie von meinem Studienarzt erhalten habe
   1: stimme voll zu 2: stimme eher zu 3: stimme eher nicht zu
   4: stimme überhaupt nicht zu

8) Ich bin mit der Unterstützung zufrieden, die ich während der Studie vom Service-Center erhalten habe
   1: stimme voll zu 2: stimme eher zu 3: stimme eher nicht zu
   4: stimme überhaupt nicht zu 5: Ich habe keine Unterstützung benötigt

9) Es ist für mich interessant, Zugang zu Daten über meinen Gesundheitszustand (z.B. mein Aktivitätsniveau) zu haben
   1: stimme voll zu 2: stimme eher zu 3: stimme eher nicht zu
   4: stimme überhaupt nicht zu

10) Um eine verbesserte Behandlung zu erhalten, würde ich meinem Arzt Zugang zu gesundheitsbezogenen Daten in Echtzeit (z.B. Atemfrequenz, Herzfrequenz, Temperatur, …) gewähren
   1: ziemlich wahrscheinlich 2: vielleicht 3: wahrscheinlich nicht

11) Ich benutze mein eigenes Smartphone (nicht das Smartphone in der Studie) täglich
1: stimme zu 2: stimme nicht zu 3: Ich besitze kein Smartphone

14.1.2 Mapping of Objectives, Outcomes and Variables

Number of objective	Objective	Outcome definition	Variables and Sources
1	To describe the distribution of sensor collected data on physical activity, heart rate, heart rate variability, temperature, respiration rate, cough frequency, and sleep pattern, by severity of COPD exacerbations	Severe/moderate COPD exacerbations (requiring a physician's intervention, emergency room visit or hospitalization) during the observation period.	COP exacerbation from the **physician charts (for the severe/moderate exacerbation):** - Occurrence (Yes/No) of COPD exacerbation - Severity of COPD exacerbation (moderate, severe) Sensor data (**Vivalink wearable device**) collected daily: - Physical activity including stair climbing *(derived parameter)* - Heart rate as beats per minute [daily average] *(derived parameter)* - Resting heart rate [daily average] *(derived parameter)* - Heart rate variability [daily average] *(derived parameter)* - Temperature [daily average, minimum -maximum values] - Respiration rate (breath per minute) [daily average] *(derived parameter)* - Ratio of in- vs expiration time [daily average min-max] *(derived parameter)* - Cough frequency *(derived parameter)* - Sleep pattern *(derived parameter)* Self-reported activities as collected daily by the **participant app**: - Coughing - coughing with sputum production - spray use, non-scheduled spray use - eating, going to bed, waking up - walking, climbing stairs - physical exercise

Number of objective	Objective	Outcome definition	Variables and Sources
2	To predict moderate or severe COPD exacerbations by building a statistical model employing sensor-derived data and demographic and medical covariates.	Severe/moderate COPD exacerbations (requiring a physician's intervention, emergency room visit or hospitalization) during the observation period.	COPD exacerbation from the **physician charts (for the severe/moderate exacerbation):** - Occurrence (Yes/No) of COPD exacerbation - Severity of COPD exacerbation (moderate, severe) Sensor data (**Vivalink wearable device**) collected daily: - Physical activity including stair climbing *(derived parameter)* - Heart rate as beats per minute [daily average] *(derived parameter)* - Resting heart rate [daily average] *(derived parameter)* - Heart rate variability [daily average] *(derived parameter)* - Temperature [daily average, minimum -maximum values] - Respiration rate (breath per minute) [daily average] *(derived parameter)* - Ratio of in- vs expiration time [daily average min-max] *(derived parameter)* - Cough frequency *(derived parameter)* - Sleep pattern *(derived parameter)* Self-reported activities (e.g., coughing, sports, sleeping) as collected by the **participant app**: - Coughing - coughing with sputum production - spray use, non-scheduled spray use - eating, going to bed, waking up - walking, climbing stairs - physical exercise Other covariates (at Day 0) from the **physician chart**: - Demographics data at baseline: (sex, age, height, and weight, race and ethnicity) - Body mass index will be calculated based on height and weight - Smoking status (current, ex-, non-smoker) - Medical history at baseline - Date of diagnosis of COPD

Number of objective	Objective	Outcome definition	Variables and Sources
			- Number of moderate or severe exacerbations prior to baseline visit (preceding 36 months, in case available) - Comorbidities at baseline - Current medication including COPD treatment at baseline - COPD severity (GOLD stage) Other covariates (Lung Function and Laboratory variables at Day 0, moderate/severe exacerbation visit and End of study visit) from the **physician chart**: - Body plethysmography parameters: FEV1 [L], FVC [L], FEV1/FVC, TLC [L] (total lung capacity), RV [L] (residual volume), FRCpleth [L] (functional reserve capacity), IC [L] (inspiratory capacity), Raw [kPa s L-1] (=ratio of sRaw to FRCpleth; airway resistance), sRaw [kPa s] (specific airway resistance), VT [L] (mean tidal volume), ERV [L] (expiratory reserve volume), IRV [L] (inspiratory reserve volume). - Blood gas analysis:(capillary) pO2 [mmHg], O2 [%] saturation and pCO2 [mmHg] - Serum CRP [mg/l] and serum procalcitonin levels [ng/ml] - - Blood count (CBC with differential); only values that are available with routine blood counts: Hb [g/dL], Hct [%], Erythrocyte count [10^6/µL], MCV [fL], MCH [pg], MCHC [g/dL], Reticulocytes [x10^3/µL] [‰ (of erythrocytes)], RDW [], platelet count [10^3/µL], WBC count [x10^3/µL], Lymphocytes [x10^3/µL] [%], Monocytes [x10^3/µL] [%], Neutrophils [x10^3/µL] [%], Eosinophils [x10^3/µL] [%], Basophils [x10^3/µL] [%]
3	To evaluate the correlation of sensor collected data with a) patients´ self-assessed health status and symptoms (CAT) at baseline and study end, b) lung function and lab values at baseline and study end, c) and with history of mild, moderate and severe exacerbations at study end.	a) Patients' health status and symptoms at baseline (Day 0) and study end will be measured as the summary score across items of the CAT questionnaire that consists of 8-items in which participants can choose a score from 0 to 5, for each visit b) Lung function will be assessed using plethysmography and lab values including Complete Blood Count with differential, Blood Gas	Patients' health status and symptoms at baseline visit and at study end visit from **patients app/questionnaire:** Summary CAT score Lung function and Laboratory values at baseline visit and study end visit **from physician charts**

Number of objective	Objective	Outcome definition	Variables and Sources
		Analysis, procalcitonin and CRP will be assessed as per standard practice at baseline (Day 0) and at study end (for details see Section 9.3) c) number, date of onset and duration of mild, moderate, and severe exacerbations, respectively, during the observation period	- Body plethysmography parameters: FEV1 [L], FVC [L], FEV1/FVC, TLC [L] (total lung capacity), RV [L] (residual volume), FRCpleth [L] (functional reserve capacity), IC [L] (inspiratory capacity), Raw [kPa s L-1] (=ratio of sRaw to FRCpleth; airway resistance), sRaw [kPa s] (specific airway resistance), VT [L] (mean tidal volume), ERV [L] (expiratory reserve volume), IRV [L] (inspiratory reserve volume). - Blood gas analysis:(capillary) pO2 [mmHg], O2 saturation [%] and pCO2 [mmHg] - Serum CRP [mg/l] and serum procalcitonin levels [ng/ml] - Blood count (CBC with differential); only values that are available with routine blood counts: Hb [g/dL], Hct [%], Erythrocyte count [10^6/µlL, MCV [fL], MCH [pg], MCHC [pg/L], Reticulocytes [x10^3/µL] [‰ (of erythrocytes)], RDW [], platelet count [10^3/µL], WBC count [x10^3/µL], Lymphocytes [x10^3/µL] [%], Monocytes [x10^3/µL] [%], Neutrophils [x10^3/µL] [%], Eosinophils [x10^3/µL] [%], Basophils [x10^3/µL] [%] COPD exacerbations during the observation period from the **physician charts (for the severe/moderate exacerbation)** and from the **patients app (for the mild exacerbations):** Number, date of onset, duration of COPD exacerbations
4	Sensor derived data may be related to the CAT score, therefore, an additional objective is to investigate whether changes in physical activity, heart rate, heart rate variability, temperature, respiration rate, cough frequency, and sleep pattern in the 3-month observation period, are associated with changes of the patient self-assessed symptoms (CAT).	Please see above (3a) During the observation period the CAT score will be obtained on a daily basis. Daily summary score across items of the CAT questionnaire will be computed.	Self-reported COPD symptoms via the CAT questionnaire daily obtained from the **patients app**: - Daily summary score (The total CAT score will have a maximum = 40). - Change of the CAT score of 2 points or more Sensor data (**Vivalink wearable device**) collected daily: - Physical activity including stair climbing *(derived parameter)* - Heart rate as beats per minute [daily average] *(derived parameter)* - Resting heart rate [daily average] *(derived parameter)* - Heart rate variability [daily average] *(derived parameter)* - Temperature [daily average, minimum -maximum values]

Number of objective	Objective	Outcome definition	Variables and Sources
			- Respiration rate (breath per minute) [daily average] *(derived parameter)* - Ratio of in- vs expiration time [daily average min-max] *(derived parameter)* - Cough frequency *(derived parameter)* - Sleep pattern *(derived parameter)* Self-reported activities as collected by the **patients app:** - Coughing - coughing with sputum production - spray use, non-scheduled spray use - eating, going to bed, waking up - walking, climbing stairs - physical exercise
5	To predict the CAT score and changes thereof by building a statistical model employing sensor-derived data and demographic and medical covariates.	Patients' health status and symptoms at baseline (Day 0) will be measured as the summary score across items of the CAT questionnaire that consists of 8-items in which participants can choose a score from 0 to 5. During the observation period the CAT score will be obtained via a digital application on a daily basis.	Self-reported COPD symptoms via the CAT questionnaire daily obtained from the **patients app**: - Daily summary score (The total CAT score will have a maximum = 40). - Change of the CAT score of 2 points or more Sensor data (**Vivalink wearable device**) collected daily: - Physical activity including stair climbing *(derived parameter)* - Heart rate as beats per minute [daily average] *(derived parameter)* - Resting heart rate [daily average] *(derived parameter)* - Heart rate variability [daily average] *(derived parameter)* - Temperature [daily average, minimum -maximum values] - Respiration rate (breath per minute) [daily average] *(derived parameter)* - Ratio of in- vs expiration time [daily average min-max] *(derived parameter)* - Cough frequency *(derived parameter)* - Sleep pattern *(derived parameter)* Self-reported activities as collected by the **patient app:** - Coughing - coughing with sputum production

Number of objective	Objective	Outcome definition	Variables and Sources
			- spray use, non-scheduled spray use - eating, going to bed, waking up - walking, climbing stairs - physical exercise Other covariates (at Day 0) from the **physician chart**: - Demographics data at baseline: (sex, age, height, and weight, race and ethnicity) - Body mass index will be calculated based on height and weight - Smoking status (current, ex-, non-smoker) - Medical history at baseline - Date of diagnosis of COPD - Number of moderate or severe exacerbations prior to baseline visit (preceding 36 months, in case available) - Comorbidities at baseline - Current medication including COPD treatment at baseline - COPD severity (GOLD stage) Other covariates (Lung Function and Laboratory variables at Day 0, moderate/severe exacerbation visit and End of study visit) from the **physician chart**: - Body plethysmography parameters: FEV1 [L], FVC [L], FEV1/FVC, TLC [L] (total lung capacity), RV [L] (residual volume), FRCpleth [L] (functional reserve capacity), IC [L] (inspiratory capacity), Raw [kPa s L-1] (=ratio of sRaw to FRCpleth; airway resistance), sRaw [kPa s] (specific airway resistance), VT [L] (mean tidal volume), ERV [L] (expiratory reserve volume), IRV [L] (inspiratory reserve volume). - Blood gas analysis:(capillary) pO2 [mmHg], O2 saturation [%] and pCO2 [mmHg] - Serum CRP [mg/l] and serum procalcitonin levels [ng/ml] -

Number of objective	Objective	Outcome definition	Variables and Sources
			- Blood count (CBC with differential); only values that are available with routine blood counts: Hb [g/dL], Hct [%], Erythrocyte count [10^6/µl], MCV [fl], MCH [pg], MCHC [g/dL], Reticulocytes [x10^3/µL] [‰ (of erythrocytes)], RDW [], platelet count [10^3/µL], WBC count [x10^3/µL], Lymphocytes [x10^3/µL] [%], Monocytes [x10^3/µL] [%], Neutrophils [x10^3/µL] [%], Eosinophils [x10^3/µL] [%], Basophils [x10^3/µL] [%]

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14.2 Signature Pages and Responsible Persons for the Study

Signature Page – Protocol Lead

Study Title:	A study to investigate the association of real-world sensor-derived biometric data with clinical parameters and patient-reported outcomes for monitoring disease activity in patients with COPD
Study Protocol Date / Version:	01 MAR 2023 / 3.0

Protocol Lead responsible for designing the study:

I approve the design of PPD

PPD

Signature

Date of Signature

Name, academic degree: PPD

Function / Title: Associate Director Clinical Research Bioelectronics

Institution: Merck Healthcare KGaA
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Telephone number: PPD

Fax number: NAP

E-mail address: PPD

Company substance code **INN**
MS202559_0001

Signature Page – Coordinating Investigator

Study Title	A study to investigate the association of real-world sensor-derived biometric data with clinical parameters and patient-reported outcomes for monitoring disease activity in patients with COPD
Study Protocol Date / Version	01 MAR 2023 / 3.0

I approve the design of the study and I understand and will conduct the study according to the study protocol, any approved protocol amendments, Good Clinical Practice (GCP) and all applicable Health Authority requirements and national laws.

PPD

Signature

PPD

Date of Signature

Name, academic degree: PPD

Function / Title:

Institution:

Address:

Telephone number:

Fax number:

E-mail address: