Protocol

	Document Number:	**c39406431-01**
EudraCT No. **EU Study No.**	N/A	
BI Study No.	1490-0005	
BI Investigational Product(s)	[redacted]	
Title	A multi-center, longitudinal 12-week pilot study to evaluate cough severity and its impact, utilizing a next generation cough monitor, in participants with idiopathic pulmonary fibrosis (IPF) or Non IPF Pulmonary Fibrosis	
Lay Title	A study in people with pulmonary fibrosis to monitor cough with a wearable device	
Clinical Phase	N/A	
Clinical Trial Leader	[redacted] On behalf of [redacted] Phone [redacted] / Fax: [redacted] Email: [redacted]	
Coordinating Investigator	[redacted] Phone: [redacted] Email: [redacted]	
Current Version and Date	Version 1.0 / 16 Sep 2022	
Original Protocol Date	16 Sep 2022	**Page 1 of 71**

PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Original Protocol date	16 Sep 2022
Revision date	N/A
BI study number	1490-0005
Title of study	A multi-center, longitudinal 12-week pilot study to evaluate cough severity and its impact, utilizing next generation cough monitoring, in participants with idiopathic pulmonary fibrosis (IPF) or Non IPF pulmonary fibrosis.
Coordinating Investigator	[redacted]
Study site(s)	Multi-centre study in approximately 5-7 countries.
Clinical phase	N/A
Study rationale	A further understanding of the similarities and differences in cough among persons with Non IPF forms of pulmonary fibrosis and IPF, together with insight into the pattern and impact of cough in these patients is required. The current pilot aims to assess cough frequency, indirect measures of cough intensity and the association between objective cough measures and lung physiology and various patient-reported outcome measures in a patient cohort with Non IPF forms of pulmonary fibrosis and IPF.
Study objective(s)	The primary objective of this study is to objectively quantify cough frequency over 12 weeks in a cohort of subjects with IPF or Non IPF pulmonary fibrosis using a digitally enabled cough monitor. Additionally, we will assess the feasibility of hybrid study design, utilizing [redacted] cough monitoring and remote video-assisted home spirometry.
Study endpoints	Primary Endpoint: Cough count per hour (CC/hr) measured over a 24-hour period at baseline visit, Week 4(V4), Week 8(V5), Week 12 (V6). Secondary Endpoints: • Change from baseline in CC/hr at Week 4, Week 8, Week 12 • FVC (mL) at baseline • FVC (mL) at Week 12 • Change from baseline in FVC (mL) at Week 12 • Feasibility of remote cough data capture (defined as % of analysable data per 24-hour recording) • Feasibility of hybrid study design (successful completion of all elements of remote visit)
Study design	Low intervention, 12-week pilot study, utilizing a digitally enabled cough monitor and hybrid study design, in subjects with IPF or Non IPF pulmonary fibrosis.

Total number of patients	50
Number of patients per assessment	50
Diagnosis	Idiopathic Pulmonary Fibrosis (IPF) or Non IPF pulmonary fibrosis
Main inclusion and exclusion criteria	Inclusion: • Subject ≥ 18 years old • Subject diagnosed with IPF by ATS/ERS/JRS/ALAT guidelines or Non-IPF Pulmonary Fibrosis (≥ 10% fibrosis on HRCT as per PI assessment) within the past 12 months • FVC ≥ 40% predicted at baseline • Life expectancy > 6 months (per assessment of treating physician) Exclusion: • Current smokers • Upper respiratory tract infection (URTI) or Lower respiratory tract infection (LRTI) [including COVID-19 infection] within 4 weeks • Airflow obstruction (FEV1/FVC ≤ 0.70) at baseline or known history of significant spirometry response to BD • Initiation or change in dose or type of anti-tussive medication, angiotensin-converting enzyme (ACE) inhibitors, or corticosteroids in the 4 weeks prior to study entry • Initiation or change of opiate dose within 4 weeks of study entry • Subject with ILD exacerbation as defined by the investigator within 4 weeks prior to study entry
Device	[redacted] Wearable Cough Monitor
Mode of administration	Transcutaneous - adheres to chest wall
Comparator product(s)	Not applicable
Duration of assessment	12 weeks
Statistical methods	Descriptive statistics will be presented for all primary and secondary endpoints. Additionally, CC/hour will be log transformed and summarized in terms of geometric mean and 95% confidence intervals. [redacted]

FLOW CHART

Study Periods	Screening*	Baseline* Visit	Remote Study Visits				EoS Visit
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7/EoS**
Days	- 1 wk	1	3	28	56	82	84
Time window for visits			+ 2 days	± 5 days	± 5 days	- 2 days	± 5 days
Informed consent	X						
Review of in-/exclusion criteria	X						
[redacted]	[redacted]	[redacted]		[redacted]	[redacted]		[redacted]
[redacted]		[redacted]		[redacted]	[redacted]		[redacted]
Demographics	X						
Smoking Status/history	X						
Medical history (Comorbidities)	X						
Pregnancy status (where available)	X						X
COVID-19 history (including vaccination status)	X						
Non IPF Pulmonary Fibrosis (including ILD diagnosis category) or IPF	X						
Progressive Pulmonary Fibrosis Phenotype (Y/N)	X						
Concomitant therapy (including prescription medications for Pulmonary Fibrosis)		X		X	X		X
Historical Pulmonary Function Tests (FVC & DLCO)[2]	X						
Historical HRCT Pattern[3] (UIP, Probable UIP, Indeterminate for UIP, Inconsistent w/UIP)	X						
Physical examination		X					X
Vital signs[4]		X					X
SpO_2		X					X
In-Office Spirometry[5]		X					X
[redacted]		[redacted]					[redacted]
Distribute & provide instruction on cough monitor		X					
Distribute & provide instruction on home spirometer		X					
Home Spirometry			X[7,9]	X	X	X[7,9]	
Reporting of AEs/SAEs[10] & Unscheduled clinical visits		X		X	X		X
Videoconference remote visit				X	X		
24-hour cough monitor [redacted] recording[11]		X		X[11]	X[11]	X[11]	
24-hour cough monitor data upload[12]		X		X	X	X	
Remote Procedures Compliance Check [13] (Home spirometry, Videoconference remote visit (V4, V5), [redacted] & Cough recordings)			X	X	X	X	
Return of cough monitor & home spirometer							X
Patient survey regarding use of cough monitor and home spirometer							X

Study Periods	Screening*	Baseline* Visit	Remote Study Visits				EoS Visit
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7/EoS**
Days	- 1 wk	1	3	28	56	82	84
Completion of patient participation							X

*Screening and Baseline Visit can occur on the same day.

[redacted]

2) Most proximate historical FVC & DLCO within 6 months and most distant FVC & DLCO within 12 months should be recorded
3) Most proximate historical HRCT performed within the previous 12 months
4) Measurements of vital signs should precede blood sampling
5) Site personnel should confirm that FVC continues to meet eligibility criteria for study inclusion prior to preceding with additional study procedures

[redacted]

7) Patients will need to complete home spirometry within 72 hours, but not on the same day as Visit 2/Baseline study visit.
8) Patients will need to complete home spirometry in the 72 hrs preceding the day of Visit 7/EoS
9) Efforts should be made to perform spirometric measurements at approximately the same time of the day, at least within the same half-day (morning vs afternoon).
10) As described in Section 5.2.6.1.1
11) 24-hour cough recording should be initiated immediately following the end of the remote visit.
12) 24-hour cough recording data upload should occur immediately after completion of 24-hour CC recording. Patients should place the biosensor on the charger next to the study provisioned mobile phone to allow for data to upload.
13) Study personnel conducting the visit will review whether the intended procedures for the visit have been completed. If not, the study team will inquire as to whether the patient requires assistance with any specific aspects of the visit. Site staff will receive notification via email each time a patient completes a cough count recording with successful data upload. If the site does not receive this type of notification, the site should contact the patient to assess whether the patient requires assistance with any elements of the 24 hour cough recording and upload.

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ABBREVIATIONS AND DEFINITIONS

(e)COA	(electronic) Clinical Outcome Assessment
ACE	Angiotensin-Converting Enzyme
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALAT	Asociación Latinoamericana de Tórax
ALCOA	Attributable, Legible, Contemporaneous, Original, Accurate
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATS	American Thoracic Society
AUC	Area under the Curve
BI	Boehringer Ingelheim
C3M	Fragment of type III collagen released by matrix metalloproteinase
C6M	Fragment of type VIa1 collagen released by matrix metalloproteinase-2
CA	Competent Authority
CA-125 (19.9)	Cancer antigen-125 (19.9)
CBO	Clinical Biosample Operations
CCI	Commercially Confidential Information
CDP	Clinical development plan
CES	Cough Evaluable Set
CI	Confidence Interval
CRA	Clinical Research Associate
CRF	Case Report Form, paper or electronic (sometimes referred to as “eCRF”)
CRO	Contract Research Organisation
CT Leader	Clinical Trial Leader
CT Manager	Clinical Trial Manager
CTCAE	Common Terminology Criteria for Adverse Events
CTgov	ClinicalTrials.gov
CTP	Clinical Trial Protocol
CTR	Clinical Study Report
DBL	Database Lock
DLCO	Diffusing Capacity of the Lungs for Carbon Monoxide
EC	Ethics Committee

ECD	Early Clinical Development
eCRF	Electronic Case Report Form
eDC	Electronic Data Capture
EoS	End of Study (corresponds with End of Trial)
ePRO	Electronic Patient Reported Outcome
ERS	European Respiratory Society
FAS	Full Analysis Set
FC	Flow Chart
FEV1	Forced expiratory volume in one second
FUP	Follow-up
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GERD	Gastroesophageal Reflux Disease
GPV	Global Pharmacovigilance
GRL	Global Regulatory Lead
HA	Health Authority
HRCT	High Resolution Computed Tomography
[redacted]	[redacted]
ICAM-1	Intracellular adhesion molecule 1
IEC	Independent Ethics Committee
ILD	Interstitial Lung Disease
IPF	Idiopathic Pulmonary Fibrosis
IRB	Institutional Review Board
ISF	Investigator Site File
JRS	Japanese Respiratory Society
[redacted]	[redacted]
[redacted]	[redacted]
LPLV	Last patient last visit
LRTI	Lower Respiratory Tract Infection
MMP-7	Matrix metalloproteinase 7
PF	Pulmonary Fibrosis
[redacted]	[redacted]
[redacted]	[redacted]

PPF	Progressive Pulmonary Fibrosis
[redacted]	[redacted]
PRO-C3	Fragment of N-terminal type III collagen
PRO-C6	Fragment of C-terminal type VIa3 collagen
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Steering Committee [redacted]
[redacted]	
SP-D	Surfactant protein-D
TA	Therapeutic Area
TAH	Therapeutic Area Head
TBA	Trial Bioanalyst
TBMA	Trial Biomarker Analyst
TMCP	Translational Medicine & Clinical Pharmacology
TMF	Trial Master File
UIP	Usual Interstitial Pneumonitis
URI	Upper Respiratory Tract Infection
[redacted]	[redacted]
VICM	Fragment of citrullinated vimentin released by MMP
WOCBP	Woman of childbearing potential

1. INTRODUCTION

Interstitial lung diseases (ILDs) encompass a large group of over 200 pulmonary disorders, characterized by abnormalities in the distal lung parenchyma. Irrespective of the underlying pathophysiology, the resulting alteration of the interstitial space leads to clinical symptoms such as dyspnoea and cough and physiologic abnormalities such as restrictive ventilatory deficit on pulmonary function testing [R16-0722]. Associated risk factors include cigarette smoking, environmental exposures, microbial pathogens, and genetics [R20-3543]. Idiopathic pulmonary fibrosis (IPF) is the most common and the most severe of the chronic fibrosing ILDs, and the epidemiology of this disease and its course are relatively well documented. Epidemiological data and understanding of other forms of fibrosing ILD other than IPF is limited to date, in part due to the complex nature of these diseases and their rarity [R20-3543].

In patients with IPF, refractory cough is one of the most important and burdensome symptoms with up to 80% of patients reporting chronic cough in some studies. Limited objective data in IPF suggest that persons with IPF experience higher cough counts than those with COPD or asthma [P18-00823]. In patients with non-IPF forms of pulmonary fibrosis, persistent cough is also a commonly reported symptom. The mechanisms of increased cough in this population are also not well understood. Comorbid conditions, such as GERD, obstructive sleep apnea and COPD may contribute. Other potential etiologies include mechanical distortion of peripheral nerve receptors, destruction of inhibitory nerves, upregulation of cough signalling receptors and possibly central mechanisms [R22-2500]. Nevertheless, the incidence of persistent and disruptive cough in this patient population, the cough pattern and frequency, as well as the impact of cough on quality of life, are not well-described.

Notably, cough has been shown to be an independent predictor of disease progression in patients with IPF [R12-1608]. In persons with fibrosing forms of ILD, including IPF, [redacted], was associated with higher risk of death, lung transplantation and respiratory hospitalization [P22-05773]. It has been hypothesized that cough may enhance fibrotic remodeling via cough induced mechanical stretch and stress [R22-2497]. Further physiologic consequences of cough, including potential hemodynamic impact, have not been well investigated. In sum, a better understanding of cough frequency and intensity across patients with pulmonary fibrosis and its relation to functional and physiologic parameters is important to elucidate its potential association with disease progression.

1.1 MEDICAL BACKGROUND

The assessment of cough in IPF and Fibrosing ILDs is challenging. Several patient-reported measures that were developed in non ILD disease indications have been utilized for subjective assessment of cough in persons with IPF and other forms of Non IPF pulmonary fibrosis. These include the [redacted], and the [redacted] Few studies in IPF and Fibrosing ILD have objectively assessed cough.

The majority of objective data characterizing cough in IPF has been derived from clinical trials of anti-tussive therapy. Cough frequency (i.e. cough count) reduction has been used as the preferred primary endpoint in clinical trials of anti-tussive therapy in IPF. While these trials

offer valuable insights, they have been limited in number and size and have utilized monitors with limited capacity to capture multidimensional facets of cough. For example, while cough frequency has been well studied in the refractory chronic cough population and at limited scale (as mentioned) in IPF, cough intensity has not been routinely measured in these same groups.

The lack of evaluation of cough intensity in clinical trials may stem from inherent limitations in non-invasive methods of measurement as well as lack of consensus on definitions of "cough intensity". We speculate that cough intensity, perhaps more than frequency, could be a driver of mechanical stress and micro-injury that promotes fibrosis in some patients with IPF or Fibrosing ILD. Studies demonstrating the impact of increased intrathoracic pressure and lung stretch associated with cough suggest that focusing on the "intensity" of cough in persons with pulmonary fibrosis may be well founded. Early studies suggest that healthy volunteers can generate up to 300 mm Hg of intrathoracic pressure in the context of maximal effort voluntary coughing [R22-2499, P22-05773, R22-2498]. Interestingly, Sharpey-Schafer (J. Physiol 1953) described that the rise in intrathoracic pressure associated with forceful voluntary cough was also associated with a decrease in arterial blood pressure and rise in heart rate that was "proportional to the violence of the cough" [R22-2499]. Froese et al. have shown in *ex-vivo* lung slices from pulmonary fibrosis biopsy specimens that increased mechanical stretch is associated with increased TGF-β1 release, which was not observed in control lung slices. Lastly, in animal models of lung injury, increased fibroproliferation was seen in animals exposed to higher levels of driving pressure and mechanical power [R22-2496]. In aggregate, these data provide conceptual rationale for how increased intrathoracic pressure and lung stretch associated with forceful cough may potentially impact the trajectory of cardiopulmonary disease in persons with IPF and Fibrosing ILD.

As highlighted, significant gaps in knowledge remain regarding etiology of cough, consequences of cough and appropriate treatment of cough in patients with pulmonary fibrosis. A further understanding of the similarities and differences in cough among persons with Non IPF forms of pulmonary fibrosis and IPF, together with insight into the pattern and impact of cough in these patients is required. The current pilot aims to assess cough frequency, indirect measures of cough intensity and the association between objective cough measures and lung physiology and various patient-reported outcome measures in a patient cohort with Non IPF forms of pulmonary fibrosis and IPF. We will perform these assessments with a digitally enabled cough monitor [redacted] and aim to concurrently assess the feasibility of remote monitoring in persons with pulmonary fibrosis. Achieving these aims will expand understanding of the disease and its symptoms, narrow an existing gap in knowledge, and help support the development of therapeutic compounds that target this distressing and potentially devastating symptom.

1.2 DEVICE PROFILE

The [redacted] monitor will be used to objectively measure cough and other exploratory parameters, during the pilot study.

The [redacted] is a lung sound recording system [redacted] that has achieved FDA 510K clearance and CE marking. The [redacted] has been validated to objectively measure cough count. It has been assessed in comparison to manual cough count in the inpatient and outpatient settings in persons with varying forms of cardiopulmonary disease

(COPD, asthma, COVID infection, CHF). The [redacted] consists of the [redacted] biosensor, which adheres to the chest wall via a consumable adhesive, replaced daily. Once the 24-hour recording is complete, the [redacted] biosensor will be placed on the [redacted] Charging station. The [redacted] biosensor will connect via Bluetooth to the [redacted] app on a study provided mobile phone, which should be placed next to the [redacted] Charging station. The biosensor will upload data to the [redacted] app [redacted] platform within a 24-hour period. A proprietary machine learning algorithm is utilized to annotate the recording for cough events over the recording period. An acoustic signal output is made available via the [redacted] platform. For quality control of the machine learning algorithm; all cough annotations are reviewed manually. Raw data outputs are also available for review and discussion.

1.3 RATIONALE FOR PERFORMING THE STUDY

As highlighted, significant gaps in knowledge remain regarding etiology of cough, consequences of cough and appropriate treatment of cough in patients with pulmonary fibrosis. A further understanding of the similarities and differences in cough among persons with Non IPF Pulmonary Fibrosis and IPF, together with insight into the pattern and impact of cough in these patients is required.

The current pilot aims to assess cough frequency, indirect measures of cough intensity and the association between objective cough measures and lung physiology, a host of patient-reported outcomes and blood-based biomarkers in a patient cohort with Non IPF Pulmonary Fibrosis or IPF. This study aims to expand the understanding of the disease and its symptoms, thereby narrowing the existing gap in knowledge, and to help support the development of future compounds targeting cough.

We will utilize a hybrid study design in which 4 visits will be conducted remotely and all cough data will be captured via a wearable, digitally enabled cough monitor with bluetooth capabilities that allow secure remote upload. Furthermore, patients will perform video-assisted home spirometry. The intention of incorporating 4 remote visits into the study design is to assess the potential to ease the burden of study procedures on patients and physicians, thereby broadening the subject pool to those who might otherwise not have access to enroll in this pilot. If successful, this type of study design could also be employed in Phase 2 and 3 interventional trials and allow a broader and more racially, geographically, and socioeconomically diverse patient population access to clinical trials.

1.4 BENEFIT - RISK ASSESSMENT

1.4.1 Benefits

This pilot study offers patients a unique opportunity to utilize emerging, wearable, digital technology for remote monitoring of what is typically a quite vexing symptom (cough). Additionally, patients will have the opportunity to utilize video assisted home spirometry to minimize on site visits. Other data derived from the cough monitor may also inform disease assessment in future clinical care, though may not be of imminent benefit to patients in the study.

1.4.2 Risks

The risks of utilizing a wearable cough monitor are minimal. Skin irritation caused by the adhesive used to apply the device to the chest wall is possible, though not anticipated, and if present would not be expected to be severe. Continuous audio recordings may raise concern for privacy breaches and/or inadvertent recording of conversations. The [redacted] biosensor data is fully encrypted on device and in transit to prevent unauthorized access to health information. [redacted] does not contain an open-air microphone and is not designed to acquire speech or other sounds from a patient's mouth. It is intended to acquire sounds of the lungs and airways including cough sounds, wheeze sounds and normal breath sounds. The file is reversed to avoid discernible speech (if incidentally acquired) being interpretable during a QA/QC session in addition to a speech filter being applied to the raw transmission data to remove speech signatures from review. Files are broken up into short <60 second segments to reduce the risk further of any post-processed file containing discernible speech over a long enough period of time to capture private conversations and information.

1.4.3 Discussion

In sum, patients have the opportunity in this pilot study to utilize new digital technology for self-monitoring and remote data upload from their homes. The study design also eases travel burden by including remote study visits. While both parameters may not have immediate benefit to the patient, they may have near term benefit for patients in upcoming trials of therapeutic interventions and have potential to advance the science supporting the use of wearable technology in routine clinical care. These potential benefits come with a small risk of skin irritation and the very unlikely prospect of data privacy breaches. In all, we believe the interventions in this study are non-invasive, nonintrusive, and likely to offer more benefit than risk to patients who choose to participate.

2. STUDY OBJECTIVES AND ENDPOINTS

A further understanding of the similarities and differences in cough among persons with Non IPF forms of pulmonary fibrosis and IPF, together with insight into the pattern and impact of cough in these patients is required. The current pilot aims to assess cough frequency, indirect measures of cough intensity and the association between objective cough measures and lung physiology and various patient-reported outcome measures in a patient cohort with Non IPF forms of pulmonary fibrosis and IPF. We will perform these assessments with a digitally enabled cough monitor [redacted] and video assisted remote spirometry with the concurrent aim of assessing the feasibility of remote monitoring in persons with pulmonary fibrosis.

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The primary objective of this study is to objectively describe cough frequency, utilizing four 24-hour cough recordings over 12 weeks in a cohort of subjects with Non IPF Pulmonary Fibrosis or IPF using the [redacted] cough monitor.

The secondary objectives for this study are:
- Assess the relationship between objective cough frequency and FVC (mL)
- Assess feasibility of patient performed remote cough data upload
- Assess feasibility of hybrid study design (% successful completion of remote visits)

2.1.2 Primary endpoint(s)

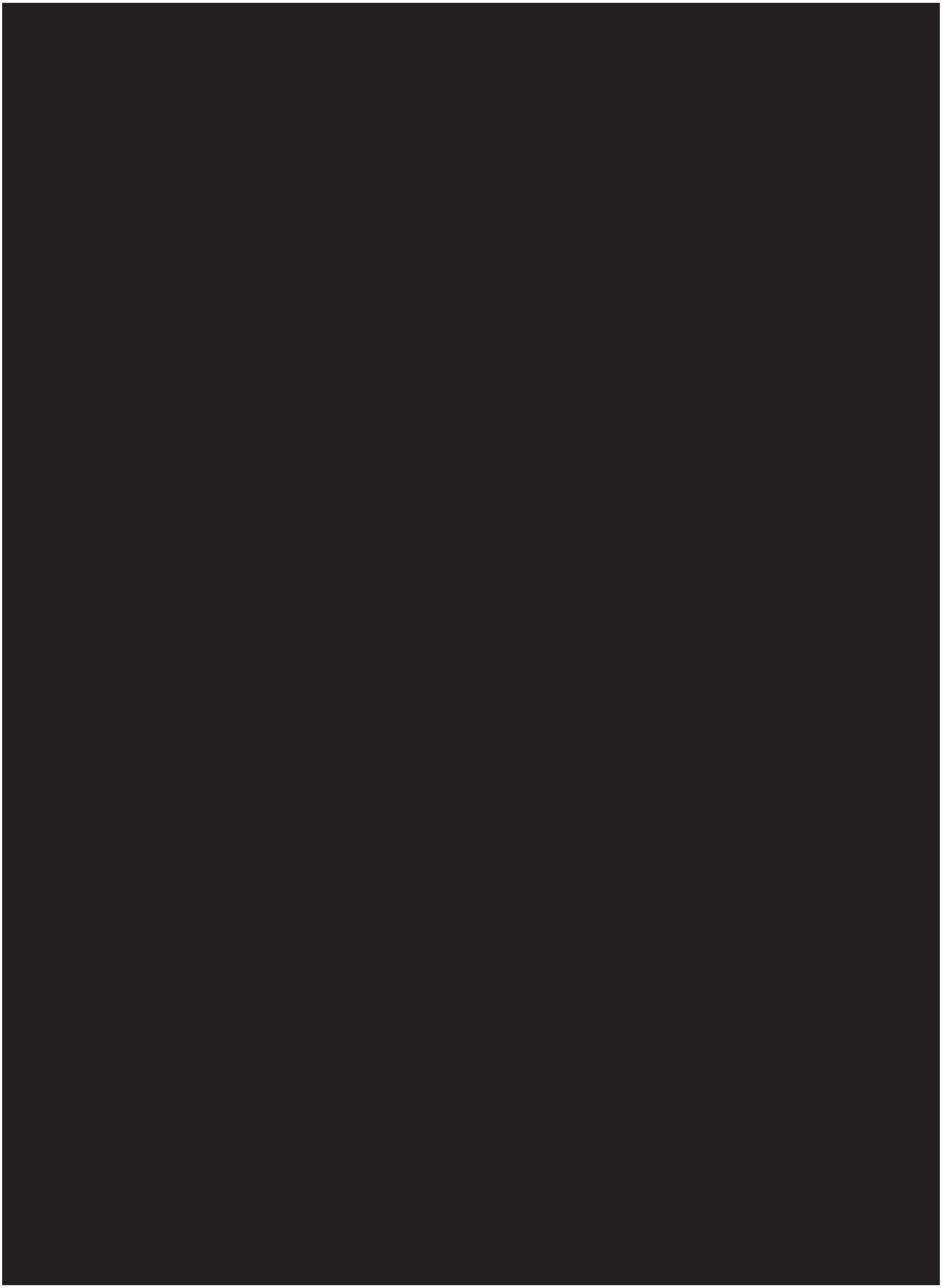
Primary Endpoints: Cough count per hour (CC/hr) measured over a 24-hour period at baseline visit, Week 4(V4), Week 8(V5), Week 12 (V6).

2.1.3 Secondary endpoint(s)

Secondary endpoints include:

- Change from baseline in CC/hr at Week 4, Week 8, Week 12.
- FVC (mL) at baseline
- FVC (mL) at Week 12
- Change from baseline in FVC (mL) at Week 12
- Feasibility of remote cough data capture (defined as % of analysable data per 24-hour recording)
- Feasibility of hybrid study design (successful completion of all elements of remote visit)

[redacted]



3. DESCRIPTION OF DESIGN AND STUDY POPULATION

3.1 OVERALL STUDY DESIGN

The proposed pilot is a multi-center, exploratory low-intervention study (without an investigational medicinal product), in which a digitally enabled cough monitoring device will be worn by approximately 50 evaluable subjects with Non IPF pulmonary fibrosis or IPF across sites in North America and Europe.

The eligible subjects will be identified by the participating specialist physicians including pneumologists involved in the diagnosis, treatment, and management of Fibrosing ILD and IPF. The participant selection process will be consecutive, and the participating specialist physicians will be provided guidance to minimize any potential selection bias. Eligible subjects must be previously diagnosed with Non IPF Pulmonary Fibrosis or IPF and will be asked to provide informed consent prior to inclusion in the study.

Consenting subjects will be followed for a maximum period of 12 weeks (Figure 3.1: 1); all subjects will participate in 7 visits, 3 in person and 4 remote visits.

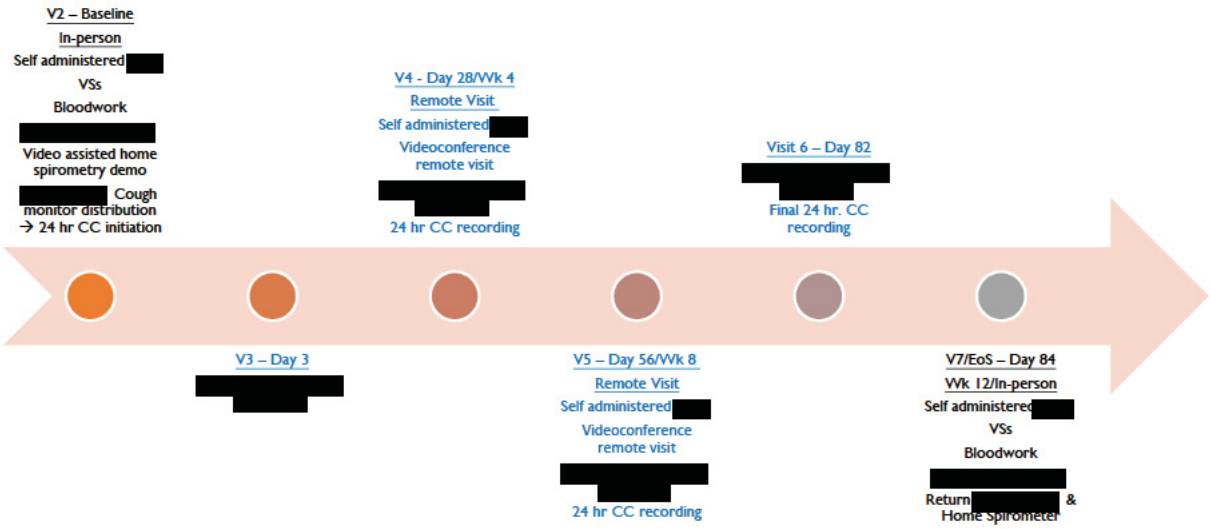


Figure 3.1: 1 Study design

[redacted], CC- cough count

3.2 DISCUSSION OF STUDY DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP(S)

The [redacted] device has been validated for the assessment of lung sounds, including cough. A principal goal of this study is to gain experience with the use of the [redacted] in evaluating cough frequency in a real-world setting in persons with pulmonary fibrosis. Additionally, the [redacted] device is capable of measuring cough intensity via assessment of the strength of the audio signal, cough frequency in relation to positional changes, and cough frequency in relation to activity. This type of multifaceted assessment of cough is not routinely provided by existing cough monitors. For these reasons, an exploratory

pilot study design will be pursued in which all subjects will utilize the [redacted] cough monitor to characterize their cough.

3.3 SELECTION OF STUDY POPULATION

The study population will include subjects (aged 18 and above) with Non IPF Pulmonary Fibrosis (defined as ≥ 10% fibrosis on high resolution Chest CT as per principal investigator assessment) or IPF who are residing in one of the target countries and follow the routine clinical practice of the participating sites. We will target enrolment of 25 subjects with Non IPF Pulmonary Fibrosis and 25 with IPF.
Screening of patients for this study is competitive, i.e. screening for the study will stop at all sites at the same time once a sufficient number of patients has been screened. Investigators will be notified about screening completion and will then not be allowed to screen additional patients for this study. Patients already in screening at this time will be allowed to continue to enrollment if eligible.

A log of all patients enrolled into the study (i.e. who have signed informed consent) will be maintained in the Investigator Site File (ISF) irrespective of whether they chose to complete the study or not.

3.3.1 Main diagnosis for study entry

The study population will include subjects (aged 18 and above) with Non IPF Pulmonary Fibrosis or IPF, who are residing in one of the target countries. The study population will be enriched (70% of study population) for persons with clinically significant cough at the Screening Visit, defined as having [redacted]

3.3.2 Inclusion criteria

Subjects fulfilling all the following inclusion criteria will be eligible for participation in the study:

1. Provision of signed informed consent in writing prior to study data collection
2. Subject aged 18 years or over
3. Subject diagnosed with Non IPF Pulmonary Fibrosis (≥10% fibrosis on HRCT by principal investigator assessment) or IPF as per ATS/ERS/JRS/ALAT Guidelines [P22-03204] within the past 12 months
4. FVC ≥ 40% predicted at baseline visit
5. Life expectancy > 6 months (per assessment of treating physician)

3.3.3 Exclusion criteria

Subjects fulfilling any of the following exclusion criteria will not be eligible for participation in the study:

1. Current smokers
2. URI or LRTI (including COVID-19 infection) within 4 weeks of screening visit
3. Airflow obstruction (FEV1/FVC ≤ 70%) at baseline or known history of significant spirometry response to bronchodilator
4. Cough due to etiology other than ILD (e.g., allergic rhinitis, GERD)

5. Other respiratory disorders including, but not limited to, a current diagnosis of any obstructive disease including chronic obstructive pulmonary disease (COPD) and asthma, active tuberculosis, lung cancer in treatment or in medical history, sleep apnea, known alpha-1 antitrypsin deficiency, cor pulmonale, clinically significant pulmonary hypertension, clinically significant bronchiectasis, or other active pulmonary diseases.
6. Initiation or change in dose or type of anti-tussive medication, angiotensin-converting enzyme (ACE) inhibitors, opiates, and systemic or inhaled (excluding intranasal) corticosteroids in the 4 weeks prior to study entry
7. Subject with ILD exacerbation as defined by investigators within 4 weeks prior to study entry
8. Subject participating in a clinical study of a systemic or inhaled drug at the time of enrollment
9. Visual, cognitive, motor or health impairment that, as judged by the investigator, may cause concern regarding the subjects' ability to complete study assessments
10. Subject not being fluent and literate in one of the main languages of the country

3.3.4 Discontinuation of patients from assessments

Patients may discontinue study participation or withdraw consent to study participation at any time ("withdrawal of consent"). If the patients agree, they should stay in the study. Even if continuing to wear the cough monitor is not possible, they should attend further study visits to collect important study data.

An individual patient will discontinue the study if:

- The patient has repeatedly shown to be non-compliant with important study procedures and, in the opinion of both, the investigator and contracting entity representative, is not willing or able to adhere to the study requirements in the future.

- The patient can no longer perform the study procedures for medical reasons

Measures to control the withdrawal rate include careful patient selection, appropriate explanation of the study requirements and procedures prior to study enrolment, as well as the explanation of the consequences of withdrawal.

The decision to discontinue or withdraw consent to study participation and the reason must be documented in the patient files and CRF.

3.3.4.1 Withdrawal of consent to participation

Patients may withdraw their consent to participation at any time without the need to justify the decision.

If a patient wants to withdraw consent, the investigator should be involved in the discussion with the patient and the options for continued follow-up after discontinuation of remote monitoring and other study procedures.

3.3.4.2 Discontinuation of the study by the contracting entity

Boehringer Ingelheim reserves the right to discontinue the study overall or at a particular study site at any time for the following reasons:

1. Failure to meet expected enrolment goals overall or at a particular study site.
2. New safety information invalidating the earlier positive benefit-risk-assessment, please see Section 1.4.
3. Deviations from GCP, the study protocol, or the contract impairing the appropriate conduct of the study.

Further assessment and follow up of patients affected will occur as described in Section 3.3.4.1.
The investigator / the study site will be reimbursed for reasonable expenses incurred in case of study termination (except in case of the third reason).

4. TREATMENTS

4.1 INVESTIGATIONAL INTERVENTION

The [redacted] cough monitor will be worn by all study participants over 4 24-hour recordings during the 12-week study period. No investigational medicinal product will be administered. Please see Section 1.2.

4.1.1 Method of assigning patients to intervention group

All enrolled subjects will receive the intervention of utilizing a wearable cough monitoring device with an accompanying mobile application (App) for data. All enrolled subjects will also receive a home spirometry device and accompanying mobile application and study provisioned smart phone (for the study duration).

4.1.2 Storage conditions

The [redacted] sensor and charger are provided to the patient with custom packaging. This hardware can be stored and transported within standard environmental conditions (-25°C to 50°C, 15% to 93% RH ± 3%, 700hPa to 1,070hPa). When not in use and between measurements the patient can store the wearable device on the charger. The charger was designed to fit within a small footprint on a table or desktop.

4.1.3 Device accountability

The investigator or designee will receive the [redacted] system kit, as delivered by the contracting entity or delegate when the following requirements are fulfilled:

- Approval of the study protocol by the IRB / ethics committee and/or HA approval
- Availability of a signed and dated study protocol contract between the contracting entity contracting entity or delegate and the investigational site,
- Approval / notification of the regulatory authority, e.g. competent authority,
- Availability of the curriculum vitae of the Principal Investigator,
- Availability of a signed and dated study protocol,
- Availability of the proof of a medical license for the Principal Investigator,
- Availability of FDA Form 1572 (if applicable).

Investigational devices are not allowed to be used outside the context of this protocol. They must not be forwarded to other investigators or clinics. Patients should be instructed to return unused devices and/or devices upon study completion.

The investigator or designee must maintain records of the product's delivery to the study site, the inventory at the site, the use by each patient, and the return to the contracting entity of unused products.

These records will include dates, quantities, batch / serial numbers, expiry ('use- by') dates, and the unique code numbers assigned to the study patients. The investigator or designee will maintain records that document adequately that the patients were provided the device(s) specified by the study protocol. At the time of return to the contracting entity the investigator

or designee must verify that all unused supplies have been returned by the study protocol patient and that no remaining supplies are in the investigator's possession.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

There are no special emergency procedures to be followed.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

As per the Exclusion criteria (3.3.3), persons who have had initiation of a change in dose of ACE-I therapy, inhaled steroid therapy (excluding intranasal), systemic corticosteroid, anti-tussive therapy (including over the counter medications) or opiate therapy within 4 weeks of study entry are not eligible for inclusion. If a patient experiences a clinical deterioration requiring initiation of or a change in dose of one of the aforementioned classes of medication during the study period, the site principal investigator must notify the contracting entity within 72 hours.

4.2.2.2 Restrictions on lifestyle

Patients can perform most forms of exercise, typical daily activities and shower while wearing the [redacted] device. Full submersion into water (e.g. swimming, hot tub use or baths) is not advised as it may lead to device malfunction and compromise any further data collection.

4.2.2.3 Contraception requirements

No contraception requirements are necessitated by use of the [redacted] device.

4.3 DEVICE USE COMPLIANCE

Compliance with cough recordings will be assessed based on patient adherence to cough monitoring (defined as % of time over the 24-hour recording period that the patient is wearing the cough monitor) and remote cough data capture (defined as % of analyzable data per 24-hour recording).

Site staff will receive notification via email each time a patient completes a cough count recording with successful data upload. If the site does not receives this type of notification, the site should contact the patient to assess whether the patient requires assistance with any elements of the 24 hour cough recording and upload.

5. ASSESSMENTS

Subjects will complete 7 study visits (Figure 3.1: 1), 3 on site and 4 remotely. At the Screening Visit (V1), demographic information, pregnancy status (where available), medical history, ILD diagnosis category, HRCT pattern (most recent study within previous 12 months), presence or absence of progressive pulmonary fibrosis phenotype, active medications (related to Non-IPF Pulmonary Fibrosis or IPF and unrelated concomitant medications), and historical FVC and DLCO (within the prior 12-month period) will be recorded into the EDC by the on-site study team. At the baseline visit (V2), which can occur on the same day as the Screening visit, [redacted] a physical exam including vital signs will be performed, and blood will be drawn [redacted] At V2, patients will be given a [redacted] cough monitor system kit, instructed on use and supervised to self-apply the biosensor to their chest wall and turn on the 24-hour recording setting. Patients will also be given a home spirometer at the baseline visit. They will receive an introduction to the home spirometry device and platform and instruction on use of the home spirometer.

5.1 ASSESSMENT OF EFFICACY

No medical therapeutic intervention will be administered. Accordingly, no primary efficacy analyses will be performed in this low intervention pilot study. However, measures of cough frequency and FVC will be integral to the primary and secondary outcome analyses; descriptions are included below. Cough intensity will also be examined in exploratory analyses.

Cough Severity

Cough severity will be evaluated based on both a) cough frequency – measured as 24-hour log-transformed cough count and b) cough intensity. The [redacted] monitor utilizes a proprietary algorithm to analyze 24 hour or periodic recordings for respiratory and cough sounds. Four 24-hour cough recordings will be performed over the course of the 12-week pilot study. Data will be uploaded via Bluetooth interface from the [redacted] biosensor to the [redacted] Mobile App and subsequently from the [redacted] Mobile App to the [redacted] Cloud. Both artificial intelligence driven cough data analyses as well as cough reports in which audio and spectrographic recordings are manually overread will be available.

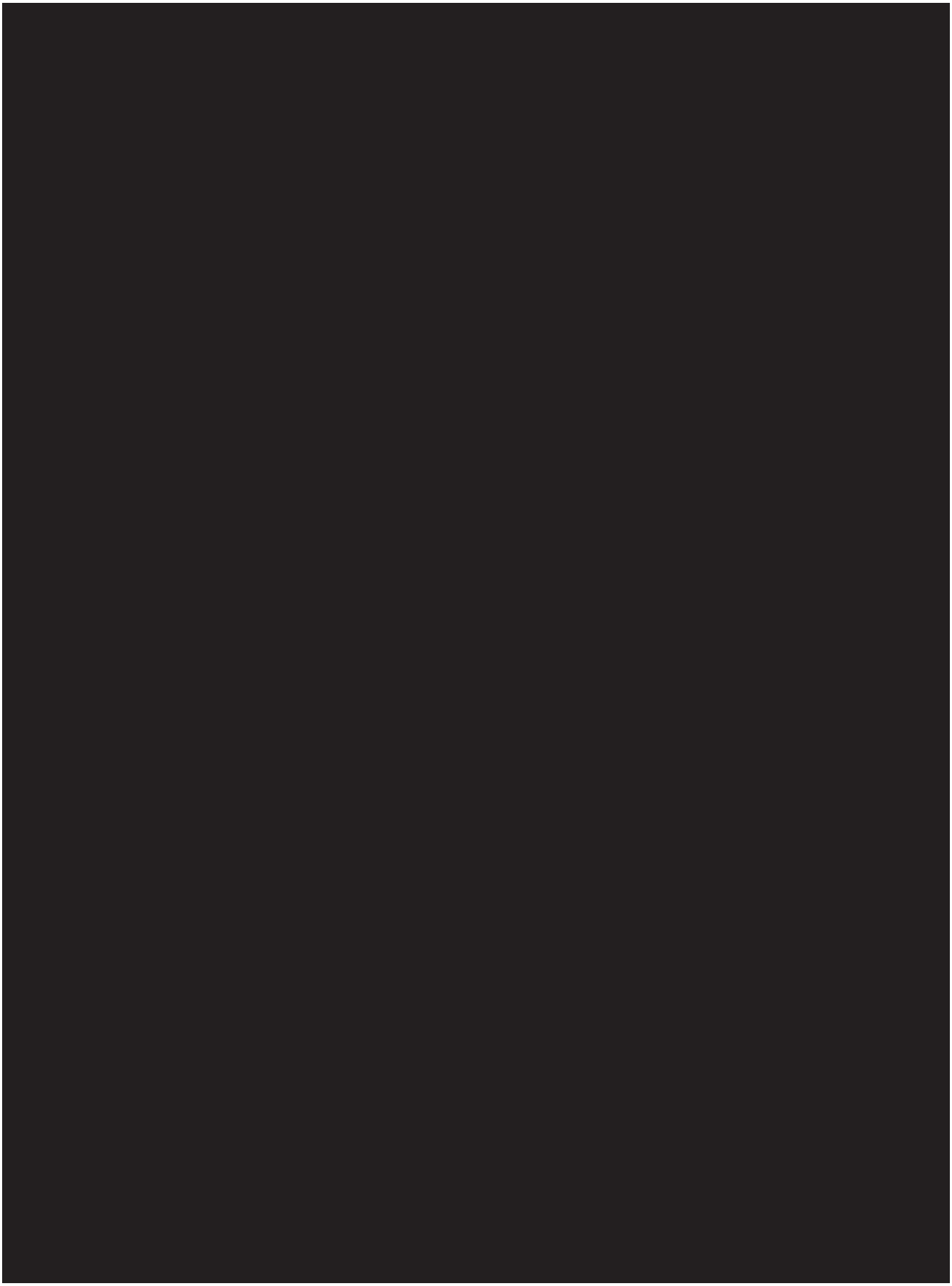
FVC

On-site spirometry measurements will be performed according to ATS/ERS 2019 guideline [R20-2419]. FVC will be assessed using standardised spirometry equipment which will be provided centrally with supplies of precalibrated disposable flow sensors. These sensors meet International Organization for Standardization (ISO) 26782 standards, but with a maximum permissible accuracy error of ±2.5%, in accordance with the American Thoracic Society (ATS)/European Respiratory Society (ERS) Technical Statement [R20-2419]. As such there is no need to conduct daily calibration prior to use. Only these spirometers are to be used for this study.

Spirometry will be conducted with the patient in a seated position. It is preferable that the same trained individual performs the PFTs for a given patient. The best of three efforts will be defined as the highest FVC obtained on any of three blows meeting the 2019 ATS/ERS criteria (with a maximum of eight attempts). Predicted normal values will be calculated according to GLI (Global Lung Initiative). Efforts should be made to schedule the spirometric measurements at approximately the same time of the day, at least within the same half-day (morning vs afternoon), with reference to baseline measurement (Visit 2). On days of study visits, patients should be encouraged to refrain from vigorous activity within 1 hour of pulmonary function testing. If treated with bronchodilators, washout should be advised before spirometry and documented in the source documents. If treated with bronchodilators, wash-out of 24 hours for long acting and 8 hours for short acting bronchodilators should be observed before spirometry and documented in source. Spirometry results will be electronically transmitted. To ensure the quality of the spirometry measures, a manual overread will be performed by the spirometry vendor. Further instructions regarding FVC measurements will be provided in the ISF.

Video supervised home spirometry measurements will be performed. Patients will receive instruction on the video supervised home spirometer use at the Baseline Visit (V2). The first "home spirometry" measure will be performed at home two days following the baseline study visit (with study coordinator instruction and video assisted supervision). Patients will also perform video supervised home spirometry measurements at remote Visits 4, 5, and 6. For the video-assisted home spirometry, patients will use a handheld spirometer [redacted] together with a mobile phone with the installed [redacted] App provided by site. These home spirometry measurements will not replace the onsite FVC measurement at Visit 2 and Visit 7 (Week 12).

[redacted]



Biosensor

As noted in Section 1.2, the Biosensor will be used to capture 24-hour recordings of cough frequency data. Additionally, data acquired in this study using the cough monitor might be analyzed further to e.g. build diagnostic, prognostic and predictive models and develop new algorithms for the analysis of cough data. This exploratory analysis might be performed in collaboration with an independent third party nominated by the contracting entity.

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

A complete physical examination will be performed at Visit 2 and 7, as specified in the Flow Chart. It includes at a minimum general appearance, neck, lungs, cardiovascular system, abdomen, extremities, and skin. Measurement of height and body weight will be performed at Visit 2 and 7. The results must be included in the source documents.

5.2.2 Vital signs

Vital signs will be evaluated at Visit 2 and 7, as specified in the Flow Chart, prior to blood sampling. This includes systolic and diastolic blood pressure and pulse rate (electronically or by palpation count for 1 minute) in a seated position after 5 minutes of rest. The results must be included in the source documents.

5.2.3 Safety laboratory parameters

Safety laboratory parameters will not be performed.

5.2.4 Electrocardiogram

ECGs will not be routinely performed.

5.2.5 Other safety parameters

Should the patient demonstrate a $\geq$ 10% absolute or relative drop in forced vital capacity (FVC) during on-site or home spirometry, the site principal investigator will be notified and asked to assess whether any further evaluations are needed.

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of AEs

5.2.6.1.1 Adverse event

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medical intervention and which does not necessarily have to have a causal relationship with this Intervention.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical intervention, whether considered related or not.

The following should be recorded as an AE in the CRF (if applicable):
- AEs related to study procedures
- AEs or SAEs that fufill the following criteria:
    - Events leading to lung transplantation
    - COVID-19 Infection
    - Events leading to death

5.2.6.1.2 Serious adverse event

A serious adverse event (SAE), is defined as any AE, which fulfils at least one of the following criteria:
- results in death

- is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe,
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity,
- is a congenital anomaly / birth defect,
- is deemed serious for any other reason if it is an important medical event when based on appropriate medical judgement which may jeopardise the patient and may require medial or surgical intervention to prevent one of the other outcomes listed in the above definitions. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse.

SAEs related to study procedures, or as defined in Section 5.2.6.1.1, should be recorded in the CRF.

No SAE reporting to drug safety will occur, hence no SAE reconciliation required.

5.2.6.1.3 AEs considered “Always Serious”

Not applicable

5.2.6.1.4 Adverse Events of Special Interest

Not applicable

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE Collection

The investigator shall maintain and keep detailed records of all AEs in the patient files.

The following must be collected and documented on the appropriate CRF(s) by the investigator:

- From signing the informed consent onwards until the individual patient’s end of study (= the End of Study (EoS) visit): all AEs (serious and non-serious) as defined in Section 5.2.6.1.1.

5.2.6.2.2 AE reporting to the contracting entity and timelines

Not applicable

5.2.6.2.3 Exemptions to SAE reporting

Not applicable

5.4 BIOBANKING

Not applicable

5.5 OTHER ASSESSMENTS

Resource use data will include unscheduled hospitalizations, healthcare provider visits, and emergency room use.

5.6 APPROPRIATENESS OF MEASUREMENTS

Cough count or frequency of cough is a standard and routine measure utilized in studies of anti-tussive therapy. In the current pilot, we will also measure, “cough intensity”, which is not routinely captured by current cough monitors. As such, it is not a measure that is routinely included in published literature to date. In the current study, we will assess cough

intensity, measured as an analysis of a combination of the following parameters: cough duration (% of minute recordings taken up by cough), variability of minute-to-minute cough%/minute, time interval of coughs (msec) on x axis, amplitude of cough on y-axis, AUC of cough per cough or cough spasm, and within cough power (measured by color - clear, blue, yellow, red; worst color present and change in color over time).

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

A multi-center, real-world low intervention pilot study based on newly collected data from approximately 50 evaluable subjects with Non IPF Pulmonary Fibrosis and IPF will be conducted in various sites in the North America and Europe.

The eligible subjects will be identified by the participating specialist physicians including pneumologists involved in the diagnosis, treatment, and management of Non IPF Pulmonary Fibrosis or IPF. The participant selection process will be consecutive, and the participating specialist physicians will be provided guidance to minimize any potential selection bias. Eligible subjects must be previously diagnosed with Non IPF pulmonary fibrosis or IPF and will be asked to provide written informed consent prior to inclusion in the study.

Consenting subjects will be followed for a maximum period of 12 weeks (Figure 3.1: 1); all subjects will participate in 7 clinical visits, 3 in person and 4 remote visits.

During the screening visit (V1) and the baseline visit (V2), baseline data will be collected, including on-site spirometry, historical HRCT pattern (most recent study within the previous 12 months), historical FVC% (most recent value within 6 months prior to V2 & most distant value within 12 mos. of V2), DLCO% predicted (most recent value within 6 months prior to V2 & most distant value within 12 mos of V2), [redacted]

Where allowed by local regulations, a subject screening log will be kept at each site, recording basic information such as age at Non IPF Pulmonary Fibrosis or IPF diagnosis, sex, information on the eligibility (or reasons for non-eligibility/non-enrollment, including a reason for refusal [if known]) and [redacted]. In addition, a log of all subjects enrolled into the study (i.e. having provided informed consent) will be maintained in the Investigator Site File (ISF).

Subjects will be followed prospectively from the time of enrollment until the earliest of death, loss to follow-up or end of the study period. Subjects who are alive and not lost to follow-up, will complete their study participation once study procedures have been completed for Visit 7.

If a patient misses a visit, the site is asked to alert the contracting entity to determine if the visit should be rescheduled. Subjects are free to discontinue or withdraw from the study at any time. Reason for discontinuation or withdrawal will be collected; however, reasons for withdrawal of consent do not have to be disclosed. Unless otherwise requested by the participant, all data obtained up to consent withdrawal will be retained in the database.

Screening Period (Visit 1)

- Following provision of informed consent, Inclusion & Exclusion criteria should be reviewed as per the FC
- During the screening visit, demographic information will be collected.
    - Age on the day of informed consent (in years)

  - Sex (male, female; to describe the patient's sex at birth)
  - Ethnicity and race in order to sufficiently characterize the patient population, to support possible subgroup analyses if needed unless not acceptable according to local regulations.
- Medical history (Comorbidities, COVID-19 infection history and vaccination status)
- Pregnancy status (where available)
- Non IPF pulmonary fibrosis (including ILD diagnosis category) or IPF Diagnosis
- Presence or absence of progressive pulmonary fibrosis (PPF) phenotype
- Smoking status/history
- Concomitant medications
- HRCT pattern (most recent study within previous 12 months)
- FVC & DLCO (most recent value within 6 months prior to V2 & most distant value within 12 months of V2)

Visit 2/Baseline Visit – On site

The Screening Visit and Baseline Visit can occur on the same day. [redacted] Vital signs will be taken, and a physical exam performed. Subsequently, a pulmonary function test will be performed to measure FVC. [redacted] Instructions for utilizing and storing the [redacted] cough monitor will be reviewed. The patient will place the biosensor onto their chest wall with supervision and assistance (as needed) from the study team. The sensor will be set and started on recording mode for the planned 24hrs. recording. At completion of 24hrs. of recording the next day, the patient will place the [redacted] sensor onto a charger to allow for data upload via Bluetooth connected [redacted] app on the study-provided mobile phone. The sensor will be charged for the next visit and stored as per vendor instructions until the next recording at Visit 4. At Visit 2, patients will additionally receive a home spirometer and instructions for use will be reviewed with the patient including access to the video assist portal on the provisioned mobile phone for study use. [redacted]

Visit 3- Remote

On Day 3 of the study (+ 2 days) the patient is asked to complete home spirometry (Visit 3) via video-assisted supervision by a trained member of the site study team.

Visit 4 - Remote

Visit 4 (V4) will occur on the 28th day (+/- 5 days) after study enrollment/baseline visit. Visit 4 will be fully remote. [redacted]

[redacted] On the day of the visit, the participant will logon to the [redacted] platform for a videoconference visit with the site study team preceding home spirometry. [redacted] Subsequently, interval history will be obtained, followed by video-assisted supervised home spirometry with the site study team. Immediately following the end of the study visit, the patient will initiate a 24-hour cough recording. At completion of 24 hrs. of recording the next day, the patient will remove the [redacted] sensor from their chest wall and place the sensor onto a charger to allow for data upload via Bluetooth connected [redacted] app on the study-provided mobile phone. The charger will be placed next to the study provided mobile phone, which is "pre-loaded" with the [redacted] app, to allow for data upload. The sensor will be charged for the next visit and stored as per vendor instructions until the next recording at Visit 5.

Visit 5 - Remote

Visit 5 (V5) will occur on the 56th day (+/- 5 days) after study enrollment/baseline visit. Visit 5 will be fully remote. [redacted] On the day of the visit, the participant will logon to the [redacted] platform for a videoconference visit with the site study team preceding home spirometry. [redacted] Subsequently, interval history will be obtained, followed by video-assisted supervised home spirometry with the site study team. Immediately following the end of the study visit, the patient will initiate a 24-hour cough count recording. At completion of 24 hrs. of recording the next day, the patient will remove the [redacted] sensor from their chest wall and place the sensor onto a charger to allow for data upload via Bluetooth connected [redacted] app on the study-provided mobile phone. The charger will be placed next to the study provided mobile phone, which is "pre-loaded" with the [redacted] app, to allow for data upload. The sensor will be charged for the next visit and stored as per vendor instructions until the next recording at Visit 6. The site study team will confirm that the prior 24-hour cough recording was completed and offer to assist the patients with any part of the 24-hour cough recording that they were having trouble with.

Visit 6- Remote

Visit 6 will occur on the 82nd day (-2 days) prior to the EoS visit. On the day of the study visit, the patient is asked to complete home spirometry (Visit 6) via logon to the [redacted] platform for video supervision by a spirometry trained member of the site study team. Immediately following the end of the study visit, the patient will initiate a 24-hour cough recording. At completion of 24 hrs. of recording the next day, the patient will remove the [redacted] sensor from their chest wall and place the sensor onto a charger to allow for data upload via Bluetooth connected [redacted] app on the study-provided mobile phone. The charger will be placed next to the study provided mobile phone, which is "pre-loaded" with the [redacted] app,

to allow for data upload. Once data upload is complete, the sensor and study provided phone will be stored for return to the site at the EoS visit (Visit 7).

Visit 7 – On site

The End of Study Visit (EoS/V7) will occur on the 84th day (+/- 5 days) following study enrollment/baseline visit. [redacted] Interval history will be obtained; vital signs and a physical exam will be performed. Participants will then undergo spirometry on-site. [redacted]
The [redacted] and home spirometry devices will be returned to the site as will the provisioned mobile phone.

In the event of force majeure or other disruptive circumstances (e.g. pandemic, war) the investigational plan as per this study protocol may not be feasible at a site. With the consent of the patient, contracting entity and investigator may agree on alternative, back-up or rescue methodology which may include but will not be limited to virtual patient visits and assessments and home healthcare nurse visits.

6.2 DETAILS OF STUDY PROCEDURES AT SELECTED VISITS

6.2.1 Screening and run-in period(s)

Screening Period
Patients will be eligible to screen and enroll on the same day or day of the baseline visit.

- During the screening visit, demographics information will be collected. This includes:
  - Age (on the day of informed consent, in years)
  - Sex (male, female in order to describe the subject`s sex at birth)
  - Gender identity (male, female, non-binary, not answered, or other in order to describe how the trial participant self-identifies, regardless of their genotypic or phenotypic sex) if 1) locally accepted (ie., based on HA/EC/IRB acceptance, independent of acceptance by investigators or participants), 2) investigators are willing to ask, and 3) participants are willing to reply.
  - For women: of childbearing potential yes / no in order to characterize the patient population
  - Ethnicity and race in order to sufficiently characterize the patient population, to support possible subgroup analyses if needed
- Baseline conditions and medical history
- Concomitant medications
- Smoking status
- Pregnancy status (where available)
- Non IPF PF or IPF
- Presence or absence of PPF
- HRCT pattern (historical, within prior 12 months)
- FVC & DLCO (historical, within prior 12 months)

Baseline Conditions & Medical History

- Will be collected at the Screening/Baseline visit

6.2.2 Intervention period

Patients will receive the cough monitor and conduct cough recordings over a period of 12 weeks from study entry until the End of Study visit.

6.2.3 Study completion

Patients will complete study procedures at Visit 7/EOS and return the cough monitor, provisioned mobile phone and home spirometer at this visit. Completion of study procedures and return of the provisioned equipment at this visit will constitute study completion.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 NULL AND ALTERNATIVE HYPOTHESES

This is an exploratory study with no treatment intervention aiming to assess the use of a new generation of cough monitoring device and describe cough frequency over 12 weeks. No confirmatory testing is performed and hence no null and alternative hypotheses are defined. A justification of the sample size is provided in Section 7.4.

7.2 PLANNED ANALYSES

7.2.1 General considerations

Cough count/hr will be log transformed for analysis. Standard statistical parameters (number of non-missing values, mean, standard deviation (SD), median, quartiles, minimum and maximum) or frequency tables will be calculated where appropriate. All individual data will be listed.

Patient analysis sets:

Entered Set (ES): those patients who were entered into the study.

Additional patient analysis sets may be defined in the SAP.

7.2.2 Handling of Intercurrent Events

This section is not applicable as there is no comparison of interventions.

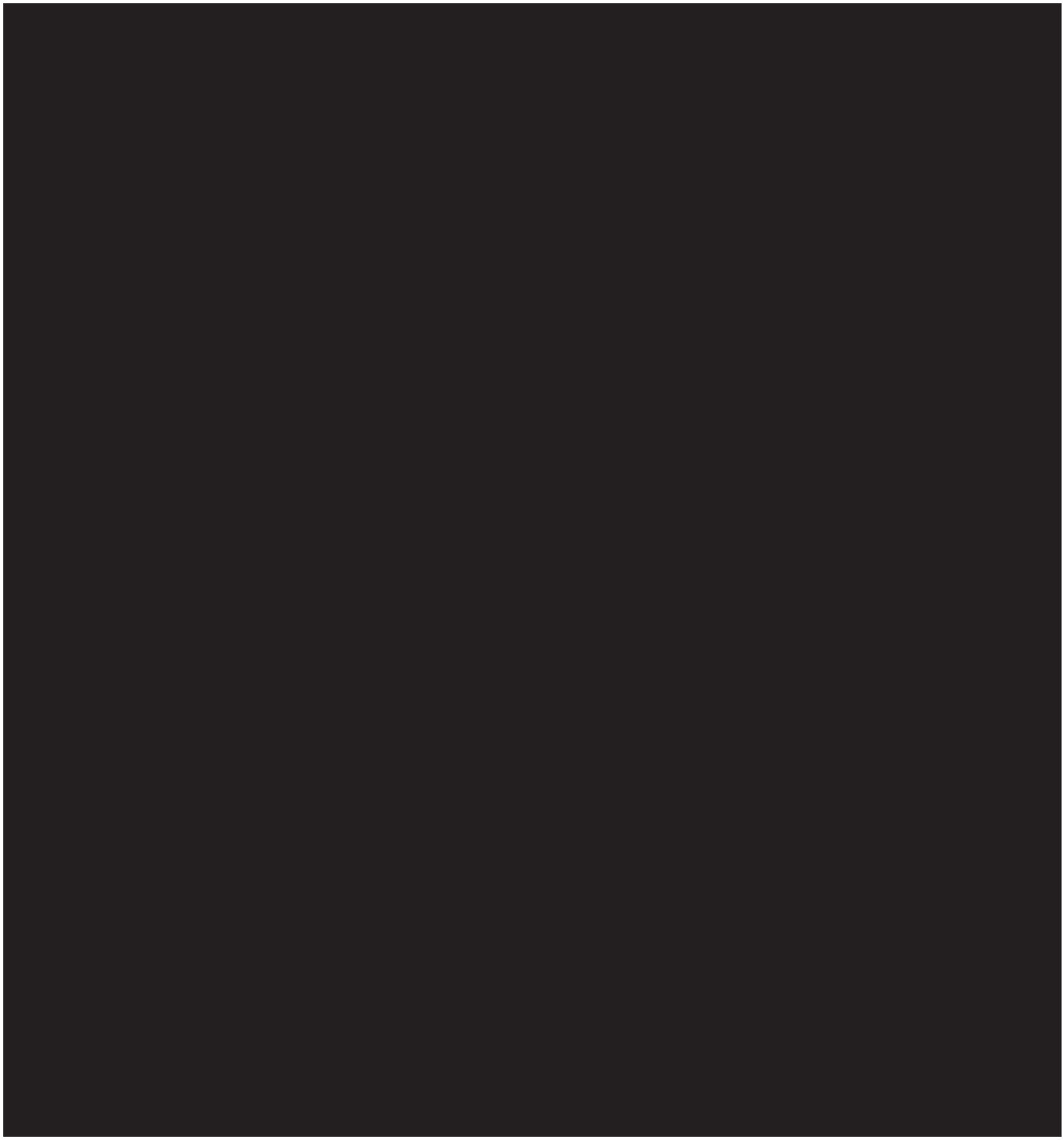
7.2.3 Primary objective analyses

The cough count (CC) frequency, measured over 4 24-hour recordings in 12 weeks will be analysed as CC/hour and will be log-transformed for data summaries. On each day for which cough monitoring is completed, the log-transformed cough count is calculated as:

$$\text{Log-transformed cough count} = \log \frac{\text{Number of coughs}}{\text{Length of recorded time (hours)}}$$

Cough count for each visit will be reported descriptively. Summary statistics will be tabulated on original scale of CC/hr as well as the geometric mean and 95% confidence intervals after back-transforming the summarized log transformed data. [redacted] Summary measurements and individual values of CC/hr over time will also be presented graphically.

Additional details will be included in the SAP.



The primary endpoints will be summarized in the same fashion as described above by each subgroup level.

7.2.3.3 Supplementary Analyses

Not applicable

7.2.4 Secondary objective analyses

Secondary endpoints will be summarized descriptively by visit.

Change from baseline in CC/hr at Week 4, Week 8, and Week 12 will be summarized in terms of absolute changes in CC/hr and in terms of geometric mean ratios. Model based estimates for changes from baseline at Week 12, for example least squares means adjusted for baseline CC/hr or other covariates, may be calculated.

Standard descriptive statistical parameters will be tabulated for all other secondary endpoints.

To assess the relationship between objective cough frequency and FVC (mL), correlations (spearman and Pearson) will be calculated between the following variables:

- Baseline CC/hr (log-transformed) and Baseline FVC (mL)
- Baseline CC/hr (log-transformed) and FVC (mL) at Week 12
- Baseline CC/hr (log-transformed) and change from baseline FVC (mL) at Week 12
- CC/hr at Week 12 (log-transformed) and FVC (mL) at Week 12
- Change in CC/hr at Week 12 (calculated from log-transformed values) and change from baseline in FVC (mL) at Week 12

Graphical presentations of the secondary endpoints and correlations may also be produced. Further details will be included in the SAP.

7.2.6 Safety analyses

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Standard BI summary tables and listings will be produced.
All enrolled patients will be included in the safety analysis. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

Frequency and severity of adverse events related to the study procedure will be tabulated by system organ class and preferred term after coding according to the current version of the Medical Dictionary for Drug Regulatory Activities (MedDRA) at database lock.

[redacted]

7.2.8 Interim Analyses

Interim analyses will be performed as needed to inform subsequent studies.

7.3 HANDLING OF MISSING DATA

Imputation of missing data will not be done. Unless otherwise noted, analysis will be conducted using all patients with the endpoint available.

Missing or incomplete AE dates will be imputed according to BI standards.

7.4 RANDOMIZATION

but to gain experience using the [redacted] device in a real-world setting, therefore no randomization is needed for this single group study.

7.5 DETERMINATION OF SAMPLE SIZE

[P22-04417] was a phase 2a study which investigated the effect of inhaled RVT-1601 (cromolyn sodium) on 24-hour average cough counts in patients with IPF. 97 patients were randomized to four arms (RVT-1601 10mg, 40mg, 80mg, or placebo for 12 weeks). The baseline measurements of the mean 24-hour cough count were 38.0 ± 26.6 (RVT-1601 10mg; n=27); 36.8 ± 21.7 (RVT-1601 40mg arm; n=22); 35.7 ± 17.8 (RVT-1601 80mg arm; n=23); 34.3 ± 19.6 (Placebo; n=25).

Assuming we observe similar standard deviations for cough count as the SCENIC trial, the table below reports the 95% confidence interval range we expect for the 24-hour cough count assuming a sample size of 50 patients that are normally distributed. For example, when the sample size is 50, a two-sided 95% confidence interval for a mean will extend 7.484 from the observed mean, assuming that the standard deviation is known to be 27 and the confidence interval is based on the large sample z-statistic.

Table 7.5: 1 Confidence Interval ranges based on N=50 patients for different standard deviations

Standard Deviation	19	21	23	25	27
95% CI Range*	±5.266	±5.821	±6.375	±6.930	±7.484

*CI Range calculated using the NQuery 8, Version 8.2.7.0 program for "Confidence Interval for One Mean using Normal Distribution"

8. INFORMED CONSENT, STUDY RECORDS, DATA PROTECTION, PUBLICATION POLICY, AND ADMINISTRATIVE STRUCTURE

The study will be carried out in accordance with the Medical Devices Directive (93/42/EEC) and the harmonised standards for Medical Devices (ISO 14155, current version).

The study will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the EU directive 2001/20/EC / EU regulation 536/2014. Investigators and site staff must adhere to these principles. Deviation from the protocol, the principles of ICH GCP or applicable regulations as will be treated as “protocol deviation”.
Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains the responsibility of the treating physician of the patient.

The investigator will inform the contracting entity or delegate immediately of any urgent safety measures taken to protect the study patients against any immediate hazard, as well as of any serious breaches of the protocol or of ICH GCP.

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. The rights of the investigator and of the contracting entity with regard to publication of the results of this study are described in the investigator contract. As a rule, no study results should be published prior to finalisation of the Study Report.

The certificate of insurance cover is made available to the investigator and the patients and is stored in the ISF.

8.1 STUDY APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

This study will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB / Independent Ethics Committee (IEC and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.
Prior to patient participation in the study, written informed consent must be obtained from each patient (or the patient’s legally accepted representative) according to ICH-GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the study records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient’s legally accepted representative.
The patient must be given sufficient time to consider participation in the study. The investigator or delegate obtains written consent of the patient’s own free will with the informed consent form after confirming that the patient understands the contents. The investigator or [redacted] delegate must sign (or place a seal on) and date the informed consent form. If a study collaborator has given a supplementary explanation, the study collaborator also

signs (or places a seal on) and dates the informed consent.
Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the contracting entity's instructions.
The consent and re-consenting process should be properly documented in the source documentation.

8.2 DATA QUALITY ASSURANCE

A risk-based approach is used for study quality management. It is initiated by the assessment of critical data and processes for study subject protection and reliability of the results as well as identification and assessment of associated risks. An Integrated Quality and Risk Management Plan or alternative plan, in line with the guidance provided by ICH Q9 and ICH-GCP E6, for fully outsourced studys, documents the rationale and strategies for risk management during study conduct including monitoring approaches, vendor management and other processes focusing on areas of greatest risk.
Continuous risk review and assessment may lead to adjustments in study conduct, study design or monitoring approaches.
A quality assurance audit / inspection of this study may be conducted by the contracting entity, contracting entity's designees, or by IRB / IEC or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's study-related files and correspondence, and the informed consent documentation of this study.

8.3 RECORDS

CRFs for individual patients will be provided by the contracting entity.

8.3.1 Source documents

In accordance with regulatory requirements, the investigator should prepare and maintain adequate and accurate source documents and study records that include all observations and other data pertinent to the investigation on each study patient. Source data as well as reported data should follow the "ALCOA principles" and be **a**ttributable, **l**egible, **c**ontemporaneous, **o**riginal and **a**ccurate. Changes to the data should be traceable (audit trail).
Data reported on the CRF must be consistent with the source data or the discrepancies must be explained.
The current medical history of the patient may not be sufficient to confirm eligibility for the study and the investigator may need to request previous medical histories and evidence of any diagnostic tests. In this case, the investigator must make at least one documented attempt to retrieve previous medical records. If this fails, a verbal history from the patient, documented in their medical records, would be acceptable.
Before sending or uploading those copies, the investigator must ensure that all patient identifiers (e.g. patient's name, initials, address, phone number, social security number) have properly been removed or redacted from any copy of the patients' source documents.
If the patient is not compliant with the protocol, any corrective action e.g. re-training must be documented in the patient file.
For the CRF, data must be derived from source documents, for example:

- Patient identification: gender, year of birth (in accordance with local laws and regulations)

- Patient participation in the study (substance, study number, patient number, date patient was informed)
- Dates of patient's visits.
- Medical history (including study indication and concomitant diseases, if applicable)
- Medication history
- Adverse events and outcome events (onset date (mandatory), and end date (if available))
- Serious adverse events (onset date (mandatory), and end date (if available))
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available)
- Completion of patient's participation in the study (end date; in case of premature discontinuation document the reason for it).
- Prior to enrolment of a patient to this study, there must be documented evidence in the source data (e.g. medical records) that the study participant meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records, verbal documented feedback of the patient or testing conducted specific for a protocol) to support inclusion / exclusion criteria does not make the patient eligible for the study.

8.3.2 Direct access to source data and documents

The investigator / institution will allow site study-related monitoring, audits, IRB / IEC review and regulatory inspections. Direct access must be provided to the CRF and all source documents / data, including progress notes, copies of laboratory and medical test results, which must always be available for review by the CRA, auditor and regulatory inspector (e.g. FDA). They may review all CRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in Section 8.3.1. The contracting entity or delegate will also monitor compliance with the protocol and GCP.

8.3.3 Storage period of records

Study site(s):
The study site(s) must retain the source and essential documents (including ISF) according to contract or the local requirements valid at the time of the end of the study (whatever is longer).
Contracting entity:
The contracting entity must retain the essential documents according to the contracting entity's SOPs.

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

BI is responsible to fulfil their legal and regulatory reporting obligation in accordance with regulatory requirements.

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 7 and 12 of the WHO GCP handbook.
To ensure confidentiality of records and personal data, only pseudonymised data will be transferred to the contracting entity by using a patient identification number instead of the patient's name. The code is only available at the site and must not be forwarded to the contracting entity. In case patient's records will be forwarded e.g. for SAE processing or adjudication committees, personal data that can identify the patient will be redacted by the site prior to forwarding. Access to the patient files and clinical data is strictly limited: personalised treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated at the site as a result of the study need to be available for inspection on request by the participating physicians, the contracting entity's representatives, by the IRB / IEC and the regulatory authorities.

A potential data security breach will be assessed regarding the implications for rights and privacy of the affected person(s). Immediate actions as well as corrective and preventive actions will be implemented. Respective regulatory authorities, IRBs / IECs and patients will be informed as appropriate.

8.6 STUDY MILESTONES

The **start of the study** is defined as the date when the first patient in the whole study signs informed consent.
The end of the study is defined as the date of the last visit of the last patient in the whole study ("Last Patient Completed"). **Early termination of the study** is defined as the premature termination of the study due to any reason before the end of the study as specified in this protocol.
Temporary halt of the study is defined as any unplanned interruption of the study by the contracting entity with the intention to resume it.
Suspension of the study is defined as an interruption of the study based on a Health Authority request.

8.7 ADMINISTRATIVE STRUCTURE OF THE STUDY

The study is sponsored by Boehringer Ingelheim (BI).

A Coordinating Investigator is responsible to coordinate investigators at the different sites participating in this study. Tasks and responsibilities are defined in a contract.

Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF.

BI has appointed a Clinical Trial Leader responsible for coordinating all required activities, in order to

- manage the study in accordance with applicable regulations and internal SOPs,
- direct the study team in the preparation, conduct, and reporting of the study,
- ensure appropriate training and information of Clinical Trial Managers (CT Managers), Clinical Research Associates (CRAs), and investigators of participating countries.

In the participating countries the study will be performed by the respective local or regional BI-organisation (Operating Unit, OPU) in accordance with applicable regulations and BI SOPs.

Data Management and Statistical Evaluation will be done by BI according to BI SOPs.

Tasks and functions assigned in order to organise, manage, and evaluate the study are defined according to BI SOPs. A list of responsible persons and relevant local information can be found in the ISF.
A central laboratory service will be used in this study. Details will be provided in the Central Laboratory Manual, available in the ISF.

9. REFERENCES

9.1 PUBLISHED REFERENCES

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R22-2499 Sharpey-Schafer E. Effects of coughing on intra-thoracic pressure, arterial pressure and peripheral blood flow. The Journal of Physiology. 1953;122(2):351-357.

R22-2500 Wakwaya Y, Ramdurai D, Swigris JJ. Managing cough in idiopathic pulmonary fibrosis. Chest. 2021;160(5):1774–82.

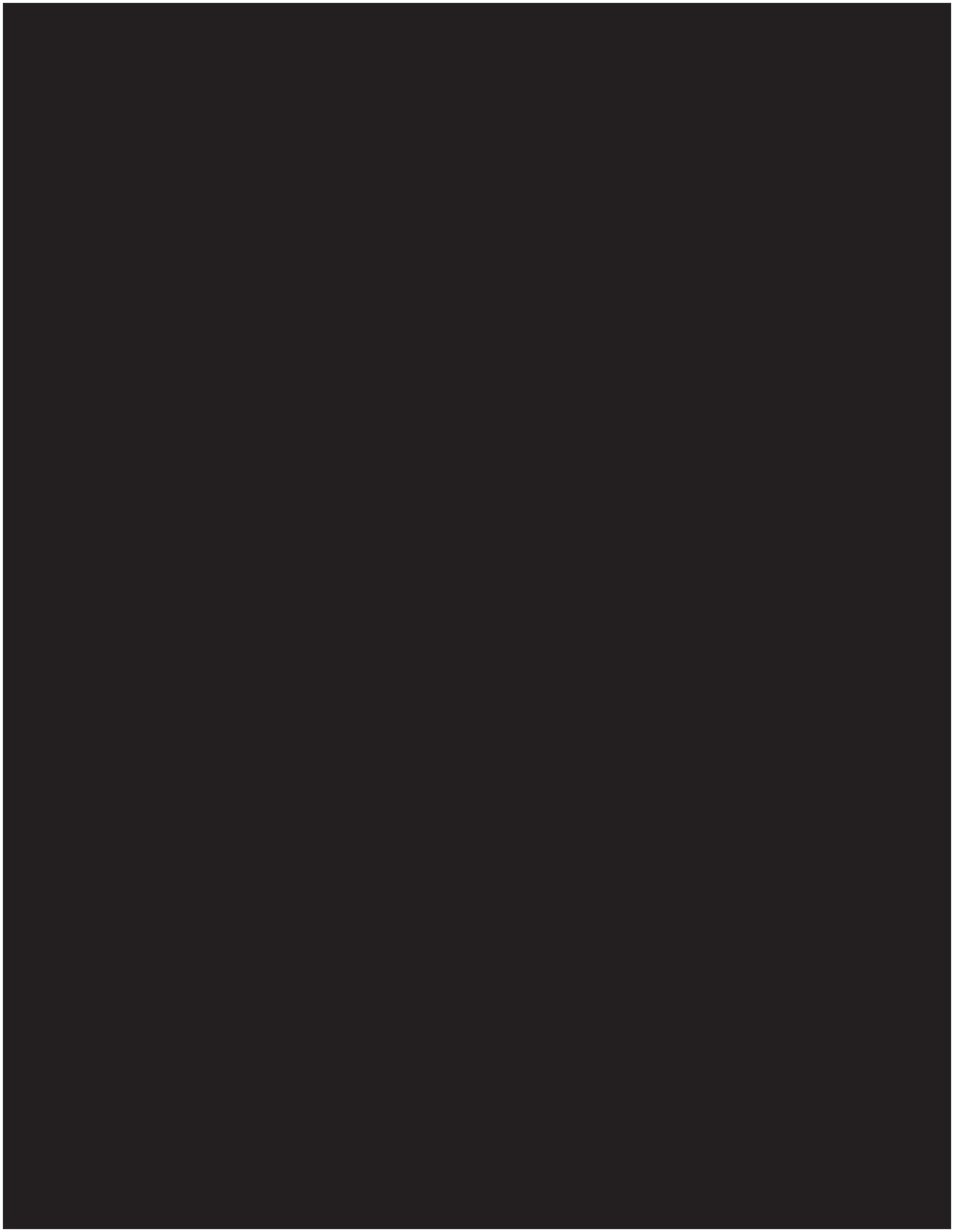
9.2 UNPUBLISHED REFERENCES

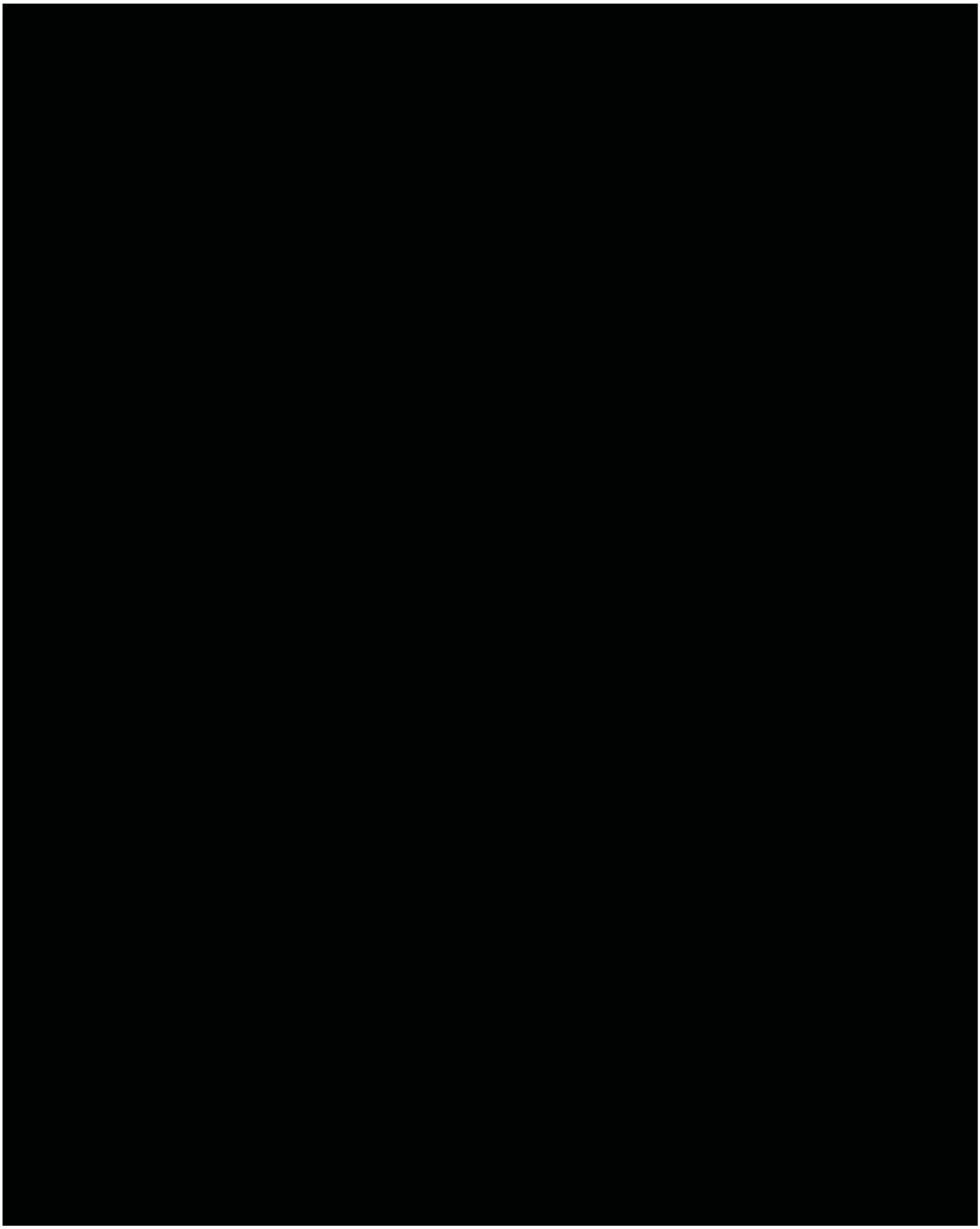
Not applicable

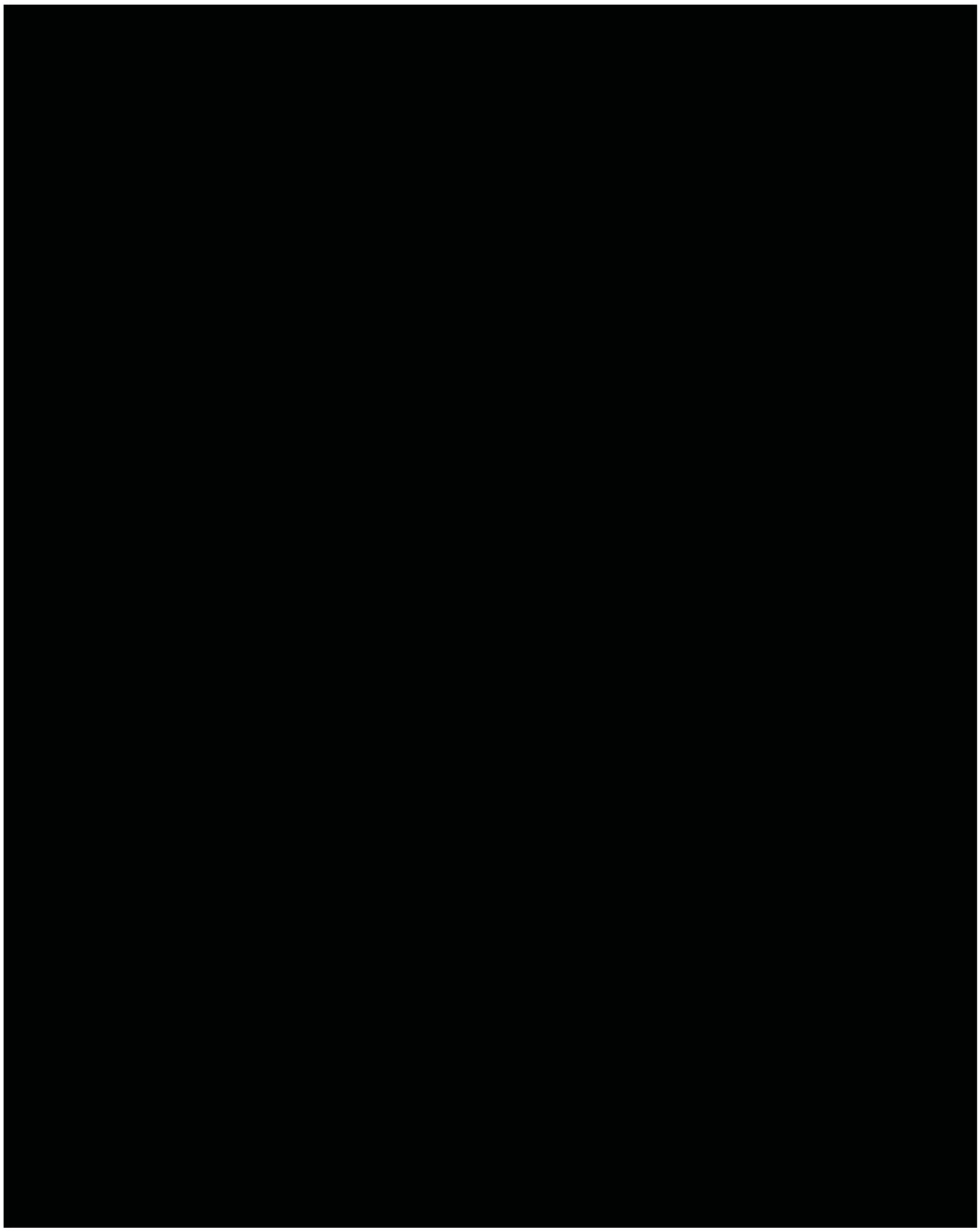
10. APPENDICES

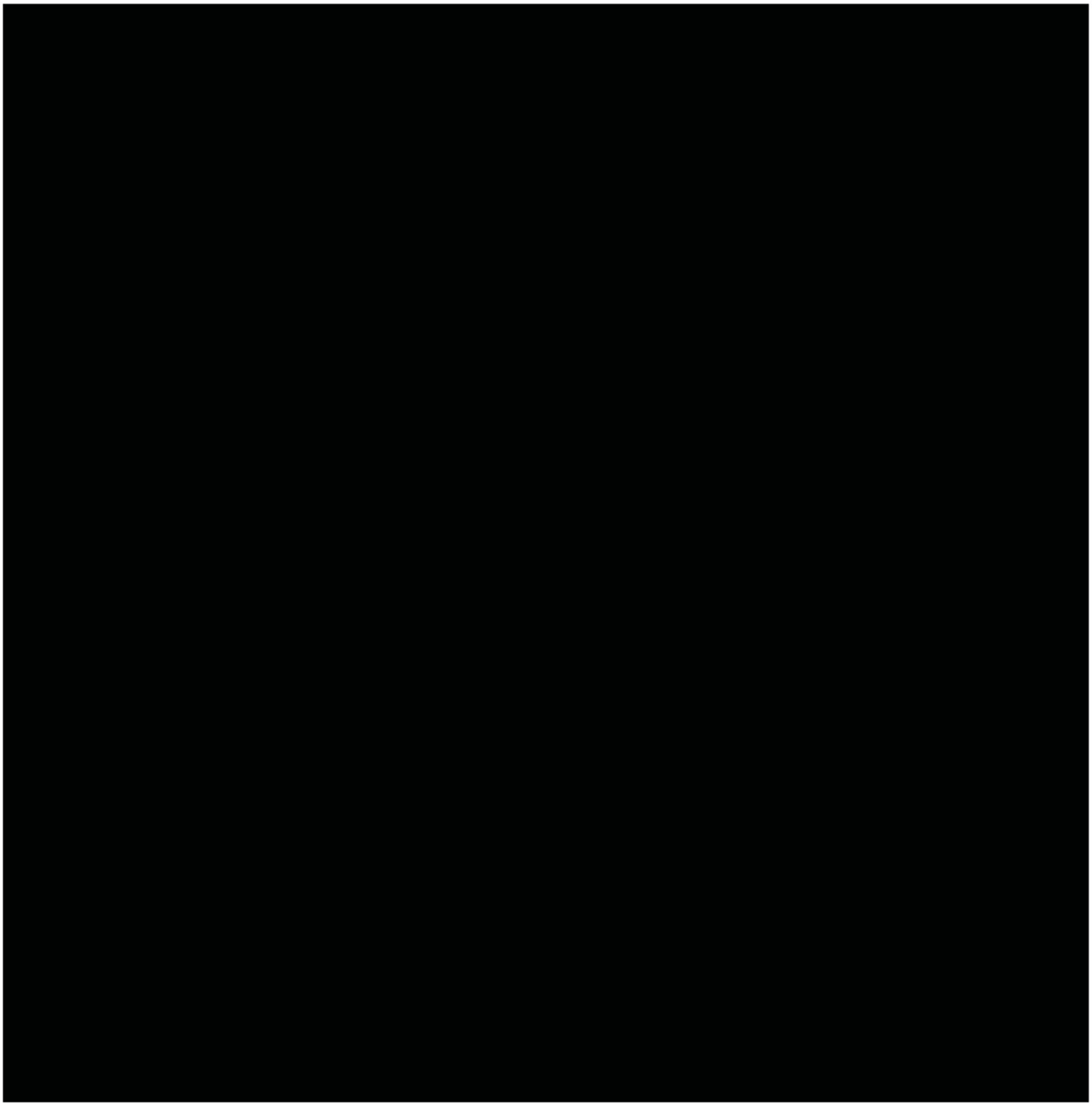
10.1 INSTRUCTIONS FOR USE

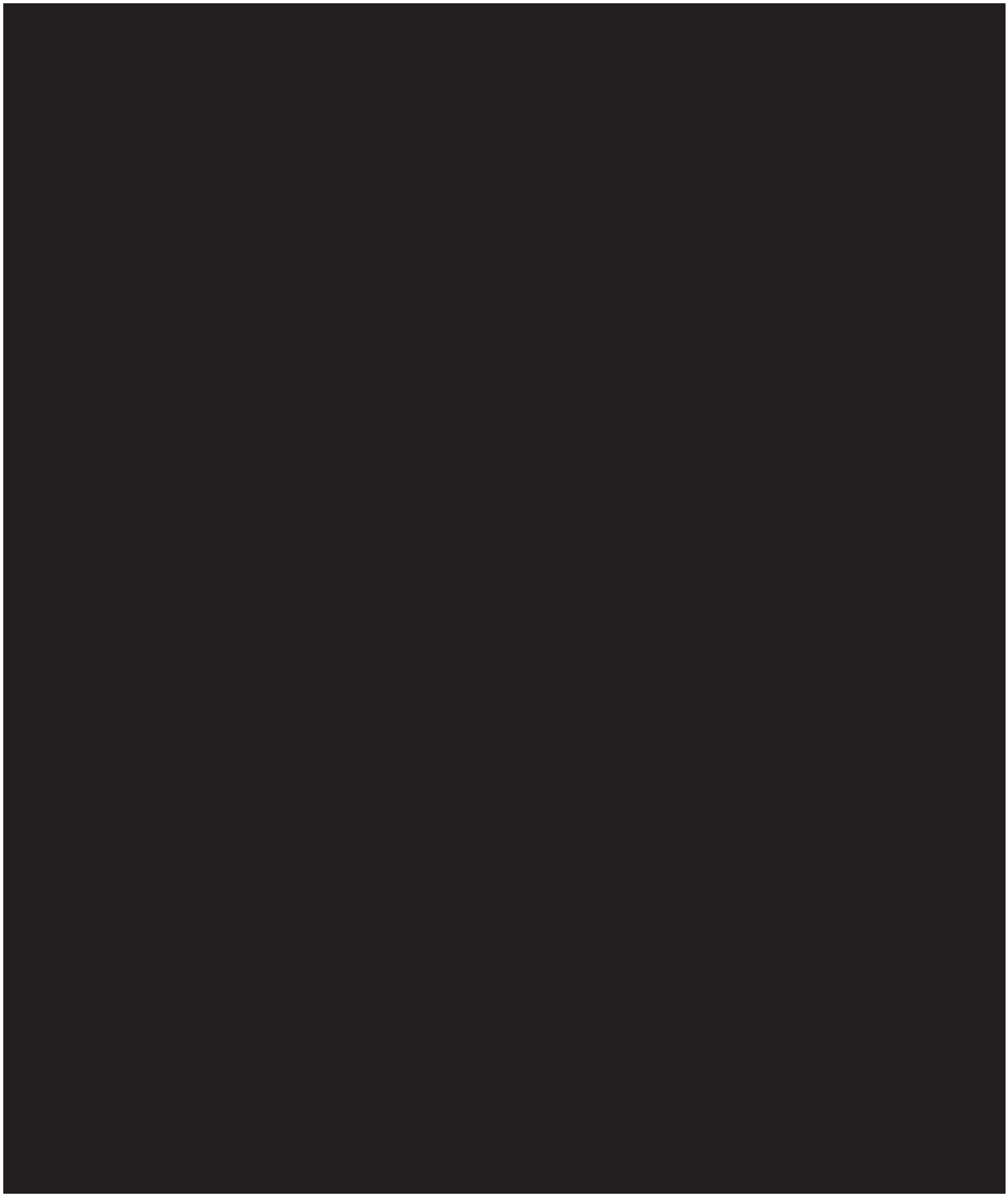
Patient will be provided with User Manuals for the study devices

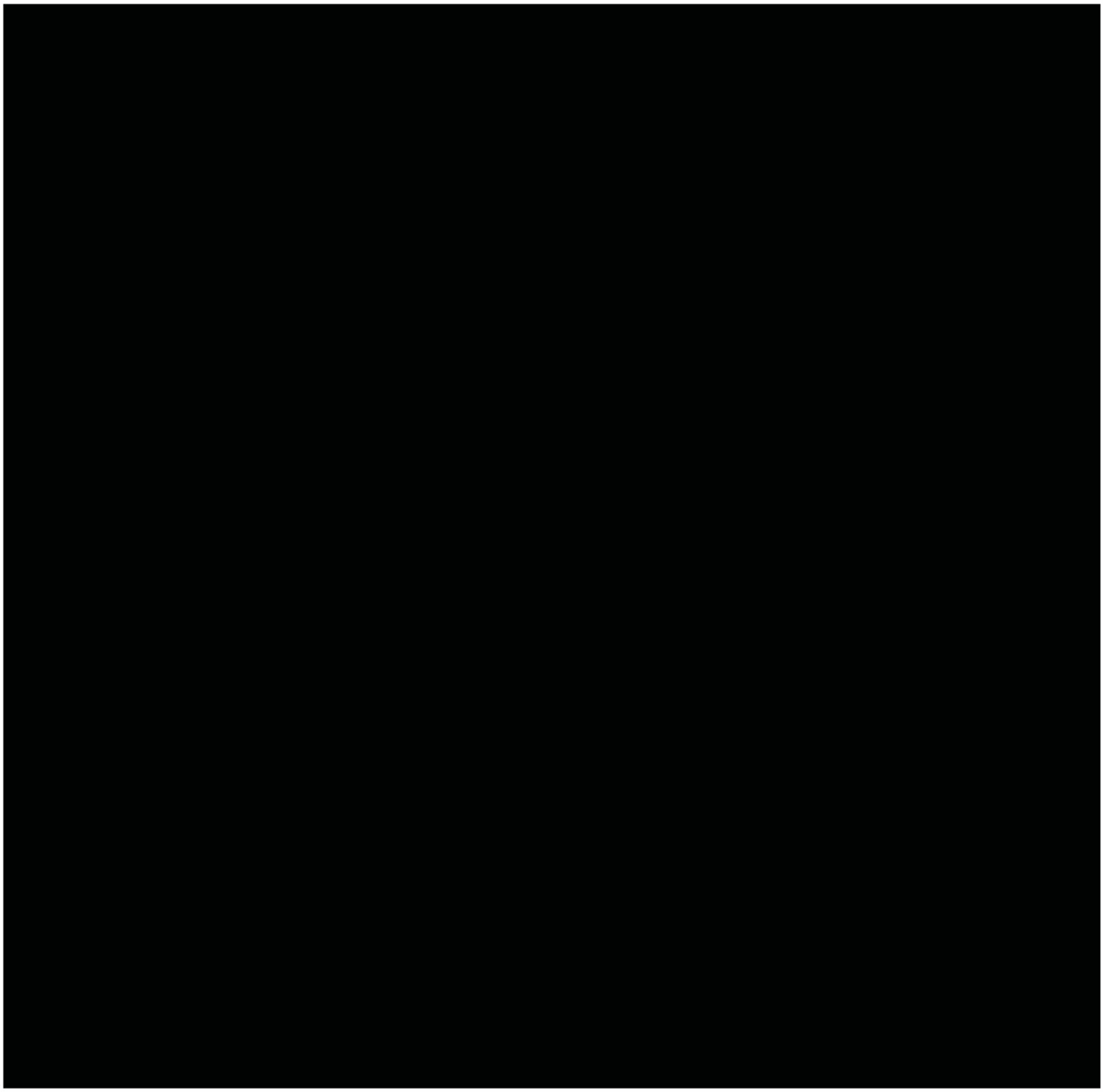


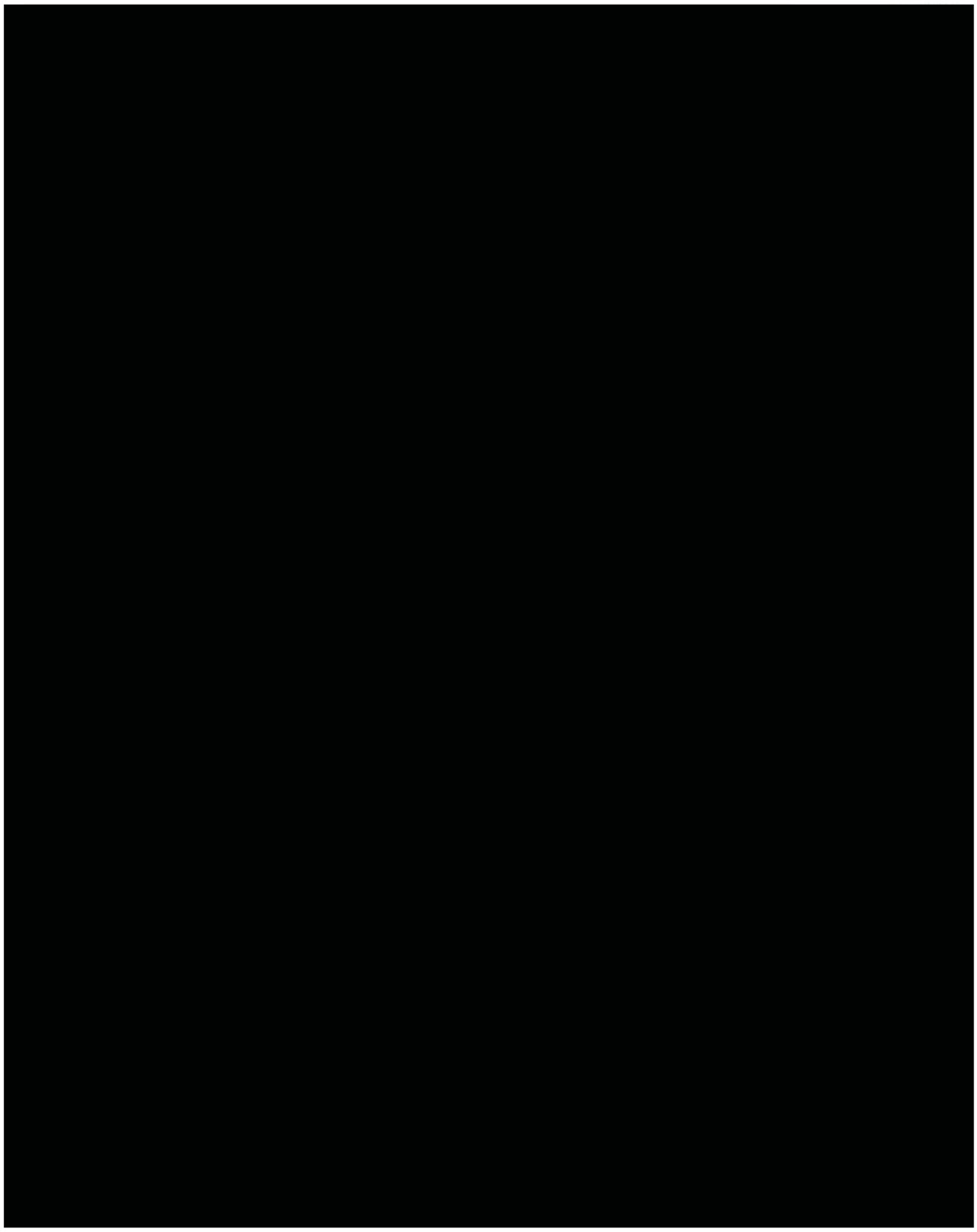


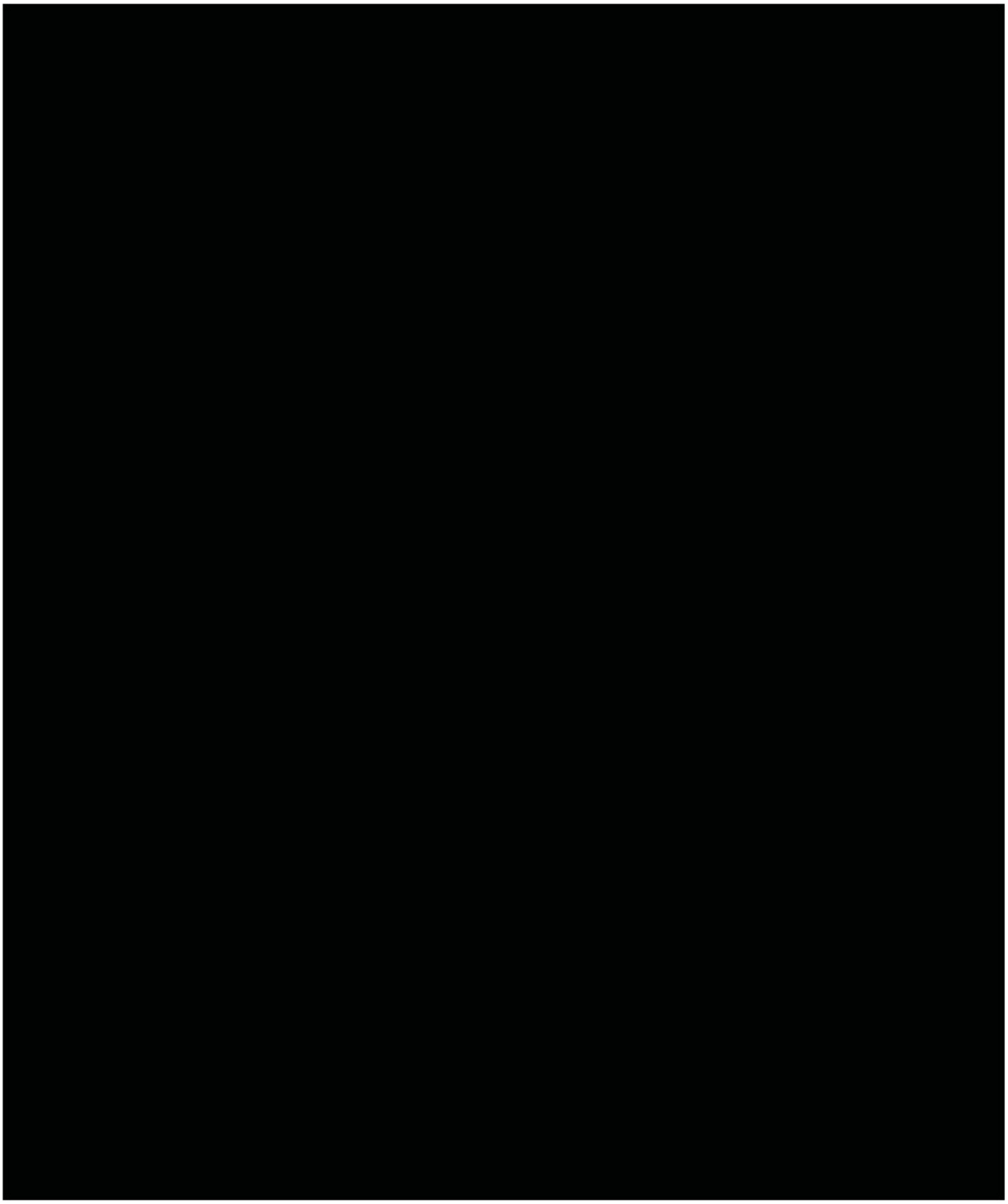


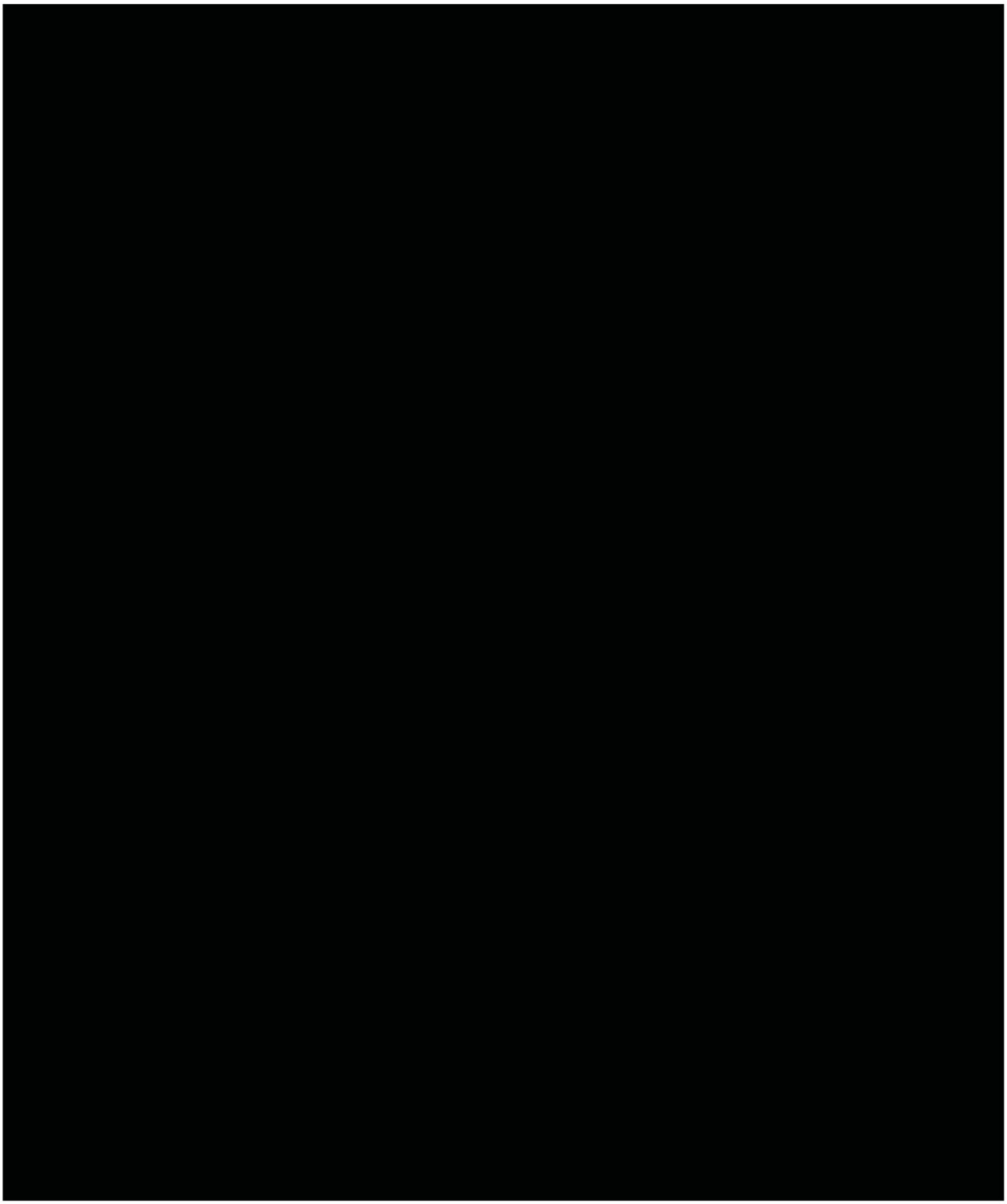


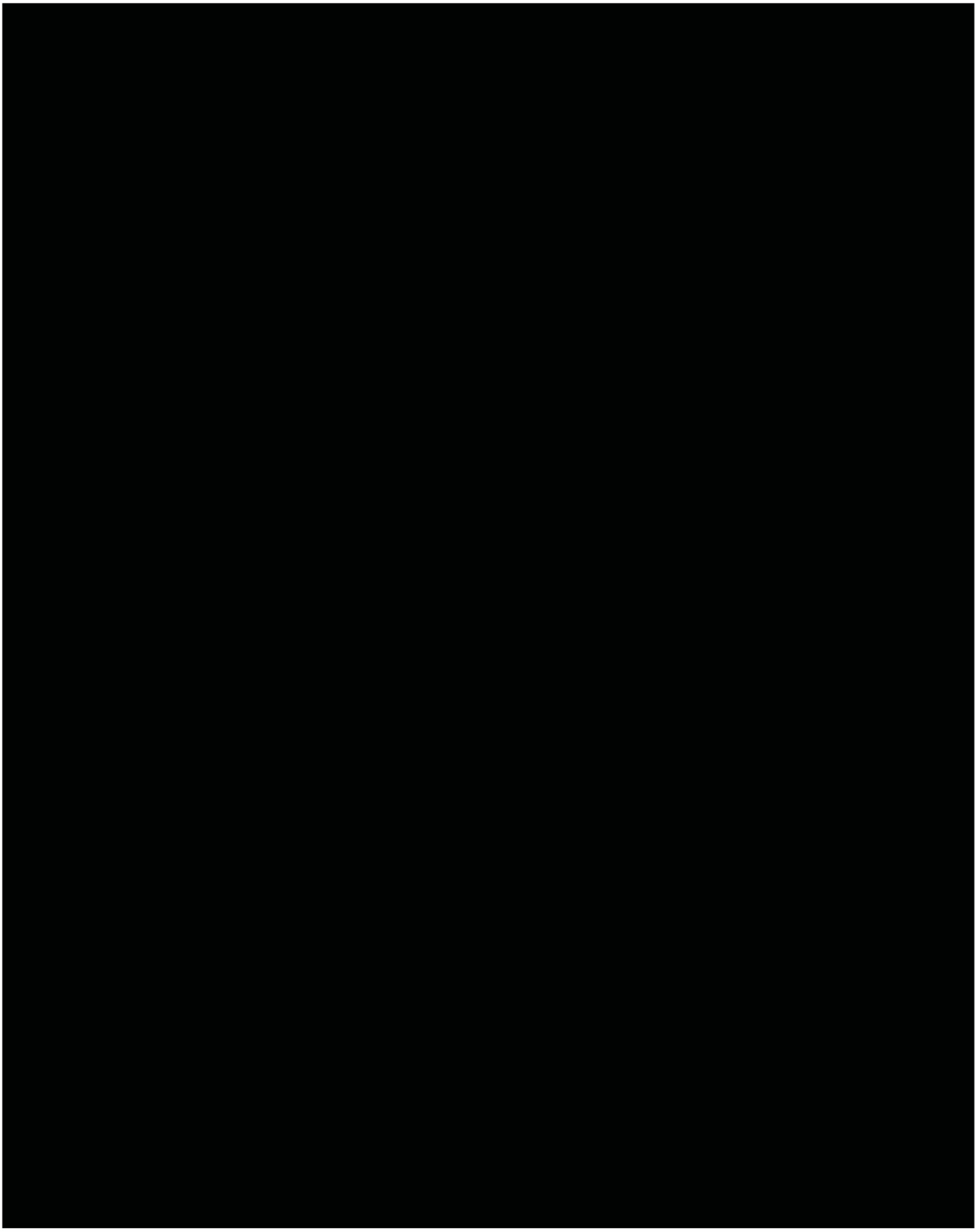


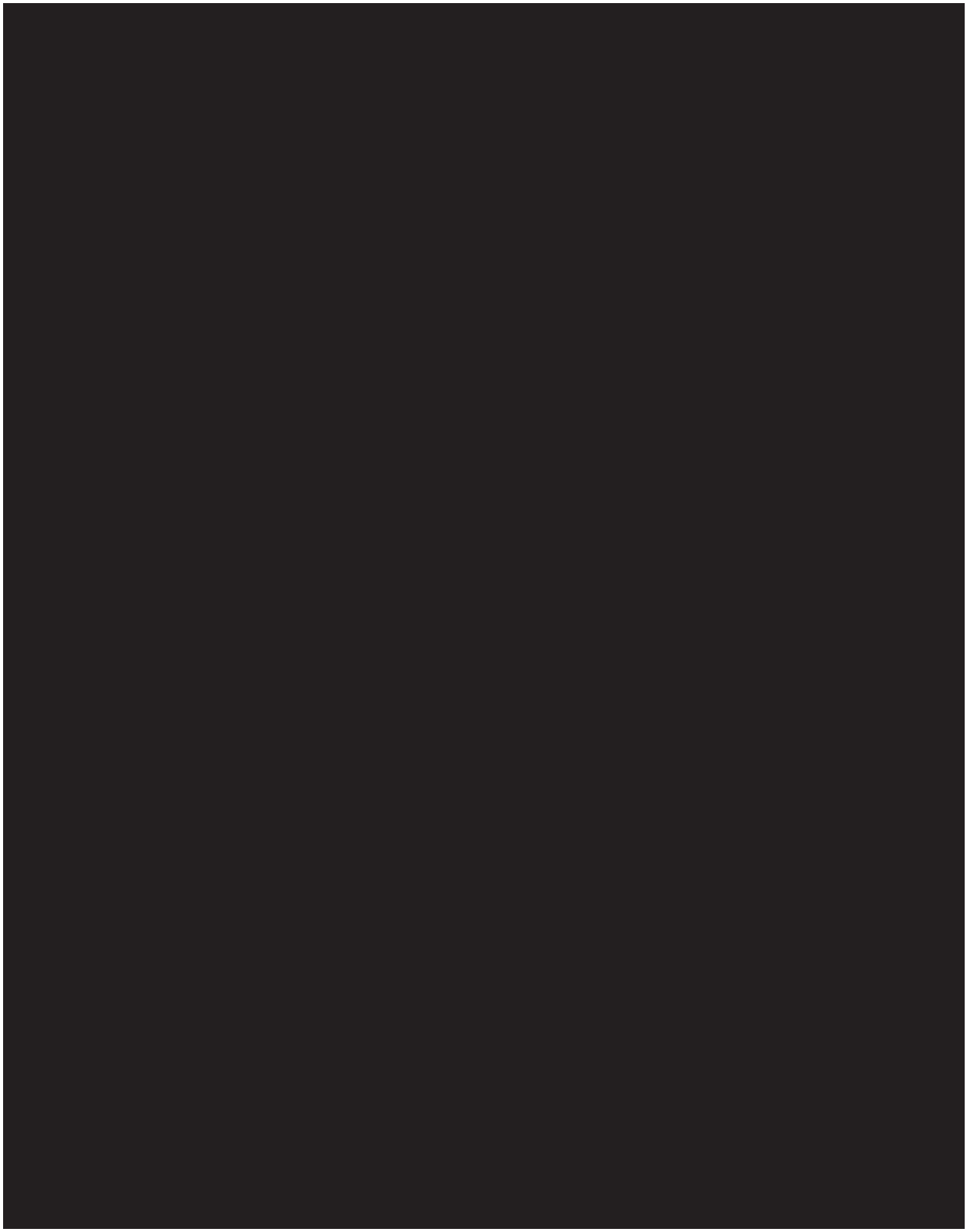












10.4 PATIENT SURVEY

Boehringer Ingelheim

Patient Feedback Survey – 1490-0005

Dear Participant,

Thank you for participating in Boehringer Ingelheim study 1490-0005. We would like your feedback on your experience in using **remote technologies** in this study. Your feedback (all optional) will not affect your study participation in any way.

The completion of this survey should take you approximately 10 minutes.

Experience with the cough monitor system [redacted]

Please mark the box that best represents how you feel about your recent use of the [redacted] ***cough monitor system*** *for each of the statements below.*

Statements:	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
1) The OVERALL EXPERIENCE with the cough monitor system was good.					
2) The INSTRUCTIONS for the cough monitor system (written patient guide) were easy to understand.					
3) It was easy to SET UP the cough monitor system at home (including finding the right position for placement of the Biosensor on the chest, attachment with adhesive, starting the sensor)					
4) Wearing the [redacted] Biosensor during DAYTIME was comfortable.					
5) Wearing the [redacted] Biosensor while ASLEEP was comfortable.					
6) I was able to REMOVE the [redacted] Biosensor including adhesive from my chest without any difficulties.					
7) Using the [redacted] Biosensor CHARGING STATION was easy.					
8) UPLOADING the cough monitor results via the app was easy.					

9) Was there any INFORMATION MISSING in the instructions (written patient guide)?

☐ No ☐ Yes, please specify _____

10) What did you LIKE about the cough monitor system (including but not limited to instructions, biosensor patch, charging station, measurements, uploading results, app)?

Comment _____

11) What did you DISLIKE about the cough monitor system (including but not limited to instructions, biosensor patch, charging station, measurements, uploading results, app)?

Comment _____

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12) What could be changed to IMPROVE your experience with the cough monitor system?
Comment _____

13) Is there any OTHER feedback you would like to share about the cough monitor system?
Comment _____

Experience with the video call assisted home spirometry [redacted]

Please mark the box that best represents how you feel about your recent use of the ***video call assisted home spirometry*** *for each of the statements below.*

Statements:	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
[redacted]					

Experience with the Virtual Visits

*Please mark the box that best represents how you feel about your recent use of the **virtual visit function** for each of the statements below.*

Statements:	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree

Please provide any further comments about your experience in the comment box.

Thank you!

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11. DESCRIPTION OF GLOBAL AMENDMENT(S)

This is the original protocol.

APPROVAL / SIGNATURE PAGE

Document Number: c39406431 **Technical Version Number:1.0**

Document Name: clinical-trial-protocol-version-01

Title: A multi-center, longitudinal 12-week pilot study to evaluate cough severity and its impact, utilizing a next generation cough monitor, in participants with idiopathic pulmonary fibrosis (IPF) or Non IPF Pulmonary Fibrosis

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Statistician	[redacted]	16 Sep 2022 15:01 CEST
Approval		16 Sep 2022 15:09 CEST
Approval-Clinical Program [redacted]		16 Sep 2022 18:10 CEST
Verification-Paper Signature Completion		19 Sep 2022 07:45 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed