Digital Incentive Spirometer for Assessing Incentive Spirometry Adherence

Airalux Digital Incentive Spirometer

CLINICAL RESEARCH PROTOCOL

INVESTIGATIONAL PRODUCT(S):		Airalux Digital Incentive Spirometer
STUDY NUMBER(S):	IRB Number	**ebebfaib**
	Other Protocol Identifiers	N/A
PROTOCOL(S) TITLE:		Digital Incentive Spirometer for Assessing Incentive Spirometry Adherence
NUMBER:		N/A
REGULATORY SPONSOR:		Principal Investigator-Initiated Study
FUNDING SPONSOR(S):		N/A, internal Penn study
MEDICAL DIRECTOR		Doraid Jarrar, MD
ORIGINAL PROTOCOL DATE:		N/A
VERSION NUMBER:		2.0
VERSION DATE:		August 19, 2024

PRINCIPAL INVESTIGATOR SIGNATURE

STUDY SPONSOR:	Principal Investigator-Initiated Study
STUDY TITLE:	Digital Incentive Spirometer for Assessing Incentive Spirometry Adherence
STUDY ID	ebebfaib
PROTOCOL VERSION	2.0

I have read the referenced protocol. I agree to conduct the study in accordance to this protocol, in compliance with the Declaration of Helsinki, Good Clinical Practices (GCP), and all applicable regulatory requirements and guidelines.

Principal Investigator Name	Doraid Jarrar, MD	Signature	Doraid Jarrar
Affiliation:	Univ of Pennsylvania	Date	8/19/2024

Abbreviations

IS	Incentive Spirometer
SpO2	Oxygen saturation
ePHI	Electronic Protected Health Information
HIPAA	Health Insurance Portability and Accountability Act
HUP	Hospital of the University of Pennsylvania
PPMC	Penn Presbyterian Medical Center

1 STUDY SUMMARY

1.1 Synopsis

Title:	Airalux Digital Incentive Spirometer
Short Title:	Digital Incentive Spirometer
Study Description:	This single-arm proof-of-concept research study aims to assess the effect of a digital incentive spirometer (IS) device and a companion mobile-based app on incentive spirometry adherence in patients post-surgery. The digital IS utilizes a sensor to measure inspiratory breaths, and these data are transmitted wirelessly to a secure cloud database. The spirometer and app include a patient reminder system, exercise gamification strategies, progress tracking, and additional features designed to promote patient IS use.
Objectives:	The objective of this study is to evaluate the effect of a digital IS that provides gentle auditory and haptic reminders and exercise guidance on patient adherence to incentive spirometry. Secondarily, this study will evaluate metrics relating to lung function to assess post-surgery lung recovery in patients using the digital IS.
Primary Endpoint:	Total incentive spirometry adherence - Number of inspiratory breath attempts performed with the digital IS per day. Consistency of incentive spirometry adherence throughout postoperative stay - Percent of recorded hours in which at least one inspiratory breath was attempted using the digital IS.
Secondary Endpoints	Quality of inspiratory breaths attempted with the digital IS - quality refers to inspiratory volumes achieved. Blood oxygen saturation - Postoperative SpO2 Pain Scores - Postoperative pain scores will be reported on a scale from 0 (no pain) to 10 (unbearable pain). Pulmonary function testing lab results – preoperative spirometry results from pulmonary function lab

Study Population:	30 patients (of adult categorization) undergoing anatomic lung resection surgery and receive an incentive spirometer as standard-of-care. No restriction on gender, demographic group, or geographic location. We will be enrolling patients that receive surgery from Dr. Doraid Jarrar (Principal Investigator), Dr. Sunil Singhal (Chief of Thoracic Surgery), and/or Dr. Taine Pechet (Chief of Surgery, PPMC) at the sites listed below.
Phase:	Exploratory
Description of Sites/Facilities	Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104 Penn Medicine Valley Forge, 1001 Chesterbrook Blvd, Berwyn, PA 19312 Penn Medicine University City, 3737 Market Street Philadelphia, PA 19104 Penn Medicine Cherry Hill, 1865 Route 70 East Cherry Hill, NJ 08003 Penn Thoracic Surgery Presbyterian, Presbyterian Medical Center of the University of Pennsylvania, 3737 Market St Philadelphia PA, 19104 Perelman Center for Advanced Medicine, 3400 Civic Center Boulevard Philadelphia, PA 19104
Enrolling Sites:	Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104 Penn Medicine Valley Forge, 1001 Chesterbrook Blvd, Berwyn, PA 19312 Penn Medicine University City, 3737 Market Street Philadelphia, PA 19104 Penn Medicine Cherry Hill, 1865 Route 70 East Cherry Hill, NJ 08003 Penn Thoracic Surgery Presbyterian, Presbyterian Medical Center of the University of Pennsylvania, 3737 Market St Philadelphia PA, 19104 Perelman Center for Advanced Medicine, 3400 Civic Center Boulevard Philadelphia, PA 19104
Description of Study Intervention:	Patients will be instructed to periodically perform inspiratory breaths from the mouthpiece of the digital IS device during their postoperative stay similar to how standard-of-care incentive spirometers are instructed. The digital IS utilizes a sensor to measure inspiratory flow rates and volumes. These data will be displayed to the patient during inspiratory breaths on the device screen. The screen and a speaker in the device along with the mobile

	app will provide visual and auditory cues to guide patients in performing inspiratory breaths and periodically remind patients to perform them.
Study Duration:	Estimated length of time to enroll all subjects and complete the study: 3 months.
Participant Duration:	For the entirety of a patient's postoperative hospital stay until they are discharged (on average 2-3 days) or up to 1 week post-surgery.

1.2 Key Roles and Study Governance

Sponsor	Medical Director
N/A, principal investigator-initiated study	Doraid Jarrar, MD
	Division of Thoracic Surgery, Hospital of the University of Pennsylvania
	3400 Civic Center Blvd, Philadelphia PA 19104
	215-662-7878
	Doraid.Jarrar@pennmedicine.upenn.edu

– 1.3 Schema

Office (within 1-30 days prior to surgery) - Informed Consent - Obtain informed consent *alongside surgery consent* - (Optional) Obtain patient or family member email address (linked to their Apple ID) to approve access to the Airalux app on their App Store (IOS only)   - The Airalux app provides guided IS exercise sessions, allows patients and family members to view past IS exercise measurements, and gamifies adherence metrics.
Pulmonary function lab – Spirometry Testing - Patients will receive spirometry testing at the pulmonary function lab. This is part of routine care. This is not a study intervention.
Pre-op holding (morning of surgery) - Baseline Measurement - Patients receive the Airalux device and use it to perform a baseline IS measurement - Research team records the device identification key of the device that the patient is receiving - (Optional) For patients with the Airalux app, they can sign in to the app with their device identification key.
Post-anesthesia care unit (2-4 hours post-surgery) - Study Intervention Administered - Patients are instructed to perform IS exercises with their device - The device will gently vibrate/buzz every 15 minutes to prompt patients to complete an IS exercise - (Optional) Patients can follow guided exercises on the app if desired
Inpatient hospital floor (0-7 days post-surgery) - Study Intervention Administered, Collection of Endpoints - Patients are instructed to perform IS exercises with their device throughout their hospital stay - The device will vibrate every 15 minutes to prompt patients to complete IS exercise - (Optional) Patients can follow guided exercises on the app if desired - Patient pulse oximetry data is collected every 4 hours. This is part of routine care. This is not a study intervention. - Patient pain scores are collected at minimum every 12 hours (at least once per shift). This is part of routine care. This is not a study intervention.
Discharge - Study Ends (conclusion of hospital stay) - Patients will not be able to use the Airalux device outside of the hospital - Patients will receive a standard of care incentive spirometer to use at home - Patients will complete a survey on their experience with using the device

2 INTRODUCTION AND RATIONALE

2.1 Study Rationale

Incentive spirometry is frequently prescribed as a standard-of-care for patients post-surgery to reduce the risk of developing postoperative pulmonary complications associated with atelectasis. An incentive spirometer (IS) is a mechanical breathing device that assists with pulmonary rehabilitation through improving lung expansion by encouraging deep breathing. While performing incentive spirometry exercises is effective at lowering atelectasis severity, ventilation time, and pulmonary complication rates, patient adherence to performing exercises is very poor. Medical staff, due to time constraints, often cannot supervise all of their patients' entire incentive spirometry regimens (usually every 10-15 min during wakeful hours), contributing to low adherence and incorrect exercise completion. This is compounded by current incentive spirometers lacking a method for accurately collecting patient exercise and adherence data. The present study seeks to evaluate the effect of a digital IS that provides instruction signals and exercise reminders on patients' incentive spirometry adherence.

2.2 Background

Prior studies have demonstrated that adherence to incentive spirometry is widely considered to be low. In a 2018 national survey among 1,681 respiratory therapists and nurses, 86% of providers agreed that incentive spirometry adherence is poor, with the most commonly cited reason for poor adherence being that patients forget to use their ISs (83.5% of respondents).[1] Recent efforts have also demonstrated that increased incentive spirometry adherence may correlate with improved patient clinical outcomes. In a 2-arm RCT with 147 cardiac surgery patients, a bell-reminder system was found to double incentive spirometry adherence (17.1 vs 35.4 daily exercises). Patients with the reminder system had reduced length of stay (7 vs 6 days in nonelective surgery patients), ventilation use rates (37% vs 19%), and post-op fever duration (5.2 vs 3.2 hours).[2] Another RCT investigating the impact of incentive spirometry prior to cardiac surgery found that patients performing incentive spirometry preoperatively also had reduced length of stay (7 vs 6 days) and duration of mechanical ventilation (6 vs 4 hours).[3]

This device has been tested in the Penn Biomedical Engineering Stephenson Lab for its ability to accurately measure and record inspiratory breaths. Specifically, the device has demonstrated accuracy in measuring inspiratory volume using a 3L calibration syringe in testing derived from ISO26782 spirometry guidance. The body of the device and mouthpiece are made out of biocompatible plastic making it safe to touch and inhale from with no risk of toxicity. Furthermore, all electronic components and the battery are housed within the device and are insulated to prevent any electronic mishaps.

2.2.1 Pharmacokinetics, Pharmacodynamics and Toxicology

Not applicable, the digital IS is a noninvasive external medical device that poses minimal risk to the patient. The only critical point of contact between the device and the patient will be the mouthpiece that the patient will inhale from.

2.2.2 Assessment for Potential Study Products Drug-Drug, Drug-Device, Device-Device Interactions

The digital IS will not physically interact with any other products. The device will send patient incentive spirometry performance data wirelessly to the integrated mobile-based app or secure cloud database via WiFi. The digital IS will not receive communications from any device.

2.3 Risk/Benefit Assessment

2.3.1 Known Potential Risks

The digital IS is a lightweight, handheld device that poses no significant risk to the patient. The 2 main components of the device (the main device body and the mouthpiece) are both large enough such that they pose a very low risk for choking. All electronic components are housed inside the device and are electrically insulated.

2.3.2 Known Potential Benefits

We do not claim any immediate potential benefits to the patient. Long-term benefits would be contributing to a study that would determine the efficacy of a digital IS device on incentive spirometry adherence, which may correlate with positive post-surgery clinical outcomes.

2.3.3 Assessment of Potential Risks and Benefits

The risks discussed above are minimal and non-significant. The benefits of participating in the study and contributing to the evaluation of a digital IS device that may improve incentive spirometry adherence and post-surgery outcomes outweighs these risks.

3 STUDY OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
The primary objective is to evaluate the effect of a multifeatured digital IS and integrated phone app on patient adherence to incentive spirometry. Together the device and app will include the following functions: an auditory and haptic reminder cue, visual and auditory cues to guide exercise completion, exercise gamification, and data tracking and visualization features.	The primary endpoints are totality and consistency of incentive spirometry adherence. Specifically, total adherence is a measure of the number of inspiratory breath attempts performed with the digital IS per day, and the consistency of adherence is a measure of the percent of hours in which at least one inspiratory breath was attempted using the digital IS.	The number and frequency of inspiratory breath attempts with the digital IS will be evaluated to assess patient adherence to incentive spirometry.
Secondary		
The secondary objective is to evaluate metrics relating to lung function to assess post-surgery lung recovery in patients using the digital IS.	The secondary endpoints are postoperative blood oxygen saturation (SpO2), postoperative pain scores, preoperative pulmonary function spirometry results, and postoperative inspiratory breath quality. Pain scores will be on a scale from 0 (no pain) to 10 (unbearable pain). Specifically, quality refers to inspiratory volumes achieved over time and the flow rate at which inspiratory breaths were taken.	Blood oxygen saturation, pain scores, preoperative spirometry results, and inspiratory breath quality will be evaluated to assess post-surgery lung recovery in patients using the digital IS.
Tertiary		
The tertiary object is to evaluate patient user experience of the digital IS device.	A tertiary endpoint will be survey responses collected from patients at discharge. Please see attached survey for survey questions.	These will be used to assess user experience of the device and companion app if applicable.

4 STUDY PLAN

4.1 Study Design

We hypothesize that use of the investigational device will have a positive impact on patient incentive spirometry adherence. This is a single-arm, exploratory study that will be conducted at the Hospital of the University of Pennsylvania (HUP) and Penn Presbyterian Medical Center (PPMC). The digital IS utilizes a sensor to measure inspiratory breath volume and flow rates, and this data, as well as the time stamps, are transmitted wirelessly to a secure cloud database and a companion mobile-based app. The IS and app incorporate features to instruct and remind patients about their exercises, which include auditory and visual cues as well as a gentle auditory and haptic reminder to perform exercises. Furthermore, the app has additional features to encourage breathing exercises in the form of gamification strategies, and separate interfaces for patients and medical staff to monitor device usage. All of the features are aimed at improving patients' adherence to incentive spirometry.

Subjects will be recruited from patients undergoing any lung resection surgery performed by Dr. Doraid Jarrar, Dr. Sunil Singhal, and/or Dr. Taine Pechet at HUP and/or PPMC and for which an incentive spirometer is expected to be used by the patient after their surgery. The target enrollment for the study is 30 subjects. The duration of the subject's participation with the trial will be for their entire postoperative hospital stay up to 1 week postoperatively. At the beginning of the subject's participation, study activities will be focused on informed consent, instruction on use of the digital IS, and obtaining baseline inspiratory volume measurements. Most of the remainder of the subject's participation time will be focused on passive data collection performed by the digital IS.

4.2 Scientific Rationale for Study Design

The purpose of this exploratory study is to evaluate the effect of an investigational device on incentive spirometry adherence.

4.3 End of Study Definition

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Appendix Section 12.1.

5 STUDY POPULATION

5.1 Inclusion Criteria

To be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of signed and dated informed consent form

2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. Male or female, 18 years or older.
4. Undergoes any anatomic lung resection surgery
5. An incentive spirometer is expected to be ordered for the patient as standard-of-care
6. There is no restriction on active medications.

5.2 Exclusion Criteria

There are no exclusions based on economic status, gender, race, or ethnicity. An individual who meets any of the following criteria will be excluded from participation in this study:

1. Vulnerable populations who in the opinion of the investigator are unable to give Informed Consent for reasons of incapacity, immaturity, adverse personal circumstances or lack of autonomy.
2. History of prior non-compliance to prescribed therapy or presence or history of significant psychiatric condition (e.g., drug or alcohol addiction, psychosis, schizophrenia), or cognitive issue which would in the opinion of the investigator, make it difficult for the patient to comply with the study procedures or follow the investigators instructions.
3. Populations for whom in the opinion of the investigator, incentive spirometry is deemed inappropriate due to medical condition or otherwise.
4. Pregnant individuals due to low likelihood of meeting inclusion criteria 4 in section 5.1.

Licensed medical professionals on the clinical team will follow proper procedures in determining if the individual is consenting. Proper procedures entail doing all of the following: giving a patient adequate information concerning the study, providing adequate opportunity for the patient to consider all options, responding to the patient's questions, ensuring that the patient has comprehended this information, obtaining the patient's voluntary agreement to participate and, continuing to provide information as the patient or situation requires. There will be ample opportunity for the patient to ask questions. In the event that the patient is in a vulnerable population and unable to provide consent, they will not be eligible to participate in the study and thus will not be screened. If the individual is not able to provide informed consent or if consent is not certain due to impairments or other factors, they will not be considered for study participation. In the event that the patient is in a vulnerable population and unable to provide consent, they will not be eligible to participate in the study and thus will not be screened.

5.3 Lifestyle Considerations

Not applicable.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the study but are not subsequently evaluated with the investigational device. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to

respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

5.5 Strategies for Recruitment and Retention

The overall target study sample size is 30 subjects, with no targets by gender, race and ethnicity, or age. The medical director will identify and recruit patients who are eligible for the study based on patients that have been evaluated and consented for a robotic anatomic lung resection surgery. The medical director or another member of the attending clinical team involved in this study will approach these patients about the study, and if the patient consents to the study, they will be enrolled. Informed consent will be obtained in the same visit as consent for the surgery is obtained, which may occur 1-30 days prior to surgery, to minimize patient visits.

The time period of 3 months identified in a previous section was based on the historical frequency of such patients being screened at HUP and PPMC as well as an estimate of participation rate.

6 STUDY INTERVENTION

6.1 Study Intervention(s) Administration

6.1.1 Study Intervention Description

The device intervention being utilized in this study is a handheld digital IS composed of the following components:

- Disposable mouthpiece and airflow tube, made of biocompatible, non-conductive plastic (PLA, TPU) and/or dental resin (size: 1 in. x 1 in. x 0.5 in), and the following electronics
    - Ported pressure sensor
- Device body, made of biocompatible, non-conductive plastic material (PLA) that encases the following electronics which do not come in contact with the patient (size: 7 in. x 2 in. x 2.5 in)
    - Rechargeable Lithium-Ion battery (an off-the-shelf consumer power bank)
        - Anker Nano Power Bank with Built-in Foldable USB-C Connector, 5,000mAh Portable Charger 22.5W
    - Speaker with an output wattage of up to 2W
    - LED display screen (1.3 in diagonal)
    - Digital signal processing microcontroller
    - Coin vibration motor
    - Momentary push button

- Wiring, coated in non-conductive casing

The study intervention also includes a mobile application that can be downloaded to a portable smart device such as a smartphone or tablet.

The digital IS will be used by the patient for the duration of their postoperative stay, turned on each morning after the patient is awake, and turned off before the patient goes to sleep for the night. When turned on, the device will gently vibrate to prompt users every 15 minutes to remind patients to perform their prescribed breathing exercises.

6.1.2 Dosing and Administration

The device will be administered to the patient in the following manner. When patients are in pre-operative holding, nursing staff will record a baseline measurement of inspiratory volume with the digital IS and facilitate patients linking their device to the mobile app if patients have a compatible smartphone. Following surgery, the attending clinical staff will teach patients how to perform breathing exercises with the digital IS and instruct them regarding the quantity, frequency, and volume of inspiratory breaths (once every ~15 minutes, with an initial target inspiratory volume of at least 500 mL) to complete during their postoperative stay. For patients that are able to download the mobile app, the mobile app will include additional instructional material on how to use the digital IS device that patients can access at any time.

After initial instruction by the attending clinical team, the patient will perform inspiratory breaths with the digital IS device independently throughout their hospital stay. To perform an inspiratory breath, the patient will empty their lungs with a large exhale, put the mouthpiece of the device to their mouth, and take a deep inspiratory breath. While the patient is using the device, they will be prompted for each exercise step by audio and visual cues, and their resulting inspiratory volume will be displayed on the device screen after each breath.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Acquisition and accountability

Prior to patient enrollment, devices and extra replacement mouthpieces will be delivered to the clinical team, who will distribute the devices to patients during each patient's pre-op holding period. Each patient will receive their own personal device to keep. If a device is deemed to be no longer functional, a replacement device will be produced and delivered. Determinants of functionality will be accuracy of inspiratory breath metrics, and proper function of adherence-promoting systems (reminders, live exercise guidance, data collection and transfer to app) and electronic components of the device (speaker, LED Screen, button, battery). These features will be tested prior to returning or delivering any devices to the clinical team.

6.2.2 Formulation, Appearance, Packaging, and Labeling

The devices will be delivered in a cardboard box with foam packing material to prevent device breakage during delivery and storage. Unused devices will be stored in Room 185 of the 14th floor of the South-Pavilion at HUP and in Room 245B of PPMC. Each individual device with its charger will be packaged in a resealable clear plastic package. No other device set up is required. At patient discharge, mouthpieces will be disposed of, and devices will be recollected and stored in Room 185 of the 14th floor of the South-Pavilion at HUP or in Room 245B of PPMC.

6.2.3 Product Storage and Stability

The device will be stored on a flat surface close to the patient's bedside when not being used. The stability of the device is not anticipated to be of concern throughout the course of this study.

6.2.4 Preparation

The device must be prepared in the following fashion:

1) If the device battery is not charged, connect the device to a power cord connected to an external power outlet.
2) Turn on the device and, if the patient has downloaded the accompanying app, open the mobile app on smartphone/tablet.
3) Ensure strong WiFi connection is active.

6.3 Measures to Minimize Bias: Randomization and Blinding

This is a single-arm exploratory study which will not require participant randomization or blinding.

6.4 Study Intervention Compliance

Adherence to the protocol will largely be verified by assessing timestamped data collected by the digital IS. This data will enable the research team to confirm that baseline inspiratory volume measurements were taken prior to surgery.

Data collected by the digital IS devices will be stored on a private secure cloud-based database. Data not consent forms or linking sets, can be accessed and transferred by the members of the study team who will conduct data analysis. This transfer will be done via PennBox.

6.5 Concomitant Therapy

Not applicable.

6.5.1 Rescue Medicine

Not applicable.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

Discontinuation from protocol specified activities will result in discontinuation from the study. In this situation, the device is the only clinical intervention being utilized with patients. As such, discontinuing the use of the IS device prohibits data collection and renders the patient's data incomplete and therefore useless for analyses. Furthermore, there are no follow ups involved in this study so discontinuation from device intervention prevents collection of metrics associated with secondary endpoints and constitutes a patient's discontinuation from the study.

7.2 Participant Discontinuation/Withdrawal from the Study

Participants are free to withdraw from participation in the study at any time upon request.

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- If the participant meets any of the exclusion criteria (either newly developed or not previously recognized) that precludes further study participation.
- If the participant insists on using the standard of care IS device.

The reason for participant discontinuation or withdrawal from the study will be recorded by the study team. Given that none of the aforementioned reasons constitutes an adverse event, it may be the case that no further reporting is necessary. Subjects who sign the informed consent form but do not receive the digital IS may be replaced. Subjects who sign the informed consent form and receive the digital IS, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

7.3 Lost To Follow-Up

Not applicable, no follow-up for study participants.

8 STUDY ASSESSMENT AND PROCEDURES

8.1 Efficacy Assessments

Study Procedures and Evaluations:

1) Patient identification and eligibility screening:
    a. Once a potential participant is identified as already scheduled for a lung resection surgery, the clinical team will determine whether the patient satisfies the eligibility criteria.
    b. Any additional eligibility criteria that cannot be identified or evaluated via Penn Charts will be reviewed and confirmed by the clinical team following receipt of signed ICF forms.
2) Patient visit and informed consent:
    a. If any additional eligibility criteria need to be screened due to a lack of information in Penn Charts, the patient will be asked relevant questions after providing necessary informed consent to the clinical team.
        i. This will take place in the doctor's office that is private. Note that in-patient hospital stay will not be billed to the study as the hospital stay is unrelated to participation in the study.
3) Patient spirometry testing at the pulmonary function laboratory
    a. This is already done as part of routine care. This is not a study intervention. Lab results from spirometry testing will be a secondary endpoint.
4) Device intervention during patient visit
    a. After receiving informed consent, during preoperative holding, the clinical team will give the patient one digital IS, facilitate the download of the companion app onto the patient's personal mobile device if applicable, and obtain a baseline inspiratory volume measurement.
    b. Post-surgery, the clinical team will teach patients how to perform breathing exercises with the digital IS and instruct them regarding the quantity, frequency, and volume of inspiratory breaths to perform throughout their hospital stay.
        i. While the digital IS is powered on, an auditory and haptic reminder will occur every 15 minutes to remind the patient to perform their breathing exercises. The patient has full autonomy as to when and how often to use the digital IS. Digital IS usage and inspiratory volume data will be collected by the device whenever it is used by the patient.
        ii. At minimum twice per day, the clinical team will collect pain scores. This is already done as part of routine care. This is not a study intervention.

iii. Every 4 hours, the clinical team will record a patient's SpO2. This is already done as part of routine care. This is not a study intervention.

c. At discharge, patients will complete a short survey on their experience with the device and IS performance.

d. Use of the digital IS, and the resulting analysis on adherence, are the primary outcome of this clinical study. Metrics relating to lung function, including inspiratory volume measures, SpO2, pulmonary function lab testing, and pain scores, are the secondary outcomes of this clinical study.

e. No other vital sign data will be obtained for the study. No follow-up visits will occur. Any withdrawal from the study will occur during this visit as it is the only visit.

8.2 Safety and Other Assessments

The investigational device is not being evaluated for safety as a primary endpoint in this clinical study.

8.3 Adverse Events and Serious Adverse Events

8.3.1 Definition of Adverse Events (AE)

An adverse event is any undesirable experience associated with the use of a medical product in a subject. No adverse events are expected since the device is of nonsignificant risk. The device does not introduce energy to the patient. In addition, voltages related to the device electronics are regulated via appropriate circuitry on board the device.

8.3.2 Definition of Serious Adverse Events (SAE)

Not applicable.

8.3.3 Unanticipated Adverse Device Effect (UADE)

A UADE is any serious adverse effect on health or safety, or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

8.3.4 Classification of an Adverse Event

8.3.4.1 Severity of Event

Not applicable, no adverse events are defined given the minimal risk of device intervention.

8.3.4.2 Relationship to Study Intervention

Not applicable, no adverse events are defined given the minimal risk of device intervention.

8.3.4.3 Expectedness

The principal investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the investigational device. However, once again, no adverse events are expected with the described device intervention.

8.3.5 Time Period and Frequency for Event Assessment and Follow-Up

No adverse events are expected related to the device, device intervention procedure, or study as a whole. As such, no follow-ups will take place.

8.3.6 Adverse Event Reporting

No such reporting will occur given that no adverse events are expected or reasonably probable. In the highly unlikely case of an AE, it will be reported to the principal investigator. The principal investigator will subsequently submit appropriate documentation to the IRB within a timely fashion, as dictated by Penn IRB policy.

8.3.7 Serious Adverse Event Reporting

See previous section.

8.3.8 Reporting Events to Participants

Not applicable.

8.3.9 Events of Special Interest

Not applicable.

8.3.10 Reporting of Pregnancy

Pregnancy, in and of itself, is not regarded as an AE as there is no additional risk to the subject and no risk to the fetus.

8.4 Unanticipated Problems

8.4.1 Definition of Unanticipated Problems (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 Unanticipated Problem Reporting

Unanticipated problems (UPs) such as the following should be reported to the principal investigator:

- Complaint of a participant when the complaint indicates unexpected risks, or the complaint cannot be resolved by the research team
- Breach of confidentiality
- Premature closure of a study (e.g., due safety, lack of efficacy, feasibility, financial reasons, etc.)

The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- Any other UP will be reported to the principal investigator within 48 hours of the study team member becoming aware of the problem.

All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within 48 hours of the IRB's receipt of the report of the problem from the investigator.

8.4.3 Reporting Unanticipated Problems To Participants

Not applicable.

8.5 Device Reporting

Safety reporting for the device will be according to 21 CFR 812.150.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

Not applicable.

9.2 Sample Size Determination

A sample size of 30 patients was determined based on the frequency of patients expected to undergo lung resection at the Hospital of the University of Pennsylvania and Presbyterian Medical Center, receive an incentive spirometer during their postoperative stay, and fit the study inclusion criteria within a 3 month period.

9.3 Populations for Analyses

The population will include adult patients.

9.4 Statistical Analyses

9.4.1 General Approach

The data collected from the digital incentive spirometer for an individual patient, which will include timestamps of inspiratory attempts and inspiratory volume, will first be screened for false readings which are defined as an inspiratory attempt for which an inspiratory volume is ≤ 100.0 mL. False readings may occur from improper use of the device or the patient being interrupted during an inspiratory attempt, and will not be included in the analysis. To determine the total incentive spirometry adherence for a patient, the number of inspiratory breath attempts performed with the digital IS per day will be calculated and then averaged across the length of the patient's visit (or number of days the IS was in use). To determine the consistency of incentive spirometry adherence throughout postoperative stay, the number of 1 hour intervals in which at least one inspiratory breath was attempted using the digital IS will be calculated and represented as a percent of the total number of hours the digital IS was powered on and recorded metrics.

9.4.2 Analysis of the Primary Efficacy Endpoint(s)

As this is a one-arm study and there are no comparative analyses to be made, all of the primary endpoints will be analyzed to determine the average and standard deviation within the total

patient population. In the event that inspiratory breath data could not be collected or were unreliable because of digital IS power interruptions, mouth obstructions that preclude IS use, or other events that may influence digital IS use or inspiratory breath data collection, data from that day will be excluded for the patient.

9.4.3 Analysis of the Secondary Endpoint(s)

No secondary endpoints are dependent on findings of primary endpoints. Average change in blood oxygen saturation and pain scores over time will be calculated across the course of each patient's postoperative stay. The change in volume of inspiratory breaths will also be calculated across the course of each patient's postoperative stay. This will also be evaluated against both the baseline IS measurement taken preoperatively as well as pulmonary function lab results. The average and standard deviation of flow rates and time spent at different flow rates will also be calculated. The time spent below or above the target 200ml/s-800ml/s range will be calculated for each inspiratory breath, and used to measure the percentage of attempted inspiratory breaths that fell within this range. As this is a one-arm study and there are no comparative analyses to be made, all of the secondary endpoints will be analyzed to determine the average and standard deviation within the total patient population.

9.4.4 Safety Analyses

Not applicable.

9.4.5 Baseline Descriptive Statistics

Not applicable.

9.4.6 Planned Interim Analyses

Not applicable.

9.4.7 Sub-Group Analyses

Not applicable

9.4.8 Tabulation of Individual Participant Data

Individual patient data will be stored with a randomized patient number instead of their name (e.g., 001, 002, etc).

9.4.9 Exploratory Analyses

Not applicable.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Informed Consent Process

10.1.1.1 Consent/Assent and Other Informational Documents Provided To Participants

Consent forms describing in detail the device intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to device intervention. The following consent materials are submitted with this protocol:

- Informed Consent Form

10.1.1.2 Consent Procedures and Documentation

Prior to engagement with the patient, the physician will determine patient eligibility for the study. Procedures for diagnosis will not fall under the scope of the study itself and the participating entities of the study are not responsible for costs associated with said procedures.

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Potential participants will be provided information about the research project that is understandable and that permits them to make an informed and voluntary decision about whether or not to participate. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The patient will be asked to provide verbal assent. Amongst the information provided will be potential risks. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. This will include an overview of the device and its functionality along with the intended uses of the device. During this stage, the physician will also inform the patient that no diagnosis will be made from use of the device and that their contribution will be used to help determine the validity and capabilities of the device. The patient will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to providing verbal assent. The patient will sign the informed consent document prior to any procedures being done specifically for the study. Participants will be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be

protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. We have no proposed waivers or alternatives to informed consent apart from the patient's decision not to participate. We also do not anticipate special circumstances while obtaining consent. Due to resource constraints, speakers of a language other than English will not be allowed to participate in this study.

Note that all procedures conducted at the Hospital of the University of Pennsylvania and Penn Presbyterian Medical Center will be beholden to the Penn IRB.

10.1.2 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated by the principal investigator (PI) if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants and the investigator. If the study is prematurely terminated or suspended, the PI will promptly inform the Institutional Review Board (IRB) and provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping via ongoing statistical analysis
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the IRB. In terminating the study, the PI will ensure that adequate consideration is given to the protection of the subjects' interests.

10.1.3 Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the PI and the study team. This confidentiality is extended to cover the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the PI.

Recorded data will include the following: study participant alphanumeric key, mobile app profile anonymization ID (if applicable), incentive spirometer device identification key, exercise metrics, exercise settings, exercise dates and time stamps, SPO2 measurements, pulmonary function lab spirometry results, pain scores, survey responses, age, weight, height, and sex at birth. Age, weight, height, and sex at birth are necessary identifiers because they determine target incentive spirometry volumes for an individual.

Participant research data will be kept on PennBox and a private secure cloud-based database only accessible to members of the research team. Information regarding patient names and the dates of study participation will be collected on consent forms, which will be stored under lock and key in paper format in the investigator's office and uploaded to their patient record.

All research activities will be conducted in as private a setting as possible.

The authorized representatives of the sponsor and representatives of the Institutional Review Board (IRB) may inspect all documents and records required to be maintained by the investigator. The clinical study site will permit access to such records.

The following list provides information on the data being stored. Please note that the "final data set" constitutes any data that will be used in subsequent analysis and may be published at the discretion of study team members or the PI.

- Patient Information – collected for the purposes of evaluating eligibility
    - Identification of scheduled lung resection surgery - used in final data set
    - Randomized Alphanumeric Key to Label Patient Data - used in final data set
    - Age , weight, height, sex at birth- used in final data set
    - Birthdate - NOT used in final data set
    - Medical record number - NOT used in final data set
    - Name - NOT used in final data set
- Timestamped inspiratory breath data (inspiratory volume over time, inspiratory air flow rate over time) – will be used in the "final data set"
- Blood oxygen saturation - will be used in the "final data set"
- Pain scores - will be used in the "final data set"
- Digital incentive spirometer device identification key – will be used in the "final data set"
- Pulmonary function lab spirometry results – will be used in the "final data set"
- Discharge survey responses – will be used in the "final data set"

Separately, our consent forms (which are stored on Presbyterian Medical Center servers and are not transferred to any other location or computer):

- Patient Name
- Date of Study Participation
- Randomized Alphanumeric Key to Label Patient Data
- Digital incentive spirometer device identification key

At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB and Institutional policies. All other data/information will not be stored beyond the scope of the patient's engagement with the study.

Patient data (timestamped inspiratory breath data, blood oxygen saturation data, pulmonary function lab spirometry results, age, weight, height, sex at birth, and pain scores) will be tagged with a randomized alphanumeric combination that will distinguish the data from one another amongst study participants. Patient names, medical record numbers, and birthdates will only be used in the initial screening process and study intervention administration, and they will not appear on data used for analysis and results. The only set of data maintained with patient names, medical record numbers, and birthdates will be internally stored on Presbyterian Medical Center servers and on consent forms.

Study participant research data will be shared via the private secure cloud-based database accessible only to study members or PennBox for study analysis. Inspiratory breath data collected with the digital IS systems will be uploaded directly to the secure cloud-based database via the HUP or PPMC WiFi. Blood oxygen saturation data, pulmonary function lab spirometry results, age, weight, height, sex at birth, and pain scores will be stored on Presbyterian Medical Center computers and will not be transferred electronically (e.g., via email) to any other computer, except to study members via PennBox. A certificate of confidentiality will not be required for this study.

10.1.4 Future Use of Stored Specimens and Data

Data collected for this study will be transferred via a private secure cloud-based database and PennBox. Scanned consent forms will be stored solely on Penn Medicine computers and will not be transferred to any other computer. After the study is completed, archived data will be stored on a password-protected, encrypted computer.

No biological samples will be drawn or collected from participants during this study.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological data (i.e., diagnoses or measurements) stored for future research. At this point, the study team will access the consent forms on PPMC servers and use the linking set to determine which data needs to be eliminated from all records.

10.1.5 Safety Oversight

Internal reviews of data security by the PI will be completed to ensure human subjects' protection and data integrity. The PI will comprise the Safety Assessment Committee (SAC) and verify items such as proper data transferral to the cloud-based database, proper user interfacing with the database, etc.

10.1.6 Clinical Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial adheres as best as possible to the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

- The principal investigator will be conducting the monitoring of data collection. Monitoring will be done on-site at least once during the course of the study and at the conclusion of the study. In addition, the monitoring will be comprehensive. Steps will be taken to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial adheres as best as possible to the currently approved protocol/amendment(s), with ICH GCP, and with applicable regulatory requirement(s). Monitoring reports will be distributed to the clinical team and Sponsor within 2 weeks of that review.

- Clinical site monitoring will be conducted by the PI at least once during the course of the study to ensure that all protocols are being followed regarding patient safety and device usage. This portion of the monitoring will not be formalized in the form of a report unless any concerns arise during the review. In this case, the monitoring report will be sent to the study team within 1 week of that review.

10.1.7 Quality Assurance and Quality Control

All monitoring and audits are to be performed while adhering, as best as possible, to International Conference on Harmonisation Good Clinical Practice (ICH GCP) E6(R2).

The PI will perform internal quality management of study conduct, data collection, documentation and completion.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site for clarification/resolution.

The data quality management monitoring will be conducted by the PI. They will be responsible for both Quality Control (QC) and Quality Assurance (QA).

The monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol.

The investigational site will provide direct access to all trial related sites, source data/documents, and inspection by local and regulatory authorities.

10.1.8 Data Handling and Record Keeping

10.1.8.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the study team under the supervision of the principal investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data and follow ALCOAC standards (attributable, legible, contemporaneous, original, accurate, and complete). If any responses are illegible, the PI or member of the study team must ask the patient to clarify that response verbally. Inspiratory breath data will be recorded by the digital IS devices and transferred via HUP or PPMC's WiFi network to a secure cloud-based database for research use. Patient blood saturation, pulse oximetry, age, weight, height, sex at birth, and pulmonary function lab spirometry results will be recorded on a computer linked and managed by the Hospital of the University of Pennsylvania and Penn Presbyterian Medical Center, and then data will be obtained from EPIC and transferred via the cloud-based database or PennBox for research use. This computer will be located on the floor where all patients enrolled in the study will be managed post-operatively.

Hardcopies of the consent forms will be scanned, stored and maintained at Penn Presbyterian Medical Center in room 245B. Data recorded in the data collection software derived from source documents should be consistent with the data recorded on the source documents. Patient participation in the study will not be recorded in the EMR.

Regarding data processing, any and all listed study members may be involved in data processing (i.e., statistical analysis) as data will not contain patient names at this point in the analysis.

10.1.8.2 Study Records Retention

Study documents (namely consent forms) should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harmonization (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the PI.

10.1.9 Protocol Deviations

Protocol deviations will be continuously monitored through ongoing verification of patient information to ensure they fit eligibility criteria. In the event that protocol deviations are needed to broaden eligibility criteria, the principal investigator must approve of such a change in order to allow the study to fully enroll. The principal investigator must subsequently report this change to the IRB. Any protocol deviations made by the clinical team must be immediately reviewed and relayed to the principal investigator. These scenarios should be reported to the Sponsor within 10

business days of discovery. Reporting to IRB should follow local requirements. The PI and the study team should document all scenarios where the protocol is not followed and provide, in particular:

- Who deviated from the protocol
- What was the deviation
- When did the deviation occur
- How did the deviation happen
- What is the impact of the deviation
- A root cause analysis of why the deviation occurred

If the assessment is determined to be of limited impact (minor deviation), the documentation for this assessment and the outcome should be reported to the Sponsor at the time of annual report. Reporting to the IRB should follow specific local requirements.

If the assessment results in a determination that any of the following are potentially affected, the deviation would be considered of significant impact:

- adversely affects the integrity of the data; OR
- violates the rights and welfare of participants, OR
- affects the subject's willingness to participate in research.
- there is a potential for an overall impact on the research that should be shared with the IRB for consideration and development of next best steps to address it

10.1.10 Publication and Data Sharing Policy

This study will comply with the data sharing agreement. The PI must approve all sharing of information/data prior to its occurrence. Data from this study may be published at a later time by the PI in a fashion that retains patient security in all possible ways.

10.1.11 Conflict of Interest Policy

Any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.

11 REFERENCES

1. Eltorai, A. E., Baird, G. L., Eltorai, A. S., Pangborn, J., Antoci, V., Cullen, H. A., ... & Daniels, A. H. (2018). Incentive spirometry adherence: a national survey of provider perspectives. *Respiratory care*, *63*(5), 532-537.

2. Eltorai, A. E., Baird, G. L., Eltorai, A. S., Healey, T. T., Agarwal, S., Ventetuolo, C. E., ... & Daniels, A. H. (2019). Effect of an incentive spirometer patient reminder after coronary artery bypass grafting: a randomized clinical trial. *JAMA surgery*, *154*(7), 579-588.
3. Sweity, E. M., Alkaissi, A. A., Othman, W., & Salahat, A. (2021). Preoperative incentive spirometry for preventing postoperative pulmonary complications in patients undergoing coronary artery bypass graft surgery: a prospective, randomized controlled trial. *Journal of Cardiothoracic Surgery*, *16*(1), 241.

12 APPENDIX

12.1 Schedule of Activities (SoA)

Procedures	Day 0	0-30 day waiting period	Day 1 (day of surgery)	Day 2-7 (remainder of postoperative stay)
Informed consent	X			
Perform baseline measurement of inspiratory volume			X	
Administer study intervention and collection of study endpoints and patient survey			X	X

END OF DOCUMENT