A SINGLE CENTER STUDY ON THE FUNCTIONALITY OF THE PULSE OXIMETER AND ACCELEROMETER PORTIONS OF A NOVEL WEARABLE DEVICE

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Table of Contents

Contents

List of Abbreviations

ADE: Adverse Device Effect
AE: Adverse event
COPD: Chronic Obstructive Pulmonary Disease
CRF: Case report form
DOVE: Delivery of Opioid agonists for Ventilatory Emergencies
DSMB: Data Safety and Monitoring Board
SAE: Serious Adverse Event

Study Summary

Title	A Single Center Study on the Functionality of the Pulse Oximeter and Accelerometer Portions of a Novel Wearable Device
Short Title	DOVE Device Prototype
IRB Number	Not yet applicable.
Phase	Pilot Study
Methodology	This study will assess the reasonable functionality of the pulse oximetry and accelerometry portions of a prototype form of the DOVE medical device. The DOVE device will be designed with the intention to sense and respond to opioid overdose. Study participants will be asked to wear the DOVE prototype as well as an FDA-approved pulse oximeter. The primary objective is to assess reasonable detection of hypoxic episodes. Participant movement will be collected via the DOVE accelerometer on the night of their sleep study. Relevant variables including skin tone and comfort will be collected.
Study Duration	2 year
Study Center(s)	Single-center
Objectives	The **primary objective** is to assess the functionality of the sensor portions of a DOVE prototype. Our goal is to obtain functional data using a DOVE prototype device in patients who experience natural occurring hypoxic events. The **secondary objective** is to evaluate the effects of patient-level factors on data quality of a DOVE prototype. Our goal is to collect variables known to affect data quality and real-world practicality for standard market pulse oximetry devices.
Number of Subjects	20 subjects
Main Inclusion and Exclusion Criteria	**Inclusion Criteria** ● Males and Females ● 21 years of age or older ● Suspected to suffer from hypoxic events ● Able to provide informed consent **Exclusion Criteria** ● Pregnancy
Investigational Product	The DOVE prototype device is a wearable device meant to sense physiological data, including SpO_2 and accelerometry. Functional

	assessment of the physiological sensor portions of the device will be carried out in patients with clinical suspicion for hypoxic events. Subject skin tone and comfort while wearing the device will also be assessed. One of the main patient populations that could potentially benefit from this device are opioid users.
Statistical Methodology	1. We will use descriptive and inferential statistics to describe **baseline physiology:** mean [SD] SpO_2 and motion, and **significant respiratory depression**: SpO_2 <90% for more than 10 sec. 2. We will validate our characterization of physiological response by comparing pulse oximetry data from the DOVE prototype with data obtained from a study-provided, FDA-approved pulse oximeter.

Background and Study Rationale

This study will be conducted in full accordance with all applicable University of Pennsylvania Research Policies and Procedures and all applicable Federal and State laws and regulations. All episodes of noncompliance will be documented.

1 Introduction

Over 93,000 Americans died of a drug overdose in 2020, the highest in U.S. history and a 29.4% increase from the previous year.[1] The majority (~75%) of these deaths involved an opioid, including heroin, synthetic analogs (e.g. fentanyl), and prescription medications (e.g. oxycodone).[2] The staggering burden of opioid overdose deaths in the U.S. has been rising rapidly since the mid 2010's, but has reached a shocking trajectory during the COVID-19 pandemic.[3,4] And although opioid overdose affects almost every corner of the U.S., it has been particularly devastating in Philadelphia. Over 1200 Philadelphians died of drug overdose in 2020, with concerning disparities in rates of death among communities of color.[5] Fentanyl, the powerful synthetic analog of heroin, was involved in over 80% of overdose deaths in Philadelphia.[5,6] For almost two decades, opioid overdose has been a driver of morbidity and mortality in the U.S. Novel therapeutic interventions are desperately needed to abate this profound public health crisis.

1.1 Background and Relevant Literature

DOVE Device Prototype

One of the primary physiologic effects of opioids is respiratory depression, characterized by slower breathing rate and poor exchange of oxygen for carbon dioxide.[7] In the setting of an opioid overdose, respiratory depression can cause irreversible brain damage in as little as five minutes and can be fatal if not reversed.

However, opioid overdose is not only tragic – it is largely preventable. Naloxone is an opioid receptor antagonist and overdose antidote. It blocks the effects of opioids on their receptors and effectively draws an individual out of opioid-induced respiratory depression. Naloxone can be administered intranasally, intravenously, intramuscularly, and

subcutaneously.[8] The most common formulation is the nasal spray, brand name Narcan, administered in 4 mg doses. Its effects last between 30-60 min; at higher doses of opioids, multiple administrations of naloxone may be necessary to successfully reverse an overdose. Other than overdose reversal, naloxone has no adverse effects or other physiological consequences.

Broad distribution of naloxone has been a cornerstone of overdose prevention strategy during the opioid overdose epidemic. Over 330,000 prescriptions for naloxone were filled in 2017, and wider availability of naloxone has been correlated with decreased overdose mortality.[9] However, despite effective distribution of the nasal spray, overdose prevention efforts remain hindered by the current routes of administration. Currently, naloxone must be administered by a third-party bystander who is not only equipped with the overdose antidote, but also trained, willing, and able to use it. Unfortunately, 52% of overdose deaths occur in a setting where the individual used alone, with no possibility for bystander intervention.[10] Particularly in the context of the COVID-19 pandemic, it is critical to expand overdose prevention strategies among the vulnerable proportion of people who use opioids alone.

In the context of this pressing clinical need, our team is developing the DOVE device, a wearable sensor that detects physiological signs of opioid overdose and automatically administers naloxone. To date, we have developed a sensor system that combines a pulse oximeter and accelerometer to detect signs of respiratory depression (via decreased blood oxygen) and decreased motor activity. Our next objective is to validate our sensor system and assess its ability to detect instances of low blood oxygen. However, we are constrained by our ability to directly measure opioid overdose-induced respiratory depression due to ethical and clinical factors.

In place of validating our sensor directly on patients experiencing an opioid overdose, we propose a trial of our sensor on patients who have a medical condition in which they experience hypoxic events. For example, patients with OSA experience intermittent episodes of airway obstruction overnight, wherein relaxation of muscles in their throats causes soft tissue to collapse and obstruct the airway. OSA patients may have multiple of these episodes per night, during which their blood oxygen levels decrease below physiologically normal levels. In mild to moderate cases of OSA, SpO2 levels drop into the low 80% range on average.[11] In severe cases, it may drop as low as 70%.[12] Patients experiencing opioid overdose will commonly have SpO2 levels below 90%.

1.2 Name and Description of the Investigational Product

Device name: DOVE Prototype

Device Description: The device is a de novo device called DOVE (Delivery of Opioid agonists for Ventilatory Emergencies) Device. The data collected will be preliminary data for a future study that aims to detect opioid overdose and inject naloxone. Naloxone will not be administered during this trial. The DOVE prototype device is investigational. It has not been approved or cleared by the FDA.

While the integration of a sensor to recognize opioid overdose and a direct reversal agent response in a device is novel, there exist predicate devices that sense physiological variables and administer a drug in response to changes in those variables. For example, the $FreeO_2$ wearable

device monitors hospitalized COPD patients by assessing SpO_2.[13] In response to SpO_2 below the target range, the device adjusts a valve that changes O_2 flow. Likewise, a sweat-based glucose monitor (EOFlow) has been proposed in conjunction with transdermal glucose delivery.[14]

Device category:

Category B Device

Intended use: During this study, we will evaluate the functionality of the physiological sensor components of our DOVE device prototype.

In the future, the final DOVE device would be a wearable device that has components that can noninvasively sense overdose and administer an opioid antagonist. During this preliminary study, we will assess whether the DOVE physiological sensor components are substantially equivalent to a study-provided, FDA-approved $FreeO_2$ device in its continual assessment of a variable and threshold for response during expected hypoxic episodes. We will also verify the accuracy of the pulse oximeter across a variety of skin tones as assessed by the Pantone Skintone Guide ® and confirm the functionality of the accelerometer component of the device.

1.2.1 Nonclinical Data

There is no animal model appropriate for testing the physiological sensor components of the DOVE device, and therefore we have not done pre-clinical testing. Like $FreeO_2$'s pulse oximetry, DOVE would analyze physiologically associated waveforms and test whether those waveforms elicit a threshold clinically significant hypoxia that could prompt the device to respond in future iterations with injector capabilities. The DOVE prototype device used in this study will not have an injector component and will not administer naloxone.

2 Study Objectives

2.1 Primary Objective

The primary objective is to assess the reasonable equivalence of the sensor portions of a DOVE prototype to a study-provided, FDA-approved pulse oximeter. Our goal is to obtain functional data using a DOVE prototype device.

2.2 Secondary Objectives

The secondary objective is to evaluate the effects of patient-level factors on data quality of a DOVE prototype. Our goal is to collect variables known to affect data quality and real-world practicality for FDA-approved pulse oximetry devices.

3 Investigational Plan

3.1 General Design

The study will evaluate the functionality of a DOVE prototype biosensor in patients with clinical suspicion of suffering hypoxic events. The study will obtain descriptive data on the use of the DOVE device prototype and quantitative data to assess biofeedback sensation of this prototype in comparison to a study FDA-approved sensor. Patients will be given the opportunity to review the ICF and ask questions. Once consented, patients will be ask to wear a DOVE biosensor prototype and an FDA-approved pulse oximeter. Examples of data collected are SpO_2, including hypoxic episodes experienced via pulse oximeter, motion (and lack thereof) via accelerometer.

Due to known interference of skin tone with pulse oximetry sensor quality, participant skin tone will be assessed at sites of pulse oximetry sensation (the back of the hand, wrist, and thumb) using color patches from the Pantone Skintone Guide ®. No patient will be excluded based on the skintone. Patient comfort while wearing the device will be evaluated via 5-point Likert scale and open-ended qualitative questionnaire. This trial could enroll patients who are completing an overnight study. The study will not exceed 15hr for patients who are having an overnight study. Clinical data will not be collected for the purposes of this study and naloxone will not be administered. Device functionality will be assessed via a study-provided FDA-approved pulse oximeter and DOVE prototype to be worn for the duration of the visit. This study could potentially enroll patients during their overnight sleep test.

Devices will be collected at the end of the study visit. Comfort of the DOVE prototype will be assessed via 5-point Likert scale and open-ended qualitative questionnaire before participants leave the sleep lab. No clinical data or patient identifiers will be collected as part of the study. Pulse oximetry and accelerometry data will only be collected from SD cards housed within study-provided devices.

3.1.1 Follow Up Phase

There is no follow-up period for the study. Participants will be provided with research coordinator contact information to report adverse reactions to the wearing device, such as irritation or rash.

3.2 Study Endpoints

3.2.1 Primary Study Endpoints

Primary endpoints are designed to assess device prototype functionality and examine reasonable equivalence to FDA-approved devices already on the market. Examples of data collected include:

- Assessing the effectiveness of the DOVE device at measuring biofeedback measurements by correlating DOVE-recorded oximetry changes with hypoxic episodes measured by an FDA-approved study sensor
- Patient movement (and lack thereof) throughout the night via DOVE prototype accelerometer

3.2.2 Secondary Study Endpoints

Secondary endpoints are to evaluate the effects of patient-level factors on data quality of a DOVE prototype. Our goal is to collect variables known to affect data quality and real-world practicality for FDA-approved pulse oximetry devices. Examples of data collected are:

- Patient skin tone at the back of the hand, wrist, and thumb using color patches from the Pantone Skintone Guide ®
- Patient comfort while wearing the device via 5-point Likert scale and open-ended qualitative questionnaire

4. Study Population and Duration of Participation

Subjects will not be excluded based on race or skin tone. Due to known interference of skin tone with pulse oximetry sensor quality, participant skin tone will be assessed at.

4.1 Inclusion Criteria

- Males and Females
- 21 years of age or older
- Suspected to suffer from hypoxic events.
- Able to provide informed consent

4.2 Exclusion Criteria

- Pregnant

4.3 Subject Recruitment

Subject recruitment will occur through Penn Medicine Faculty engagement, particularly referrals from Penn physicians. The main approach for enrollment will be that the PI or study team request referrals from Penn physicians. If the physician does not respond, the study team will not approach the patient.
PI will approve study team members who can consent patients. EMR access will not be required for this trial. Study team member approved by the PI will complete study procedures.

4.4 Duration of Study Participation

Total duration of study participation for enrolled subjects will be no more than 15 hours from study consent to device collection.

4.5 Total Number of Subjects and Sites

Up to 20 subjects will be enrolled.

4.6 Vulnerable Populations:

No vulnerable populations will be used in this study.

5 Study design phase

5.1 Receipt

The design phase will consist of wearing the DOVE device. This study will only involve one study visit. For study participant enrolled in the study at the same time they undergo a sleep test they will be asked to wear the DOVE during for the entire duration of the sleep study. In the event you are being enrolled on the day you are completing an overnight sleep test the visit will last no more than 20hrs. For all other study participants, they will wear the device overnight in the conform of their home and return it the next day. The device may undergo minor changes in response to functionality and subject comfort. The prototype device consists of a pulse oximeter (oxygen sensor) and an accelerometer (movement sensor). The prototype device will be worn as a combination of a ring on your finger and bracelet on your wrist while the study-provided, FDA-approved pulse oximeter will be worn on your index finger.

Before any study procedures are done the potential study participant will have ample time to review the ICF and ask questions. Once the ICF has been signed the study team will assess the patients skin tone and then set the patient with the device. The next day when the device is collected the study team will administer a questionnaire. Study participants will be compensated $25 for completing the trial
The clinical research team will maintain records logs regarding devices dispensed and returned via device disposal logs. Devices will be labeled with a unique identifier. Study questionnaires will be labeled by both device and participant ID numbers for data quality control.

5.2 Storage

The devices and supplies will be stored in a locked room where only study personnel will have access.

5.3 Blinding

There is no blinding to the study.

5.4 Administration and Accountability

A labeled prototype of the device as well as an FDA-approved pulse oximeter will be given to each subject at the study visit. A product log will be kept in which product reconciliation will be collected at every visit with information on product dispensing, such as: date dispensed, and to which subjects the device was given and returned. A standard form will be utilized to document this information throughout the study period. Study questionnaires will be labeled with the unique identifier of the devices dispensed to ensure data quality control.

5.5 Subject Compliance Monitoring

Subject are only required to wear the device for the duration of the visit. Information regarding compliance and comfort will be included at device return as part of the open-ended patient questionnaire.

5.5.1 Return or Destruction of Investigational Product

The investigational product will be returned to the investigator for continued development at the conclusion of the study visit. Date of return will be logged on the initial reconciliation case report form (CRF). A standard form will be utilized to document the return and destruction of the prototype devices.

6 Study Procedures

Table 1: Schedule of Study Procedures

Study Procedures	Screening / Device dispensing	Device Collection
Review Inclusion/Exclusion Criteria	X	
Informed Consent	X	
Skin Tone	X	

Dispense FDA-approved sensor (Contec CMS50DA Pulse Oximeter)	X	
Dispense Investigational Product DOVE prototype	X	
Questionnaires		X
Collect Investigational Product DOVE prototype		X
Collect FDA-approved sensor (Contec CMS50DA Pulse Oximeter)		X
Assessment of possible AE		X

6.1 Screening and Baseline Data Collection

- Review of Inclusion/Exclusion criteria
- Sign informed consent
- Assess patient skin tone
- Dispense investigational product and study-provided FDA-approved pulse oximeter

6.1.1 Device Collection

- Questionnaire about comfort of device
- Collect Investigational Product
- Assessment of possible Adverse Events
- that participants will be compensated with a $25 gift card for completing the study

6.2 Follow Up Phase of the Study

There will be no additional follow-up visit after completion of the study unless subjects call to report adverse reactions to the device, such as irritation or rash.

6.3 Subject Withdrawal

Early withdrawal from the protocol poses no safety risk to participating subjects. The study participant may choose to withdraw at any point while participating in the protocol without impact to their care. They may also be discontinued from the study at the discretion of the Investigator for lack of adherence to the protocol, safety concerns, or study termination.

6.4 Data Collection and Follow-up for Withdrawn Subjects

There is no need for follow-up for subjects who complete or withdraw from the study.

7 Study Evaluations and Measurements

7.1 Medical Record Review

Referring doctor will assess inclusion criteria via medical record review.

7.2 Pregnancy Testing

There will not be any pregnancy test. Study participants will be asked whether they are pregnant.

7.3 Laboratory Evaluations

There will not be any laboratory evaluations.

7.4 Other Evaluations, Measures

Female participants will be asked about pregnancy.

Skin Tone: Participant skin tone will be assessed according to the Pantone Skin Tone Guide ®.

Comfort: Participants will also be surveyed for their subjective comfort wearing the DOVE prototype device. The interview and questionnaire will ensure that key topics such as compliance and comfort are covered, while also allowing the subject to discuss issues and experiences with the prototype device that the investigational team has not considered.

Possible Adverse Events: The interview and questionnaire will ensure that key adverse events, such as irritation and rash, are covered while also allowing the subject to discuss issues and experiences with the prototype device that the investigational team has not considered. Because protected health information will not be collected at any point in the study, participants are responsible for reporting any suspected long-term adverse events to a study-provided phone number.

7.5 Safety Evaluations

The principal investigator will be responsible for evaluating and maintaining the highest safety standards and practices. For the purposes of this trial, there will not be a DSMB. Any adverse device events will be reported to the principal investigator and sponsor.

8 Statistical Plan

DOVE and FDA-approved device data will be collected in SD cards and stored in a locked cabinet. Data will be maintained in locked files to which only authorized study personnel will have access and analyzed using descriptive and inferential statistics. Survey answers will be entered into a RedCap database and responses will be aggregated and summarized using descriptive statistics. To compare differences in survey responses among study participant subgroups, we will use t-tests or Wilcoxon rank-sum tests (F-tests or Kruskal-Wallis test) for continuous variables and Pearson chi square tests or Fishers exact tests for categorical variables. Linear and logistic regression will be used to assess for differences in the continuous and dichotomous outcomes, respectively. All hypothesis tests will be two-sided using a two-sided alpha of 0.05 as our threshold for statistical significance. We will use Stata and/or SAS to analyze the data.

8.1 Primary Endpoint

As the primary objectives are designed as a functionality study, no power analysis will be performed. The sample size is one of convenience and limited by resources.

8.2 Secondary Endpoints

The secondary endpoints related to comfort-level factors are descriptive and designed to further prototype designs for the DOVE prototype for later device iterations. Skin tone will be evaluated as a measure of the function of the SpO_2 sensor as part of the primary endpoint.

8.3 Sample Size and Power Determination

As the primary objectives are designed as a functionality study, no power analysis will be performed. The sample size is one of convenience and limited by resources.

8.4 Statistical Methods

For the primary objective, functional biosensor components of the DOVE device will be analyzed against a study-provided, FDA approved SpO_2 sensor. Skin tone will be incorporated as a factor of SpO_2 function to ensure the device can reasonably detect hypoxia across a diverse user base. Comfort, design preference, and other individual-level factors will be analyzed by descriptive and inferential statistics.

Survey answers will be entered into a RedCap database and responses will be aggregated and summarized using descriptive statistics. To compare differences in survey responses among study participant subgroups, we will use t-tests or Wilcoxon rank-sum tests (F-tests or Kruskal-Wallis test) for continuous variables and Pearson chi square tests or Fishers exact tests for categorical variables. Linear and logistic regression will be used to assess for differences in the continuous and dichotomous outcomes, respectively. All hypothesis tests will be two-sided using a two-sided alpha of 0.05 as our threshold for statistical significance. We will use Stata and/or SAS to analyze the data.

8.4.1 Baseline Data

Baseline and demographic characteristics will be summarized by standard descriptive statistics (including mean and standard deviation for continuous variables such as age and standard percentages for categorical variables such as gender).

8.5 Subject Population(s) for Analysis

Any subjects enrolled in the study will be included in the data.

9. Safety and Adverse Events

9.1 Definitions

9.1.1 Adverse Event

An **adverse event** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms

- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

For FDA regulated studies, the FDA defines an adverse event as the following:

Adverse event means any untoward medical occurrence associated with the use of a drug in humans whether or not considered drug related.

9.2 Serious Adverse Event

Adverse events are classified as serious or non-serious.
A **serious adverse event** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as **non-serious adverse events**.

9.2.1 Recording of Adverse Events

Any AE/ADE will be recorded by the Clinical Research Coordinator on the AE CRF, and signed off by the PI. Recording of adverse events will begin when the first subject is enrolled and will end when the last subject has completed all study procedures. Unanticipated adverse events (serious and non-serious) will be reported to the Penn IRB, in accordance with federal and institutional requirements.

At each contact with the subject, the investigator will seek information on adverse events by specific questioning and, as appropriate, by examination. Upon removal of the device, research personnel will evaluate for lesions at the site of placement on the subject via inspection and palpation. Information on all adverse events will be recorded immediately in the adverse event case report form (CRF).

All adverse events occurring during the study period (from study intervention start to end of the study) will be recorded by research personnel. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study intervention or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any serious adverse event that

occurs after the study period and is considered to be possibly related to the study intervention or study participation will be recorded and reported immediately.

9.3 Relationship of AE to Study

All adverse events and adverse device effects will be reported according to the timeline below:

Serious Adverse Event	Within 24 hours

The PI shall immediately evaluate and assess each adverse events, serious adverse event and adverse device effects.

9.4 Reporting of Adverse Events, Adverse Device Effects and Unanticipated Problems

Investigators must conform to the adverse event reporting timelines, formats and requirements of the various entities to which they are responsible.

The minimum necessary information to be provided at the time of the initial report includes:

● Study identifier ● Study Center ● Subject number ● A description of the event ● Date of onset	● Current status ● Whether study intervention was discontinued ● The reason why the event is classified as serious ● Investigator assessment of the association between the event and study intervention

Additionally, all other events (unanticipated problems, adverse reactions, unanticipated adverse device effects and subject complaints will be recorded and reported with respect to institutional and federal policies.

9.5 Follow-up reports

There will be no additional follow-up visit after completion of the study.

9.5.1 Unresolved SAEs

If an SAE has not resolved at the time of the initial report and new information arises that changes the investigator's assessment of the event, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) should be submitted to the IRB. The investigator is responsible for ensuring that all SAEs are followed until either resolved or stable.

9.5.2 Adverse Device Effects

After reporting an ADE to the Sponsor, within the following 48 hours, the investigator shall provide further information, as applicable, on the device effect in the form of a written narrative. This should include any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing unanticipated adverse device effects shall be provided promptly to the study sponsor.

9.5.3 Protocol Exceptions and Deviations

Protocol exceptions from the protocol must receive PI approval before they are initiated. Any protocol deviations initiated without PI approval that may affect the scientific soundness of the study, or affect the rights, safety, or welfare of study subjects, must be reported to the PI as soon as a possible, but no later than 5 working days of the protocol deviation.

9.6 Investigator reporting: notifying the Sponsor

9.6.1 Adverse Events, Serious Adverse Events, & Adverse Device Effects

Any event that occurs any time during or after the research study, which in the opinion of the principal investigator is related and unexpected (see definitions under unanticipated problem) will be reported to the Penn IRB within **10** working days. Any event that is related and unexpected (see definitions under unanticipated problem) AND is **fatal or life threatening** will be reported to the IRB within **3** working days.

After reporting an ADE to the Sponsor, within the following 48 hours, the investigator shall provide further information, as applicable, on the device effect in the form of a written narrative. This should include any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing unanticipated adverse device effects shall be provided promptly to the study sponsor

9.7 Protocol Exceptions and Deviations

Protocol exceptions must receive IRB approval before they are initiated. Any protocol deviations initiated without IRB approval that may affect the scientific soundness of the study, or affect the rights, safety, or welfare of study subjects, must be reported to the IRB as soon as a possible, but no later than 5 working days of the protocol deviation.

9.8 Other Events

Certain events are required to be reported to the IRB in an expedited fashion as per 21 CFR 812.150:

- **Device Recall, Repair, or Disposal**: If the device manufacturer requests a recall, repair, or disposal of the DOVE device, the IRB will be notified **within 30 days** of the request device recall.
- **Failure to Obtain Consent**: If an investigator fails to obtain informed consent, the IRB must be notified within **5** working days.
- **Final Report**: A final report on the study will be submitted to IRB **within 6 months** of study completion.

Additionally all other events (see list below) will be recorded and reported with respect to institutional and federal policies as described in the Penn Manual. All events as defined above will be reported to the Penn IRB by **study personnel within the required timeline per the** IRB Reportable events policy.

- Any adverse event that would cause the sponsor to modify the protocol or informed consent form, or would prompt other action by the IRB to assure protection of human subjects.

- Information that indicates a change to the risks or potential benefits of the research, in terms of severity or frequency. For example:
- An interim analysis indicates that participants have a lower rate of response to treatment than initially expected.
- Safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected.
- A paper is published from another study that shows that an arm of your research study is of no therapeutic value.

- Breach of confidentiality
- Change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant.
- Incarceration of a participant when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
- Complaint of a participant when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.

10 Reporting Process

Report unanticipated problems as defined above to the Penn IRB using the form: "Unanticipated Problems Posing Risks to Subjects or Others Including Reportable Adverse Events" or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

10.1 Devices

10.1.1 Additional reporting requirements

Sponsors are also required to identify in IND/IDE safety reports all previous reports concerning similar adverse events and to analyze the significance of the current event in light of the previous reports.

10.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

10.3 Case Report Forms (CRFs)

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

11 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Full privacy will be expected to each participant in the study. To identify potential subjects in the study, research personnel responsible for consenting and enrollment will identify potential subjects via active lists of patients and referrals from pulmonary faculty. Research personnel will then read through electronic records to briefly review eligibility criteria. If the potential participant meets eligibility criteria, research personnel will then approach the subject if they are available in clinic, or call them.

If enrolled in clinic: The potential subject will be alone in the room without risk of having patient's privacy compromised during enrollment/consent. If there are family members or friends around a potential subject at time of enrollment/consent, potential subjects will be asked if they are comfortable discussing the study in the setting of other individuals.

If enrolled via telephone encounter: The patient will first be asked if he is interested in talking to research personnel about possible enrollment. They will have the opportunity to ask us to call back another time.

All research personnel will follow privacy guidelines as described in CITI training biomedical and good behavior research modules, as required by all Penn study participants.

12 Data Collection and Management

Any person that meets screening criteria will be included in the data collection and analysis throughout and at the completion of the study. All clinical trial team members will receive training in responsible conduct of research using the Penn IRB standard training requirements.

This will include data management and procedures for maintaining confidentiality and subject safety. Study team will link PHI to subject identifiers for monitoring and auditing purposes. The study team and sponsor will meet periodically to review the progress of the study, paying particular attention to any missing data – to ensure that all forms are completed on schedule and all data is entered, verified and available for analysis. Data will be stored in password protected files, on a secure research server with data backup performed nightly. No protected health information linking the assigned unique identifier to the subject identity will be collected. Study files and SD cards from the study devices will be kept in a locked filing cabinet. Data will be maintained in locked files to which only authorized study personnel will have access. Data collected will be entered in RedCap.
The DOVE device will record SpO2 and Heart rate values off the participants while storing the encrypted data on local storage (micro SD card) . The data collected will not allow us to identify the participants and is encrypted using AES encryption which is FIPS 140-2 complaint. The collected data will be then analyzed on a HIPAA-certified laptop.

13 Records Retention

It is the investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by an agreement with the sponsor. In such an instance, it is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

14 Study Monitoring, Auditing, and Inspecting

The primary investigator will be responsible for monitoring all information. The investigator will allocate adequate time for such monitoring activities.
The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities.

15 Ethical Considerations

This study is to be conducted in accordance with applicable US government regulations and international standards of Good Clinical Practice, and applicable institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study.

16 Risks

Potential study risks include the accidental breach of confidential patient health information during patient enrollment. Precautions will be taken to ensure that strict confidentiality is maintained. Study team will link PHI to subject identifiers for monitoring and auditing purposes. This risk has been mitigated by extensive privacy protection protocols, a highly secure data storage system at Penn Medicine, and a plan to exclude identifiers from the data entirely. In addition, all study personnel will be held to high standards of upholding confidentiality and safeguarding patient privacy. No protected health information linking the assigned unique identifier to the subject identity will be collected. To ensure that patient confidentiality is preserved, though, data will be stored in a single password protected system that is accessible to the principle investigator and research team. This system is hosted on site at Penn Medicine and is protected by a secure firewall. Any datasets and computer files that leave the firewall will be stripped of all identifying information, such as identifying answers to open-ended questions, besides the study ID. The study ID will also be used on all analytical files. Confidentiality of all study data will be maintained by restricting access to the identifiable information only to approved study staff who have received subject confidentiality and privacy training.
The risks of the wearable devices is that patients will wear a novel device prototype for this study. There is a risk of irritation or rash developing at the site of device placement.

17 Benefits

There are no direct expected benefits to the subjects.

Long-term, the technology aims to improve the quality of life for patients at high risk of fatal opioid overdose.

17.1 Risk Benefit Assessment

It is the investigators' belief that the benefits to society outweigh the minimal risks with the device.

17.2 Informed Consent Process / HIPAA Authorization

All study subjects who meet enrollment criteria will be required to provide personal consent. Primarily, the research coordinator will obtain consent, but other IRB approved study personnel will be permitted to obtain consent.

Consent will be obtained, when possible, via in person paper consent. Once the form is completed and signed by the individual giving consent, all consent forms will be placed with other securely stored documents.

During the consent process, the consent form will be reviewed, as well as the description of the questionnaire, device and study procedures, the purpose of the study, the risks and benefits, and the voluntary nature of research participation.

To prevent coercion and ensure all information is understood, subjects will have the opportunity to ask as many questions as they need and will have the option to withdraw from the study.

18 Study Finances

18.1 Funding Source

The study will be financed through the Coulter foundation.

18.2 Conflict of Interest

All University of Pennsylvania Investigators will follow the University of Pennsylvania Policy on Conflicts of Interest Related to Research.

19 Publication Plan

The PI and the research team will have complete access to the data collected.

It is unlikely that this particular study will lead to publication as it is intended for baseline data on the device. This foundational study will, however, be seminal to future studies that may be published as the device reaches its final development.

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