A PROOF OF CONCEPT, RANDOMIZED, SINGLE CENTER, STUDY ON FRAMEWORKS FOR WEARABLE DEVICES TO SENSE AND RESPOND TO OPIOID OVERDOSES

NCT ID # 834304
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List of Abbreviations

AE: Adverse event
CRF: Case report form
DOVE: Delivery of Opioid agonists for Ventilatory Emergencies

Study Summary

Title	Assessing opioid overdose response framework for wearable medical devices
Short Title	DOVE
IRB Number	834304
Phase	Pilot Study
Methodology	**Part 1**- is an exploratory study in which we will be conducting surveys of opioid users with the goal of being able to design a device to help the needs of this population There could be a second visit in which participants are ask to give feedback on different device protypes regarding how they look and how comfortable they are. Both visits could take place on the same day. **Part 2**- evaluates a set of pilot prototype designs of devices that would be used in future studies to help detect when a person is close to a life-threatening overdose.
Study Duration	Two years from the date of enrollment.
Study Center(s)	Single-center

Objectives	The **primary objective** is to determine the population's need for a wearable device that will treat an opioid overdose. Our goal is to obtain descriptive data and functional data on the use of a DOVE device prototype. Naloxone will not be administered during the trial. The DOVE device prototype is investigational. It has not been approved or cleared by the FDA. Examples of data collected are: • Study participant will be asked about their opioid use and overdose history. • Accessibility to Naloxone • Study participant will be asked to evaluate potential wearable device designs • Study participant evaluates which devices would be more helpful in terms of detection and comfort The **secondary objective** is to evaluate community availability status quo of opioid overdose reversal agents in patient population. • Evaluate severity and prevalence of opioid overdoses within patient population. • Assess frequency of opioid overdose.
Number of Subjects	**Part 1**: Enrollment of approximately 100 subjects. **Part 2**: Enrollment of approximately 50 subjects.
Main Inclusion and Exclusion Criteria	**Inclusion Criteria** • Males and Females • 21 years of age or older • Have used opioids for more than 3 months or will be having surgery where opioids will be administered. • Able to provide informed consent • Moderate to severe chronic pain treated (by prescription or illicitly) with opioids or recreation use **Exclusion Criteria** • Pregnancy

Investigational Product	For Part 1 there could be a second visit in which we ask patient's feedback on different device protypes regarding how they look and how comfortable they are. Both visits could take place on the same day. The device will not function while you are wearing it. For Part 2 the DOVE prototype device is a wearable device. Subjects will be ask to wear the different prototypes of the device during the study visit to assess comfort and design. The device will not function while you are wearing it.
Statistical Methodology	Survey answers will be entered into a RedCap database and responses will be aggregated and summarized using descriptive statistics. To compare differences 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.

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 including [as applicable include the following regulations as they apply 45 CFR 46, 21 CFR Parts 50, 54, 56, and 812 and Good Clinical Practice: Consolidated Guidelines approved by the All episodes of noncompliance will be documented.

1 Introduction

In 2017, 70,237 people died following an accidental overdose in the United States.[1] Of those, 47,600 (67.8%) died following an opioid overdose, a rate of one death every 11 minutes.[2] Current trends predict that accidental overdose deaths continue rising, perhaps on an exponential trajectory.[3,4]

While opioid overdoses affect almost all communities nationally, both rural and urban, Philadelphia is one of the most affected cities. Opioid overdose-related statistics are staggering and heartbreaking. Philadelphia County (City of Philadelphia) had the second highest rates of drug overdose deaths per county in 2016[5]. Although nationally 68% of drug deaths involved opioids, more than 80% of drug deaths in Philadelphia involved opioids with an average of more than 3 fatal incidents per day.[5,6] In the decade between 2007 and 2017, 5670 individuals died following an opioid overdose in Philadelphia. Until it plateaued in 2017, the number of fatal incidents increased every year.[6]

1.1 Background and Relevant Literature

In many instances, tragic overdose deaths could be avoided.[3] Within 5 minutes of an opioid overdose, an individual has irreversible brain damage caused by respiratory failure. Naloxone is a medication used to block the effects of opioids, especially in overdose. Naloxone may be combined with an opioid to decrease the risk of opioid misuse. When given intravenously, Naloxone works within two minutes, and when injected into a muscle, it works within five minutes; it may also be sprayed into the nose. The effects of Naloxone last about half an hour to an hour. Multiple doses may be required. If desired response is not obtained, doses should be repeated at 2 to 3 minute intervals. Without intervention, preventable deaths continue to occur [
Figure **1**]. Life-threatening opioid overdose requires someone to assess breathing status and if needed, administer Naloxone [Figure 2].

Figure 1: **Overdose Progression with Naloxone Intervention**

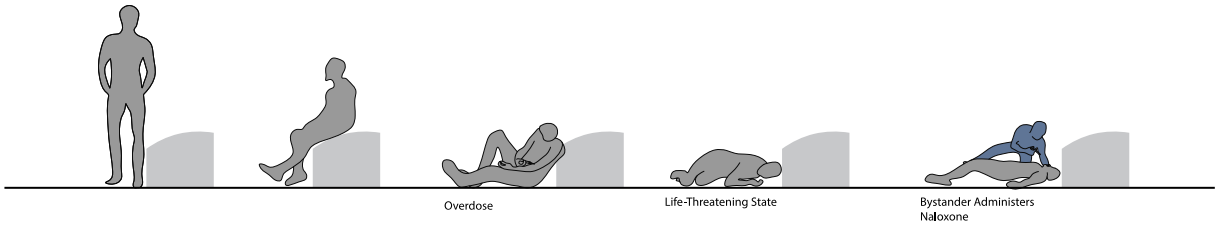
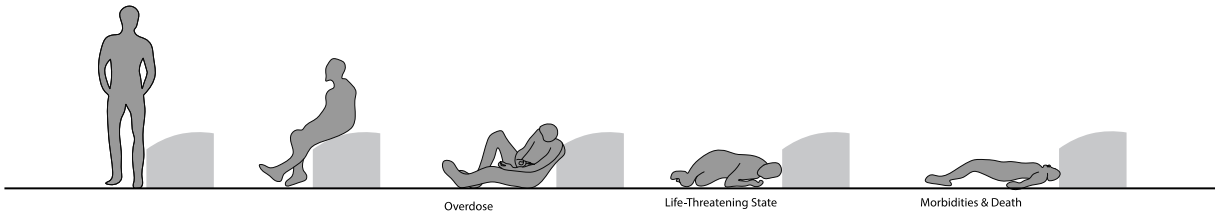


Figure 2: Overdose Progression without Naloxone Intervention



At the time of opioid overdose, the person overdosing not only needs to have Naloxone available, but they need another person to administer the Naloxone, and quickly. Since someone is needed to administer, the bystander must also be trained or, at the minimum, comfortable administering the drug. While the American Heart Association added Naloxone administration as a special situation for the cardiopulmonary resuscitation (CPR) training in 2015, the median county training rates are generally low.[8,9] In 2020, the median county training rate was just 2.39%[10]. Still, the bystander must be able to access the patient. Since 1999, a patient was found alone following fatal overdose in 70,000 cases.[11] While Naloxone is readily available today, many overdose victims are not found in time for administration of Naloxone. After five minutes without Naloxone intervention, a patient may continue to decompensate, become permanently disabled, or die.[1] Despite Naloxone being broadly distributed and used as an overdose reversal agent since the 1970's, the rate of opioid overdose fatalities has only increased.[12] Naloxone is thus a

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solution, but not the solution. For Naloxone to be successful, drug delivery is dependent on variables that must be independent of variables that require human action.

While a strategy for the opioid epidemic could rely on increasing Naloxone accessibility, designers may also be inclined to reconsider how the medication is deployed. Two major strategies are (1) for more individuals to carry Naloxone and (2) for more distribution points for Naloxone[13–16]. In Pennsylvania, Secretary of Health Rachel Levine issued a blanket standing order to permit over the counter Naloxone distribution: "this standing order may be used by Eligible Persons as a prescription or third-party prescription to obtain Naloxone from a pharmacy in the event that they are unable to obtain Naloxone or a prescription for Naloxone from their regular health care providers or another source."[17]

1.2 Name and Description of the Investigational Product

Device name: DOVE Prototype

Device Description: The device is a de novo device called the DOVE (Delivery of Opioid agonists for Ventilatory Emergencies) Device. During part 2 of the study different prototypes of the device design will be evaluated without drug for comfort, fit, design, etc. The data collected will be preliminary data for a future study that aims to detect opioid overdose and inject Naloxone.

While the integration of a sensor to recognize opioid overdose and a direct reversal-agent response in a device is novel, predicate devices sense physiological variables and administer a drug in response to a change in the physiological variable. For example, the FreeO$_2$ wearable device monitors hospitalized COPD patients by assessing SpO$_2$.[18] In response to SpO$_2$ below the target range, the device adjusts a valve that changes O$_2$ flow. [18] Likewise, a sweat-based glucose monitor (EOFlow) has been proposed in conjunction with transdermal glucose delivery.[19]

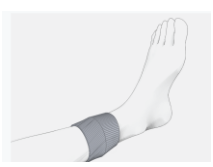
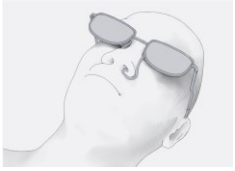
Device category:

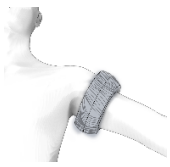
Category B Device

Intended use: During Part 2 we will evaluate different prototypes of the device.

At a future time, the final DOVE device would be a wearable device that has components that can noninvasively sense overdose and administer commercially available opioid antagonist. DOVE would be substantially equivalent to the FreeO2 device in its continual assessment of a variable and threshold for response.

Ankle Cannula Wrist Shoulder Deltoid



1.2.1 Nonclinical Data

There is no animal model appropriate for testing 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 that prompts the agent to response.

2 Study Objectives

2.1 Primary Objective

The primary objective of Part 1 is to determine the opioid user population's need for a wearable device that will treat an opioid overdose. The primary objective of Part 2 is to obtain descriptive data and functional data on DOVE device prototypes. Naloxone will not be administered during the trial. Examples of data collected are:

- Study participant will be asked about their opioid use and overdose history.
- Accessibility to Naloxone.
- Study participant will be asked to evaluate potential wearable device designs (Part 2 only).
- Study participant evaluates which devices would be more helpful in terms of detection and comfort (Part 2 only).

2.2 Secondary Objectives

The secondary object of Part 1 is to evaluate community availability status quo of opioid overdose reversal agents in study participant population.

- Evaluate severity and prevalence of opioid overdoses within study participant population.
- Assess frequency of opioid overdose.

3 Investigational Plan

3.1 General Design

The study will be a two-part, pilot study to evaluate feasibility and potential needs of opioid users. The study will obtain descriptive data on the use of the DOVE device prototype. Study population will consist of study participants who use opioids either after surgical procedure or recreationally. Part 1 will consist of a one-time short questionnaire. Healthy volunteers may be enrolled in Part 2 during the device modification phase. Part 2 can consist of more than one visit. At no point during in the study will Naloxone be administered.

Part 1 will be an exploratory study, during which will administer questionnaires to develop a better understanding of factors influencing the needs of the population. Subjects could be given the option of completing part 1 and 2 in the same day.

Part 2 is an exploratory study. Before the start of the device phase, subjects will be surveyed for comfort and subjective concerns. They will be shown the device and asked their opinion on design and comfort. The device may undergo minor modifications in response to functionality and subject comfort, and for iterative improvements such as the shape. We will test the device on participants for comfort, fit and design, using the results to improve the device, and then test the device again. This cycle will be continued until we have optimized the prototype device. We will record subject's verbal feedback, in order to guide the process of optimizing the device. At the end of Part 2, we will have optimized the design of the device for comfort and design preference. In part 2 there may be follow-up testing. Naloxone will not be administered during the study.

3.1.2 Screening Phase

Subjects will be recruited directly from clinics associated with the Hospital of the University of Pennsylvania, physician referrals, and IRB-approved advertisements targeting the Delaware Valley region. If a potential study participant is considered to be eligible, he/she will be referred to the research staff to participate in the initial telephone screening. A series of questions will be asked over the phone to confirm eligibility. Potential subjects that are eligible based on study criteria will be brought in for the baseline visit. Study participant may also be enrolled in clinic. The screening and baseline visit may occur on the same day.

3.1.2 Study Design Phase

The wearable design phase (WDP) will consist of wearing the DOVE device for part 2. During part 1 subjects will not be required to wear the device. They would only be shown the device and asked their opinion on design and comfort.

In part 2, before the start of the wearable design phase, subjects will be surveyed for comfort and subjective concerns. The device may undergo minor changes in response to functionality and subject comfort. Subjects could be given the option of completing part 1 and 2 in the same day.

3.1.2 Follow Up Phase

There is no follow-up period for the study.

3.2 Study Endpoints

3.2.1 Primary Study Endpoints

The primary objectives are descriptive and designed as a feasibility study. Descriptive data will be collected on the following:

- Assessing for subject comfort and tolerability of the DOVE device

- Documenting subject comfort and subjective participant opinions of device wearability

3.2.2 Secondary Study Endpoints

Evaluate community availability status quo of opioid overdose reversal agents in study participant population.

- Evaluate severity and prevalence of opioid overdoses within study participant population.

- Assess frequency of opioid overdose.

4 Study Population and Duration of Participation

4.1 Inclusion Criteria

- Males and Females
- 21 years of age or older
- Have used opioids for more than 3 months or will be having surgery where opioids will be administered.
- Able to provide informed consent
- Moderate to severe chronic pain treated (by prescription or illicitly) with opioids or recreation use

4.2 Exclusion Criteria

- Pregnant

4.3 Subject Recruitment

Subject recruitment will occur through Penn Medicine Faculty engagement, particularly referrals from Penn physicians. The study staff will send emails to Penn Medicine physicians, asking them to refer subjects to study personnel for contact during recruitment and/or seeking permission to contact study participant identified through screening. We also plan to use IRB-approved advertisements targeting the Delaware Valley region. All ads will be submitted for IRB approval prior to use. Subjects may also be recruited from PennSeek and Pennomics. We will seek permission to contact from their physicians to approach the patient for recruitment into the study. If the physician does not respond, the study team will send the patient an IRB-approved recruitment letter and follow up with a phone call at least one week after.

4.4 Duration of Study Participation

Total duration of study participation for enrolled subjects will be approximately 2-3 hours per visit for each of the parts.

4.5 Total Number of Subjects and Sites

For Part 1 and 2, up to 150 subjects will be enrolled.

Part 1: Enrollment of approximately 100 subjects.
Part 2: Enrollment of approximately 50 subjects.

Subjects enrolled in Part 1 will be asked if they are interested in participating in part 2 but will need to again go through screening and enrollment.

4.6 Vulnerable Populations:

No vulnerable populations will be used in this study.

5 Study design phase

5.1 Receipt

For Part 1, all questionnaires will be administered to the subjects by the clinical research team.
For Part 2, the device will be delivered by the manufacturer to the clinical research team. The clinical research team will maintain records logs regarding device dispensing and return devices. This will be in addition to any records kept by the sponsor. The sponsor will maintain the device disposal logs.

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

For Part 2, the prototype of the device study 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.

5.5 Subject Compliance Monitoring

For Part 2 subject are only required to wear the device for the duration of the visit.

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	Part 1		Part 2	
	Screening	Baseline	Screening	Baseline
Number of visits	**1**	**1**	**1**	**1-2**
Review Inclusion/Exclusion Criteria	X		X	
Informed Consent	X		X	
Demographics/Medical History	X		X	
Questionnaire		X		X
Prior/Concomitant Medications	X	X	X	X
Dispense Investigational Product				X
Collect Investigational Product				X
Assessment of possible AE				X

6.1.1 Screening (Parts 1 and 2)

- Review of Inclusion/Exclusion criteria

6.1.2 Baseline Visit

- Signed informed consent
- Review of demographics, medical history and medications
- Questionnaire
- Dispense Investigational Product (only Part 2)
- Collect Investigational Product (only Part 2)
- Assessment of possible Adverse Events (only Part 2)

6.2 Follow Up Phase of the Study

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

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

- Date of birth & Demographics
- Medications
- Medical/surgical history
- Information related to opioid use and history of overdose
- EPIC chart review to ensure subject meets inclusion criteria or does not meet exclusion criteria.

7.2 Pregnancy Testing

There will not be any pregnancy test. Study participant will be asked if they are pregnant or not.

7.3 Laboratory Evaluations

There will not be any laboratory evaluations.

7.4 Other Evaluations, Measures

Part 1- Questionnaire will be given to subjects once they have been consented.

Part 2 - Participants will also be surveyed/interviewed for their subjective experience with the DOVE prototype device. The interview and questionnaire will ensure that key topics are covered, while also allowing the subject to discuss issues and experiences with the prototype device that the investigational team has not considered.

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

Survey answers will be entered into a RedCap database and responses will be aggregated and summarized using descriptive statistics. To compare differences 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

For part 1 and 2 the primary objective is qualitative, only descriptive information will be obtained. The endpoint will be collection of feasibility and safety data.

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

8.2 Secondary Endpoints

Evaluate community availability status quo of opioid overdose reversal agents in study participant population.

- Evaluate severity and prevalence of opioid overdoses within study participant population.
- Assess frequency of opioid overdose.
- Assess frequency of opioid overdose.

8.3 Sample Size and Power Determination

As the primary objectives are descriptive and designed as a feasibility 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, qualitative data will be analyzed with descriptive charts and discussion. The secondary objective and other continuous variables 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 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.

9.1.2 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 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 personal will evaluate for lesion at site of placement on 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

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 SAE 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.

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 clinical 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 study participant 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. 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 preformed nightly. Protected health information linking the assigned unique identifier to the subject identity will only be kept as an electronic document and will be held on the shared Penn Medicine e-drive. This document will be password protected and only study personnel will have access. Study files 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, excel and/or CTMS.

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 related to the collection of survey and EMR data. Precautions will be taken to ensure that strict confidentiality is maintained. This risk has been mitigated by extensive privacy protection protocols, a highly secure data storage system at Penn Medicine, and a plan to remove identifiers from the data wherever possible. In addition, all study personnel will be held to high standards of upholding confidentiality and safeguarding patient privacy. To ensure that patient confidentiality is preserved, individual identifiers (such as name) are 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 identifiers 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.

17 Benefits

For Part 1 and 2 there are no direct expected benefits to the healthy participants for participating in this study.

Long-term, the technology aims to improve the quality of life for patients who suffer from opioid abuse.

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 meeting 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 withdrawal from the study.

18 Study Finances

18.1 Funding Source

The study will be financed through Funded by a Penn-internal grant from Penn's Medical Device Accelerator (MDA)

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.

Part 1 is currently designed for exploratory work but publication could come from it. This part is intended for baseline data on device design and population needs.
Part 2 may lead to publication. This part is intended for baseline data on the device.

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