ARM-ED: Advanced Respiratory Monitoring Events in Drug Toxicity – An Emergency Department Feasibility Study of the utilization of a wearable device in patients with sedative effects of drugs study protocol

Lisa Christine Dunlop, David J Lowe, Bruce Henderson, Osian Meredith, Chris Trueman, Christopher Carlin, Robert Docking

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Lisa Christine Dunlop[1]; David J Lowe[1, 2]; Bruce Henderson[3]; Osian Meredith[3]; Chris Trueman[3]; Christopher Carlin[1]; Robert Docking[1]

[1]Queen Elizabeth University Hospital, Glasgow Glasgow GB
[2]School of Health and Wellbeing, University of Glasgow Glasgow GB
[3]PneumoWave Ltd Motherwell GB

Corresponding Author:
Lisa Christine Dunlop
Queen Elizabeth University Hospital, Glasgow
Emergency Department, Queen Elizabeth University Hospital. 1345 Govan Road G51 4TF
Glasgow
GB

Abstract

Background: Drug-related deaths worldwide are most commonly attributed to opioids. Opioids and other sedative drugs can cause respiratory depression and airway compromise, leading to hypoxia and death. Device technology and artificial intelligence used to detect drug overdose has potential to improve outcomes. PneumoWave Ltd have developed a small chest-worn respiratory monitoring device to detect concerning breathing patterns and alert an emergency response.

Objective: The aim of this study is to investigate the feasibility of use of the PneumoWave device in hospital patients at risk of respiratory depression.

Methods: This 18-month prospective observational study is performed at the Queen Elizabeth University Hospital, Glasgow. The study investigates the use of the device on three groups of patients at risk of respiratory depression due to drugs. This includes patients attending the Emergency Department (ED) due to sedative drug overdose, patients receiving procedural sedation and analgesia in the ED, and patients receiving general anesthesia in theatres. Consenting participants will have the PneumoWave sensor monitoring paired with end-tidal CO2 and regular recordings of vital signs. Usability is tested by questionnaire of the patient, the clinician, and the nurse. The primary endpoint is to determine the feasibility of gathering respiratory data from a wearable respiratory monitoring device in the ED. Statistical analysis includes comparison of biosensor data against reference physiology time course data.

Results: This study will examine the use of the PneumoWave device in a variety of patient situations in which risk of respiratory depression is present, providing valuable insight into the use of device technology in individuals at risk of illicit drug-related harm within the relative safety of a hospital setting. A limitation to study procedure is exclusion of patients with intoxication after sedative drug overdose who lack capacity to provide informed consent.

Conclusions: This study has been designed to acquire foundation data to demonstrate the potential for continuous respiratory monitoring to improve outcomes for patients who are at risk of drug induced respiratory depression, inform product development, and inform design of future pivotal clinical investigations. Clinical Trial: The trial was registered on the 30th of March 2022 on clinicaltrials.gov, reference: NCT05358132.

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Authors:

Corresponding author:

Lisa C Dunlop

-Emergency Department, Queen Elizabeth University Hospital, Glasgow, UK

-School of Medicine, Dentistry and Nursing, University of Glasgow, Glasgow, UK

-Corresponding address: Emergency Department, Queen Elizabeth University Hospital. 1345 Govan Road, Glasgow, G51 4TF

-Email: lisa.dunlop2@nhs.scot

-ORCiD: 0000-0001-6600-4766

-Twitter: @lcd_dunlop

Other authors:

Bruce Henderson

-PneumoWave Ltd, South Suite 3, Level 2, Maxim Park, Eurocentral, ML1 4WQ

-Email: bruce@pneumowave.com

Osian Meredith

-PneumoWave Ltd, South Suite 3, Level 2, Maxim Park, Eurocentral, ML1 4WQ

-Email: Osian@pneumowave.com

Chris Trueman

-PneumoWave Ltd, South Suite 3, Level 2, Maxim Park, Eurocentral, ML1 4WQ

-Email: Chris@pneumowave.com

Christopher Carlin

-Department of Respiratory Medicine, 2nd Floor Office Block, Queen Elizabeth University Hospital, 1345 Govan Road, Glasgow G51 4TF

-E-mail: christopher.carlin@ggc.scot.nhs.uk

Robert Docking

-Intensive Care Department, Queen Elizabeth University Hospital, 1345 Govan Road, Glasgow, G51 4TF

-Email: Robert.Docking@ggc.scot.nhs.uk

David J Lowe

-Emergency Department, Queen Elizabeth University Hospital, Glasgow, United Kingdom

-School of Health and Wellbeing, University of Glasgow, Glasgow, United Kingdom

-Email: David.lowe@ggc.scot.nhs.uk

Abstract:

Background

Drug-related deaths worldwide are most commonly attributed to opioids. Opioids and other sedative drugs can cause respiratory depression and airway compromise, leading to hypoxia and death. Device technology and artificial intelligence used to detect drug overdose has potential to improve outcomes. PneumoWave Ltd have developed a small chest-worn respiratory monitoring device to detect concerning breathing patterns and alert an emergency response. The aim of this study is to investigate the feasibility of use of the PneumoWave device in hospital patients at risk of respiratory depression.

Methods

This 18-month prospective observational study is performed at the Queen Elizabeth University Hospital, Glasgow. The study investigates the use of the device on three groups of patients at risk of respiratory depression due to drugs. This includes patients attending the Emergency Department (ED) due to sedative drug overdose, patients receiving procedural sedation and analgesia in the ED, and patients receiving general anesthesia in theatres. Consenting participants will have the PneumoWave sensor monitoring paired with end-tidal CO_2 and regular recordings of vital signs. Usability is tested by questionnaire of the patient, the clinician, and the nurse. The primary endpoint is to determine the feasibility of gathering respiratory data from a wearable respiratory monitoring device in the ED. Statistical analysis

includes comparison of biosensor data against reference physiology time course data.

Discussion

This study will examine the use of the PneumoWave device in a variety of patient situations in which risk of respiratory depression is present, providing valuable insight into the use of device technology in individuals at risk of illicit drug-related harm within the relative safety of a hospital setting. A limitation to study procedure is exclusion of patients with intoxication after sedative drug overdose who lack capacity to provide informed consent. This study has been designed to acquire foundation data to demonstrate the potential for continuous respiratory monitoring to improve outcomes for patients who are at risk of drug induced respiratory depression, inform product development, and inform design of future pivotal clinical investigations.

Trial Registration

The trial was registered on the 30th of March 2022 on clinicaltrials.gov, reference: NCT05358132.

Keywords:

Wearable device, respiratory biosensor, opioid induced respiratory depression, illicit drug toxicity, benzodiazepine toxicity, emergency department observation.

Background

Over a quarter of a billion people worldwide used illicit drugs at least once during the year 2021, 60 million of which used opioids. Overdose is a significant cause of preventable morbidity and mortality globally with approximately 128,000 deaths directly due to drug use in 2019 [1]. Within Europe, Scotland holds the highest drug-related death rate at 19.8 per 100,000 population. This study is sited in a tertiary urban hospital in Glasgow, Scotland. NHS Greater Glasgow and Clyde Health Board has the highest drug-related death rate in Scotland (34 per 100,000 in 2022) and hence this research is at the epicenter of the drug death crisis [2].

Opioids are the drug group most commonly attributed to drug-related death in the world [3]. In 2021 opioids were implicated in 75% and 74% of drug-related deaths in the USA and Europe respectively [4,5]. Similarly in Scotland, post-mortem toxicology reports found the most commonly implicated drugs were opioids (82.5%,

N = 1051), and benzodiazepines (57.2%, N = 1051) [2].

Opioids are μ-receptor agonists and overdose can lead to reduced consciousness, irregular or slow breathing patterns, and potentially life-threatening or fatal respiratory depression. Death following use of opioids is due to loss of respiratory reflexes, apnea, and respiratory failure [6,7]. There is an increased risk of death in opiate naïve patients and use of another central nervous system (CNS) depressant drug such as alcohol, benzodiazepines, and other co-prescribed medications such as gabapentinoids [8,9]. Overdose of benzodiazepines, like opioids, can lead to reduced consciousness and loss of airway reflexes leading to potential death. This is the case especially when taken in the context of user naivety, high doses used, potent preparations, or co-ingestion [10,11].

Access to emergency services and the use of the opioid antagonist, naloxone, given by any individual can reduce the risk following drug overdose [12]. The user who has experienced an overdose must, however, be able to access the help and therefore is at higher risk of death when using drugs alone [13].

The use of technology may help provide a solution to reduce the risk of fatal overdose in drug users. There have been several studies investigating the use of device technology in this setting and these might be attached to or positioned somewhere away from the individual. Mobile phone apps are available for prevention and detection of harm. These often rely on the user (who may be unconscious) being able to alert help via the device [14]. A mobile app described by Nandakumar et al, 2019, found that a mobile phone which was adapted to use

sonar to detect respiratory effort and apnea reported high performance in detection of post opioid self-administration central apneic events (10 seconds or longer). The device, however, was required to be held by a second person at a 90-degree angle at just 1 meter from the individual for success [15]. Other near patient devices include in room movement sensors and help buttons, the latter again requiring that the user must be capable of pressing the button [16,17].

Several wearable sensors in development have been described, including those that deploy naloxone [18-20]. The described devices have major barriers to potential use. Mesa et al, 2023, describe a sensor which requires implantation of a drug-delivery system, which would likely not be acceptable to many individuals, plus potential increased risk of infection [19]. Chan et al, 2021 describe a bulky device which may reduce compliance of use and they found it was unreliable in deploying the naloxone [20]. Roth et al, 2021 describe a commercially available biosensor to detect movement. They showed success in collecting accelerometer data, however, detected no respiratory depression despite 385 drug administrations recorded (>90% involved fentanyl), 27 of which the user described themselves as having “too much” [21].

There are some potential barriers to the use of a device such as battery life, effective functioning, size, weight, and aesthetics [22,23]. Despite this, potential users of devices are likely to be accepting of the device if they understand the ability to reduce harm [24]. As described, the near patient device described by Nandakumar, et al was limited by requiring to be perpendicular and within 1 meter proximity to the patient to achieve stated results [15]. There is clearly a need for

innovative technology to successfully detect those at risk of overdose, enabling help to attend the individual, while also being acceptable to wear.

PneumoWave Ltd have developed a small, chest-worn, ambulatory biosensor to detect changes in a range of respiratory metrics [25]. This physical monitor is linked wirelessly to central monitoring systems via either a Bluetooth data gateway that plugs into a nearby electrical socket or a smartphone. Real-time data analysis, event detection and alert response management algorithms are located in the cloud (see figure 1).

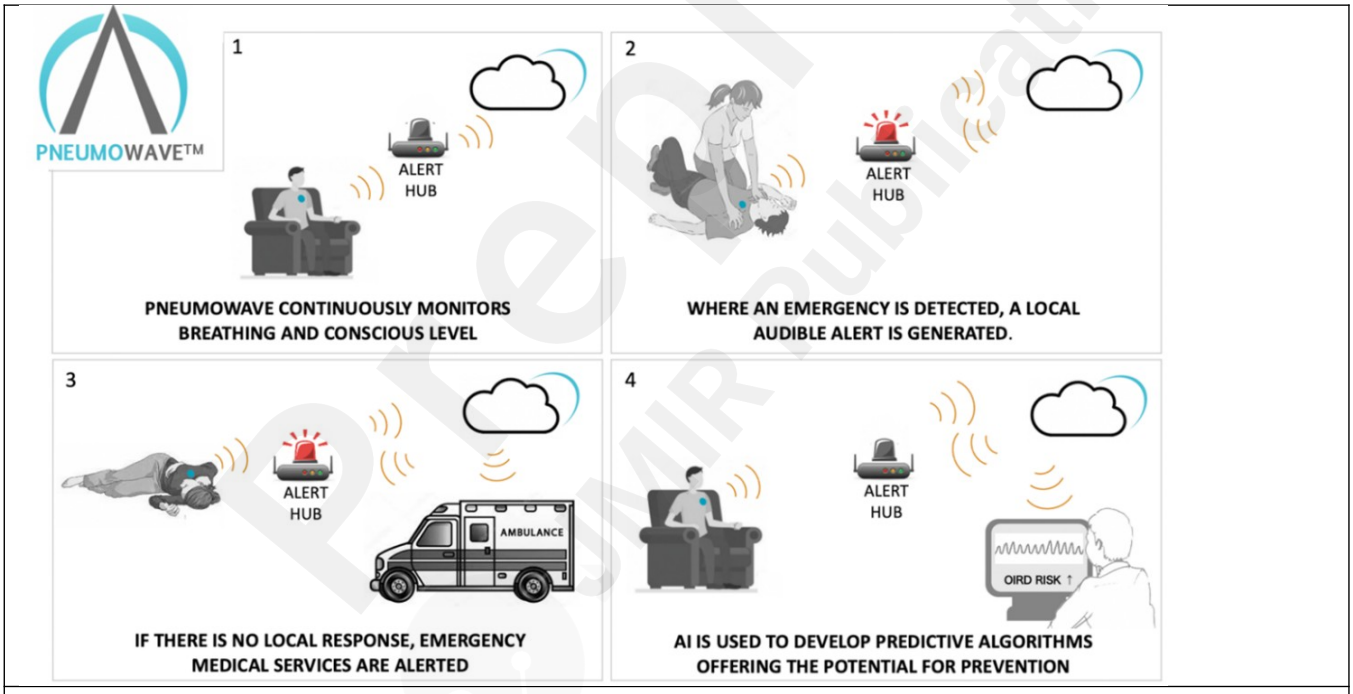

Figure 1: PneumoWave technology overview. The biosensor will detect concerning breathing patterns and will send an alert for urgent help in the individual following overdose.

This research investigates the feasibility of the use of the PneumoWave Ltd wearable biosensor in individuals at risk of drug-induced respiratory depression. The safety of a hospital setting has been utilized to understand the feasibility of use.

Risk of respiratory depression occurs in a variety of situations within hospital. As described, overdose of opioids or other sedating/respiratory depressant drugs often need medical care and attend the emergency department (ED) for treatment [26]. This group of patients are included in this trial and give a pragmatic idea of feasibility of use in patients at risk of respiratory depression. Opioids and/or sedatives are also administered in hospital for medical purposes in a setting in which the patient will need respiratory monitoring. One such example is that of procedural sedation and analgesia (PSA). This is a technique in which sedation is given with an aim to allow a painful procedure to be performed but not deep enough to cause apnea, though there is a risk, and this occasionally does occur [27]. A further example is that of induction for a general anesthetic (GA) where apnoea is either certain (with muscle relaxant), or likely (during GA induction). These two groups of patients will also be studied to understand the use of the device in settings of increased risk or definite apnea due to drug administration. End-tidal CO_2 ($ETCO_2$) is utilized in hospital in these settings to monitor respiratory function by capnography and as such is the gold standard comparator in this study [28].

Study Hypothesis

The PneumoWave device will be well tolerated by patients and will successfully capture respiratory effort and patient movement accelerometer data.

Objectives

Primary Objective:

-Assess the feasibility of collecting respiratory waveform data using PneumoWave device in ED patients from groups 1-3 (see study population).

Secondary Objectives:

-Collate respiratory data from the Pneumowave device and compare to $ETCO_2$ in patients from all 3 groups. Respiratory data will observe:

- o Normal respiratory effort
- o Reduced respiratory effort due to sedating drugs / anesthetic agents
- o Response to treatments and interventions required in patients with reduced respiratory effort

-Collate waveform and motion artefact data from the PneumoWave device in patients from all 3 groups to observe the relationship with the individual's conscious level.

-Assess the usability of PneumoWave in the opinion of the clinician, nurse, and patient.

-Understand the feasibility of gathering respiratory data from a wearable respiratory monitoring device in the ED.

Methods / Design

Study design

Single-center observational cohort study, utilizing passive non-invasive data collection.

Setting

18-month study from 9th June 2022 – 8th December 2023 at the Queen Elizabeth University Hospital, Glasgow, UK.

Study population

The overall study population are patients at risk of respiratory depression due to sedating drugs. The study observes three distinct patient groups:

-Group 1: Patients who present to the ED with actual or potential CNS or respiratory depression secondary to toxicological cause

-Group 2: Patients who undergo PSA with respiratory and central nervous system depressant drugs in the ED

-Group 3: Patients who undergo GA in the anesthetic room in theatre

Inclusion criteria

All groups:

-Age ≥16 years old

-Are willing and able to give informed consent

-Able (in the Investigators opinion) and willing to comply with all study requirements

-Can speak and read English

Group 1 – Acute toxicity group

-Presentation to ED due to presumed overdose of drug with potential for respiratory depression (intentional, accidental, recreational, therapeutic excess)

-At least one of Glasgow Coma Score (GCS) <15 or respiratory depression or risk of deterioration of GCS or respiration

Group 2 – PSA group

-Patient undergoing procedural sedation and anesthesia in ED

Group 3 – GA group

-Patient undergoing elective general anesthetic of any type in anesthetic room in theatre

Exclusion Criteria

All groups:

-Unable to provide consent and no next of kin to provide consent on participant's behalf

-Impaired consciousness / respiratory suppression most likely due to cause other than acute drug use

-Condition primarily related to alcohol use and no evidence of acute drug use

-Condition due to withdrawal of drugs / alcohol

-Treating clinician deems patient inappropriate to be included in study

-Pregnant female

-Patient has implantable device (e.g. pacemaker)

Withdrawal of subjects

All patients are able to withdraw from the study at any time. Clinical management will not be changed.

Sample size and rationale

This is a feasibility study to generate data for future prospective interventional studies therefore no formal sample size will be generated. The research group planned a target of 50 patients recruited each to group 1 and 2 as the number of minutes of data capture would successfully answer the primary outcome question of feasibility. Group 3 was included following trial commencement. Following evidence of the volume and type of data being produced from group 1 and 2 a target of 12 was used based on understanding of the number of minutes of data gathered. We aim to recruit a total of 112 patients to the study, which will provide adequate data to establish feasibility of use for larger studies. The sample size breakdown is as follows:

-Group 1: 50 patients

-Group 2: 50 patients

-Group 3: 12 patients

Primary endpoints

1. Understand the feasibility of gathering respiratory data from a wearable respiratory monitoring device in the ED

Secondary endpoints

1. Add to existing respiratory data to inform machine learning and improve sensitivity and specificity of PneumoWave device
2. Understand the usability of the device within acute care setting
3. Understand the feasibility of gathering respiratory data from a wearable respiratory monitoring device in patients undergoing GA

Outcome measures

Primary outcome measures

- Length of time device in situ on patient
- Number of times device removed by patient / other
- Ability of device to collect data while in situ

Secondary outcome measures

Observation of waveform data from Pneumowave device and compare to

- Normal care vital signs
- Continuous monitoring vital signs extracted from patient monitors

Compare Pneumowave respiratory wave patterns to clinical events:

- Normal respiratory patterns

- Clinical deterioration
- Interventions in ED or in anesthetic room in theatre

Compare respiratory waveform patterns and motion artefact data to:

- GCS
- Richmond Agitation-Sedation Scale (RASS)

Interview of the stakeholders on the usability of the device:

- Clinician
- Nurse
- Patient (if able to)

Study procedures

1: Potential participant identification

Group 1 (acute toxicity) and Group 2 (PSA) patient identification:

-Patients from group 1 and group 2 will be recruited concurrently and opportunistically.

-Patients will be recruited during the research team by:

o The researcher will observe ED attendances remotely via electronic health records and identify potential participants who are either intoxicated (group 1) or may undergo procedural sedation (group 2). They will assess the patient for eligibility.

o ED staff will be given information on study recruitment and alert the research team to assess eligibility for inclusion.

Group 3 (GA) patient identification:

-Patients will be recruited during specified elective theatre lists undergoing a general anesthetic. Patients will be approached by the anesthetist for willingness to participate with the researcher assessing for eligibility providing them with patient information sheet and gain consent from the patient.

2: Consent

-Written consent will be gained from the patient or Welfare Attorney/Welfare Guardian/Nearest Relative for group 1 and from the patient only for group 2 and group 3.

3: Source data collection and patient observation

-Source data will be collated from:

- Study participant interview
- Usual care electronic health records, anesthetic charts, medical, ambulance and nursing notes, drug charts and observation charts
- Continuous vital sign data will be downloaded from the standard emergency department /anesthetic monitors or study monitors
- PneumoWave sensor data
- Likert scale interview of clinician, nurse, and patient on opinions of usability
- Manual respiratory rate for study periods using $ETCO_2$ monitor

-Study episode data:

- Group 1: Participants will be observed for a period of time during their ED attendance
- Group 2: Participants will be observed for the duration of their procedural sedation and recovery period
- Group 3: Participants will be studied for a period of time prior to their GA while in the theatres anesthetic room during induction

4: 28 days review of notes

-Patient follow up at single time point of 28 days post recruitment via electronic case records. This will identify any adverse outcome relating to their ED attendance or anesthetic, e.g. need for critical care, disability, morbidity, or mortality as well as identify any relevant usual care drug screens performed at the time of assessment.

5: Waveform analysis and predictive modelling algorithms

-Data from PneumoWave analyzed in parallel with de-identified clinical and vital sign observational data to build artificial intelligence driven predictive modelling algorithms.

Summary Study Procedure

The table below (table 1) shows a summary of study procedures including participant enrolment, interventions and assessments.

Table 1: Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) figure of enrolment, interventions, and assessments			
Study Procedure	**Screening / Consent (1st Visit)**	**Research episode**	**28 days follow up electronically**
Obtain Informed Consent where relevant	✓		
Review Inclusion/Exclusion Criteria	✓		
Complete case report form	✓	✓	✓
Collect continuous data from standard care vital sign monitor		✓	
Collect waveform respiratory data		✓	
Review retrospective notes for adverse outcome/ available tox screen			✓

Data collection and management

Case Report Forms/Electronic Data Records:

CASTOR (castoredc.com, Netherlands) will provide a platform for data collection via an electronic case report form [29]. CASTOR EDC is compliant with 21 CFR Part 11, ICH E6 GCP, GDPR, and HIPAA. It is ISO27001 and ISO9001 certified.

Safety and Adverse events

Adverse events and serious adverse events (SAEs) will be managed in line with Good Clinical Practice guidelines. SAEs meeting the above criteria must be reported to the Pharmacovigilance Office immediately (within 24 hours) using the SAE form for a non-CTIMP SAEs meeting the above criteria must be reported to the Pharmacovigilance Office immediately (within 24 hours) using the SAE form for a non-CTIMP. All SAEs will be reported to the ethics committee within 15 days of the chief investigator or delegate becoming aware of the event.

Planned analysis

Primary outcome measure analysis:

Descriptive statistics will be utilized to analyse the primary outcome measures and assess the feasibility of studying the use of the Pneumowave device in the three patient groups. The analysis for each primary outcome measure are as per below.

Length of time device in situ on patient:

-The time between documented time the device is placed on the patient and time off the patient will be calculated. Any time the device was removed will be deducted from the total time. A final analysis of mean, median, and associated interquartile range (IQR) and standard deviation (SD) will be reported for each group.

Number of times device removed by patient / other:

-This will be reported as mean, median, and associated IQR and SD respectively for each group.

Ability of device to collect data while in situ

-The amount of data gathered for each episode will be recorded as a proportion of the

length of time the device is in situ on the patient. The proportions will then be compared using a student T-test and ANOVA.

Secondary outcome measure analysis:

The primary method of analysis will be the comparison of biosensor (device under test (DUT)) data against recorded clinical time course data. Performance will be shown graphically as ‘reference – DUT’ against ‘mean of reference and DUT’, typically referred to as a Bland-Altman plot. The data may also be expressed as the % of points within a specified range of breaths per minute (e.g. +/-2 breaths per minute) for the device under test compared to the standard.

For a given event, such as a cessation of respiration or some other clinical condition being monitored, a comparison can be made between the device under test detecting the event and the clinical time course data.

Further analysis of sensitivity and specificity will be conducted on conclusion of the trial.

Machine-learning predictive modelling analyses will also be undertaken on the de-identified data set with both binary and continuous classifications. Where appropriate data will be split into training and validation sets, with model performance determined by precision, recall, precision-recall area under the curve and where appropriate, regression analyses. These exploratory correlation, variation and predictive modelling analyses will be treated as hypothesis generating and used to determine subsequent study priorities, design, and power calculations.

Analysis of clinician, nurse and patient opinions of the use of the device will be recorded as median, means and associated analysis of variance. The averages of the three groups will be compared using student's T-test and ANOVA.

The statistical analysis will be performed using MiniTab (Pennsylvania, USA).

Discussion

This study will provide valuable insight into the use of device technology in individuals at risk of illicit drug-related harm within the relative safety of a hospital setting. It will examine the use of the device in a variety of patient situations in which risk of respiratory depression is present, requiring respiratory monitoring in the usual clinical care setting [27]. It will allow understanding of the ability to gather respiratory waveform data in comparison to the gold standard ($ETCO_2$). Apnea can be difficult to study and in hospital is often brief, as intervention is swift whilst in the care of medical professionals due to substantial risk of harm if left untreated. Therefore insight into feasibility of studying this will be invaluable. This feasibility study will inform the scaling up to larger observational and randomized diagnostic studies investigating the PneumoWave device. Recruitment to this study is performed in a pragmatic manner at the study site's adult ED. Due to Scottish adults with incapacity laws, a limitation to study procedure is the inability to recruit patients through use of a professional legal representative. It is therefore likely that recruitment to group 1 (the acute toxicology group) will be challenging. This study has been designed to improve patient outcomes who are at risk of drug induced respiratory depression

and inform future development of clinical support and prediction capability.

This hospital-based respiratory monitoring study will provide a safe environment to understand the feasibility of use of a wearable device in detecting drug induced respiratory depression and inform measures in reducing associated harm.

List of abbreviations

ARM-ED	Advanced Respiratory Monitoring Events in Drug Toxicity
CNS	Central nervous system
DUT	Device under test
ED	Emergency Department
$ETCO_2$	End-tidal CO_2
GA	General Anesthetic
GCP	Good Clinical Practice
GCS	Glasgow Coma Score
IQR	Inter-quartile range
NHS	National Health Service
PSA	Procedural Sedation and Anesthesia
SAE	Serious Adverse Event
SD	Standard deviation
UK	United Kingdom
USA	United States of America

Declarations

Ethics approval and consent to participate

Favorable ethical approval was obtained from Scotland A Research Ethics Committee (REC) prior to study commencement on 19th January 2022. REC reference: 21/SS/0083, IRAS project ID: 303922.

A substantial amendment was submitted on 28/03/2023 and gained favorable opinion on 28/04/2023 by Scotland A Research Ethics Committee.

The trial was registered on the 30th of March 2022 on clinicaltrials.gov, reference: NCT05358132, URL: https://clinicaltrials.gov/study/NCT05358132?term=NCT05358132&rank=1. The protocol information presented here has current ethical approval and is from protocol version 2.0.

Any major protocol modifications will be discussed with the research ethics committee prior to initiation of the change. Consent was obtained according to the protocol from patients or a nominated person by the co-investigators of the trial or a suitably trained member of research staff.

Consent for publication

Consent for publication was achieved during initial participant consent.

Availability of data and materials

N/A - The manuscript does not include any data.

Biosensor data and machine learning algorithms are not publicly available and subject to PneumoWave Ltd Intellectual Property security laws.

Competing interests

Lisa C Dunlop and David J Lowe have investigator time funding from the ARM-ED study derived from PneumoWave Ltd funding.

David J Lowe has investigator time funding from the ARM-ED study derived from PneumoWave Ltd funding. The author also received investigator time funding from the Chief Scientist Office for prior device validation work.

Chris Carlin received investigator time funding from the Chief Scientist Office for prior device validation work.

Bruce Henderson, Osian Meredith, and Chris Trueman are all employees of PneumoWave Ltd.

Robert Docking receive no funding from the study but receives honoraria from MSD for invited lectures and webinars**.**

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Trial sponsor

NHS Greater Glasgow and Clyde

Authors' contributions

Lisa C Dunlop conceived and coordinates the study and wrote the manuscript.

David J Lowe is principal investigator for the study, facilitated conception of the study, contributed to multiple versions of the manuscript.

Chris Carlin contributed to multiple versions of the protocol and this manuscript.

Bruce Henderson, Osian Meredith, and Chris Trueman developed the device under the company PneumoWave and contributed to multiple versions of the protocol and this manuscript.

Robert Docking contributed to multiple versions of the protocol and this manuscript.

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Additional information

SPIRIT Checklist adhered to when writing. Please see supplemental information (SPIRIT-checklist-ARM-ED protocol).

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Supplementary Files