Response to Concerns on Protection of Human Subjects

Concern: Unclear that obtaining and storing research information without consent with subsequent promise to delete if unable to contact patient or surrogate and obtain consent is an acceptable approach to the consent process, further detail and experience is warranted

Response: This is a valid concern and was raised during the initial IRB approval process. Our current IRB-approved process for deferred in-person, or phone consent was developed in close consultation with IRB committee chair, John MacMillan MD, and IRB director Cynthia Gates JD, RN. Use of a delayed consent strategy was employed to prevent biasing data collection to the later phases of mechanical ventilation, since it is common in our tertiary/quaternary referral center that surrogates may not be present at the bedside for the first hours-days of ICU admission. The only data collected prior to informed consent are physiologic waveform data from mechanical ventilators that do not contain protected health information or personally identifiable information. Subjects are only identifiable with a temporary study ID used for data provenance purposes. The IRB felt that the minimal risk nature of our study protocol, and the time-sensitive nature of studying ventilator dependent acute respiratory failure merited use of a delayed in-person, or phone consent protocol. Our consent processes were approved after UCD IRB committee review and have been reapproved multiple times, and most recently on 3/27/17. Our protocol is approved until 03/26/2027. We are happy to supply this approval letter, and any other IRB related documentation if necessary.

In our experience, the consent process has been easy to follow with surrogates identified via the treating physician team or bedside nurse, with subsequent in-person or phone consent. In rare cases where surrogates have declined to participate or no surrogate could be identified, waveform data were deleted from our data collection devices. Electronic health record data are only collected after consent has been obtained. Please see section 5 of our approved IRB protocol that is elucidated in subsequent pages for additional details.

Advanced Data Analytics for the Assessment of Pathologic Patient-Ventilator Interactions

Jason Adams, MD[1]

Jean-Pierre Delplanque, PhD[2]

Brooks Kuhn, MD[1]

Nick Anderson, PhD[3]

[1]Department of Internal Medicine, Division of Pulmonary, Critical Care, and Sleep Medicine, UC Davis School of Medicine
[2]College of Engineering, UC Davis
[3]Department of Pathology, UC Davis School of Medicine

1) Background

Mechanical ventilation is a common, life-saving therapeutic intervention for patients in the intensive care unit (ICU), providing oxygenation, ventilation, and maintenance of a patent airway. Despite its benefits, both human and animal studies have demonstrated potential harms related to mechanical ventilation.[1,2] These so-called ventilator-associated complications (VAC) include ventilator-associated pneumonia, ventilator-induced lung injury, fluid overload, barotrauma, and oversedation.[3,4,5] VACs have been associated with increased morbidity, mortality and length of stay in the ICU[6] and are thought to arise from pathologic patient-ventilator interactions (PPVI) including the delivery of injurious tidal volumes and excessive airway pressures, as well as the delivery of ventilatory support inadequate to meet patient demands, known as patient-ventilator asynchrony (PVA).[7]

One of the most clinically important types of PPVI is PVA, a frequently occurring phenomenon in mechanically ventilated patients, identified in between 10 and 63.5% of patients.[7,8] PVA is a general term encompassing a number of PPVI sub-types including but not limited to ineffective patient triggering of a ventilator-delivered breath (patient attempts to breath but does not receive a breath from the ventilator), double triggering (two breaths delivered in rapid sequence without exhalation in between), flow asynchrony (ventilator delivers inspiratory flow slower than patient's flow demand), and delayed breath termination (patient attempts to exhale before the ventilator will allow exhalation).[9] PVA has been associated with prolonged time on mechanical ventilation, subjective dyspnea, increased work of breathing, and increased use of sedative medications.[7] The gold standard for assessing PVA requires invasive monitoring through either an esophageal balloon measuring intrathoracic chest pressure or chest electromyography. Clinically, these modalities are rarely utilized due to their invasive nature.

Multiple modalities have been proposed to non-invasively evaluate PVA, but none have been able to supplant an evaluation by a trained clinician[10,11] Several groups recently used novel methods to try to capture and quantify PVA events.[12] Mellott et al. used a pressure/flow sensor placed in line in the vent circuit to export ventilator waveform data. The authors used video

annotation software and expert clinician review to capture and quantify PVA including subtypes and frequency.[13] Chanques et al. directly connected personal computers to capture pressure and flow data directly from mechanical ventilators and then used proprietary waveform analysis software to quantitate various PVA subtypes before and after changes in patient or ventilator management.[11] However, no obvious validation process was reported to confirm the accuracy of the software in capturing and quantitating PVA. Gutierrez et al. acquired pressure and flow data using the built-in data acquisition system of the Servo ventilator (Servo-i/Servos Computer Interface Emulator, Sölna, Sweden) and developed a novel analytic approach using power spectral analysis. The authors analyzed waveform data in 2.5 minute long increments and used the spectral signature of each time bin to diagnose PVA and provide a semi-quantitative measure of the frequency of PVA events. Their novel methods correlated well with manual review and quantitation of PVA.[9] In a more recent publication, Gutierrez et al. examined another metric of PPVI, respiratory rate variation, using spectral analysis and found an inverse association with mortality, although they were unable to identify a mechanism.[14]

While able to demonstrate the feasibility and relevance of analyzing PVA, previous literature is limited by small sample sizes and methodological limitations. The window for analysis has not exceeded ninety minutes in a given twenty-four hour period due to the dependency on manual review, significantly limiting correlations with clinical outcomes. In addition, most studies only evaluated double triggering, ignoring other types of PVA/PPVI. Finally, studies to date have not attempted to quantitate the severity of PVA/PPVI subtypes in addition to their frequency.

Widespread adoption of electronic health record (EHR) systems and increasing use of computerized patient instrumentation have created novel data and knowledge management challenges for healthcare systems, especially in the complex and data-driven environment of the modern ICU. EHR systems are at the center of modern healthcare in the United States, and will soon be the major source of data for healthcare quality improvement and research. EHRs integrate a broad range of heterogeneous data sources captured over the course of patient encounters, with data sources evolving rapidly in diversity, scale, and quality. EHRs have traditionally been designed to ensure that clinically acquired data is securely and persistently managed, and not with the intent to allow for computationally intense analytics across multiple data sources or patient records.

High-frequency data streams such as those from mechanical ventilators are used in real-time by clinicians at the bedside to make diagnoses, identify important clinical events, and affect changes in patient management but are often imported infrequently into the EHR. In the case of mechanical ventilators, data acquisition typically involves manual transposition of spot-checked data from the ventilator's graphical user interface into the EHR a limited numbers of times per day due to lack of ventilator integration with the EHR. The limited sampling of patient-level data and a paucity of analytic tools have hindered scientific understanding of patient-ventilator interactions. Such technical and cultural constraints, along with the dated architecture of most modern commercial EHRs, limit the translation of high volume, high velocity, high variety "big data" into scientific knowledge. As a result, modern EHRs function largely as up-to-date clinical data repositories with limited capabilities for clinical subgroup identification, event detection, or outcome recognition necessary for clinical research and quality improvement. The development of novel data acquisition, storage, and analytic platforms optimized for patient-derived big data

will dramatically improve the scientific understanding of patient-ventilator interactions, and will ensure that patients realize the benefits of this life-saving treatment.

1. ARDS Network, Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. NEJM, 342:1301-1308.
2. Dreyfuss, D et al. Respective effects of high airway pressure, high tidal volume, and positive end-expiratory pressure. Am Rev Respir Dis, 137:1159-1164.
3. Wunderlink, R. Ventilator-associated complications, ventilator-associated pneumonia, and Newtons' Thrid Law of Mechanics. AJRCCM, 189:882-883.
4. Klouwenberg, P et al. Electronic implantation of a novel surveillance paradigm for ventilator-associated events. AJRCCM, 189:947-955.
5. Slutsky, A et al. Ventilator-Induced Lung Injury. NEJM 2013,369:2126-2136.
6. Epstein, S. How Often Does Patient-Ventilator Asynchrony Occur and What Are the Consequences? Respir Care, 56:25–35.
7. Chao, D et al. Patient-ventilator trigger asynchrony in prolonged mechanical ventilation. Chest 1997, 112:1592-1599.
8. Piquiloud, L et al. Neurally adjusted ventilation assist improves patient-ventilator interaction. Intensive Care Med 2011, 27:263-271.
9. Gutierrez, G et al. Automatic detection of patient-ventilator asynchrony by spectral analysis of airway flow. Critical Care 2011, 15:167-176.
10. Chanques, G et al. Impact of ventilator adjustment and sedation-analgesia practices on severe asynchrony in patients ventilated in assist-control mode. Crit Care Med 2013, 41:2177–87.
11. Mulqueeny, Q. Automated detection of asynchrony in patient-ventilator interaction. 31st Annual International Conference of the IEEE EMBS. Sept 2, 2009.
12. Mellott, K et al. Patient ventilator asynchrony in critically ill adults: Frequency and types. Heart & Lung, 43:231-243.
13. Gutierrez, G et al. Decreased respiratory rate variability during mechanical ventilation is associated with increased mortality. Intensive Care Med, 39:1359-1367.
14. Gilstrap D et al. Patient-ventilator interactions. Implications for clinical management. Am J Respir Crit Care Med. 2013 Nov 1;188(9):1058-68.

2) Objectives

1. Develop research algorithms to allow quantitative analysis of de-identified (coded) mechanical ventilator waveform data

- We will develop research algorithms in a CTSC hosted analytic environment to allow the quantitative, breath-by-breath analysis of PPVI. We will test the abilities of these algorithms to detect common types of PPVI, such as various types of PVA, and distinguish these pathologic waveform signals from common signal artifacts and patterns of normal, synchronous breathing during mechanical ventilation.

- We are currently developing signal analysis algorithms that will allow the identification of PVA and other forms of PPVI. Derivation data sets are generated using computer-generated waveforms, a "plastic lung" used in ventilator calibration, and by one of use (Adams, PI and attending pulmonologist), breathing into a ventilator circuit to mimic common ventilator waveforms. Algorithm design will leverage techniques previously used to research other biomedical signals such as electroencephalography, electrocardiography, and arterial blood pressure. Using these methods, we will develop metrics and associated data visualization tools to allow the quantitation of the frequency and severity of PPVI/PVA for use in clinical research.

2. **Test for a quantitative relationship between both the subtype and frequency of PPVI and clinical outcomes of patients receiving mechanical ventilation at UC Davis.**
    - We hypothesize that the subtype and frequency of PPVI (the "dose" of potentially harmful mechanical ventilation) will be significantly associated with adverse patient outcomes.

    - We will prospectively identify a cohort of adult subjects age >/=18 who are receiving mechanical ventilation in either the emergency department (ED) or ICU and who are expected to require mechanical ventilation for >/= 24 hours (based on the judgment of the primary physician caring for the patient). Mechanical ventilator data will be continuously collected using the usual data export capabilities of the mechanical ventilator for the duration of use of mechanical ventilation. Data exported from the ventilators will be transferred wirelessly to a secure server using a commercially available USB-based storage drive that connects to a data export terminal on the back of the ventilator designed for this purpose to allow for unobtrusive data collection. Data representing only pressure, flow, and time, are exported in the form of special characters according to the American Standard Code of Information Interchange (ASCII) and do not contain any PHI/PII. The wireless data storage drive lacks a screen or other graphical user interface and neither the acquired data nor products of analysis will be available to treating clinicians.

    - Following the completion of ventilator data acquisition, we will use the CTSC research informatics group and Tethered Meta Registry (TMR) to retrospectively collect patient-level clinical data including demographics (age, sex, race/ethnicity), comorbidities and admission/discharge diagnoses (ICD-9 codes), procedures (CPT and ICD-9 codes), laboratory data, vital signs, imaging data, flowsheet data (such as GCS and recorded ventilator settings), medications, physician orders (e.g. mechanical ventilation orders), and SOFA scores to describe severity of illness. Other data pertinent to clinical outcomes will also be collected including hospital and ICU length of stay, time on mechanical ventilation, and vital statistics.

    - We will develop logistic (for binary outcomes) and linear regression (for continuous outcomes) models using the above data to test the hypothesis that the subtype and/or frequency of PPVI are significantly associated with the development of adverse patient outcomes.

3) Inclusion and Exclusion Criteria

Patients admitted to UC Davis Medical Center requiring mechanical ventilation will be screened in either the ED or ICU for study eligibility. The primary treating team (including but not limited to the emergency room, the medical ICU, surgical ICU, burn ICU, cardiothoracic ICU, neuro ICU, will be approached regarding acceptable patients for enrollment Adult patients >/= age 18 who are receiving mechanical ventilation will be included if the primary physician responsible for their care anticipates a need for mechanical ventilation for >/= 24 hours. Patients age < 18 years of age, those will clinical brain death, and pregnant women and prisoners will be

excluded from study. If patients ultimately require < 24 hours of mechanical ventilation, they will be included in our analysis in accordance with an intention-to-treat analytic approach. Informed consent will not be obtained given the observational, minimal risk nature of the study.

4) Number of Subjects

We will use the algorithms developed above to estimate a "dose" of PPVI in patients receiving mechanical ventilation in critical care units at UC Davis Medical Center, and test for an independent correlation between the dose and timing of PPVI and patient outcomes over the first 7 days of mechanical ventilation monitoring. We will use mixed effects regression modeling to test the hypothesis that an increasing "dose" of PPVI will be directly correlated with, and antecedent to, an increased dose of sedative medications (primary study outcome). We will adjust the model for age, sex, presence of alcohol or benzodiazepine withdrawal as the primary reason for ICU admission, and the presence of ARDS, asthma, or COPD exacerbation as primary reasons for mechanical ventilation. With 80% power to detect a 25% difference in total sedative dose (midazolam equivalents) in the first 7 days of mechanical ventilation between the highest and lowest quartiles of PPVI dose, we initially estimated a required sample size of 250 patients. Exploratory, pre-specified secondary outcomes will include the dose of analgesics (morphine equivalents), the rate of development of ARDS, time on mechanical ventilation, ICU and hospital lengths of stay, frequency of ventilator-associated events/conditions, and 30 and 90 day mortality.

Our initial enrollment was impaired by technical errors (failure of our time stamp algorithm, corrupted output due to network issues, and complete acquisition failure), inhibiting analysis of approximately 80 subjects. Furthermore, while implementation and enrollment in the medical intensive care unit has been robust, we have had difficulties enrolling patients at the start of mechanical ventilation in the emergency department (only 27 patients enrolled in the Emergency Department and not all of them from the start of mechanical ventilation). As this is the most clinically and scientifically relevant time period, we are unable to adequately test our hypothesis without enrollment of further subjects. With the same goal of enrolling 250 subjects from start to finish of mechanical ventilation and assuming a continued 10% enrollment of this group, we will request the enrollment of a total of 2500 subjects. Our current rate of enrollment at this time is 1.1 subject per day, therefore this goal is achievable in less than 5 additional years.

5) Recruitment Methods

Patients will be recruited after discussion with the primary team of the respective intensive care service (as above, this would include medical, surgical, burn, cardiothoracic, neurologic intensive care units as well as the emergency room).

Informed consent will be obtained from the patient (or their surrogate) either in person or via telephone. The overwhelming majority of patients requiring mechanical ventilation are unable to give written consent due to sedation/analgesia and the manifestations of their underlying disease. For that reason, the majority of contact will be with surrogate decision makers, who are often very hard to locate as they are not reliably at the bedside and frequently do not have access to fax machines/scanners. Given our limited staff to contact surrogates in person, we are thus requesting waiver of written consent so that we can contact surrogates by phone.

We will collect non-PHI, coded waveform data and securely store it as listed above for a 72-hour period from the time of screening while obtaining consent. No PHI will be collected during this time period. In the event that he surrogate cannot be found or consent is not granted, all information will be deleted. We hypothesize the largest effect of PVA on clinical outcomes will be early after the initiation of mechanical ventilation. As it frequently requires several days to identify a suitable surrogate in the ICU environment, this 72 hour grace period is necessary to avoid systematically excluding patients from study who are early in the course of mechanical ventilation or who suffer early death. This grace period will prevent systematic bias in the study and allow generalizability of results to real world patient populations.

- The study is minimal risk due to the lack of patient intervention, unobtrusive nature of mechanical ventilator data collection, lack of identifiable data directly linked to mechanical ventilator data, and the use of coding to de-identify data stored in REDCap.
- No biological specimens will be obtained from subjects.
- Mechanical ventilator data is simple numeric data describing pressure and flow, devoid of PHI/PII, generated in the routine course of usual clinical care, and cannot be used to re-identify subjects.
- Patient care will not be affected, as the care team will be blinded to the results of the study.
- The study involves scientific research only and will not evaluate the safety or effectiveness of the software algorithms we develop.
- Data from subjects will be used for research purposes only and will not be submitted to, or held for inspection by the FDA.

Request for a Waiver of HIPAA Authorization for Recruitment Purposes Only:

A waiver of the requirement to obtain HIPAA Authorization is limited to identification of potential subjects for recruitment purposes. There is no other method for identifying eligible subjects. HIPAA Authorization will be obtained from patients enrolled.

The review of subjects' medical records is for limited information. The data are derived from clinically indicated procedures. There is an extremely low probability of harm to the subjects' status, employment, or insurability. The precaution taken to limit record review to specified data and coding of the data further minimize the major risk, which is breach of confidentiality.

The clinically indicated procedures/care were already completed, or would be completed, regardless of the research. None of the results of the research would affect the clinical decisions about the individuals because the results are not factored into clinical care decisions. Subjects are not deprived of clinical care to which they would normally be entitled.

The protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of protected health information for which an authorization or opportunity to agree or object is not required by 45 CFR 164.512.

6) Compensation to the Subjects

There will be no compensation for participation in this study.

7) Study Timelines

We are requesting to begin data collection at the time of IRB approval up until December 31, 2021. At that point, a modification to the IRB protocol will be submitted if further study is warranted. Subjects will participate in the study as long as they are mechanically ventilated. The duration anticipated to enroll all study subjects is approximately a further 5 years. The estimated date for the investigators to complete primary analyses is December 31, 2021.

8) Study Endpoints

The primary study outcome variable is the total change in dose of sedative medications over the first 7 days of PVA assessment. Secondary outcome variables include the total change in dose of analgesic medications over the first 7 days of PVA assessment, the rate of development of ARDS in the 30 days after the start of mechanical ventilation, the number of ventilator-free days in the first 30 days after the start of mechanical ventilation, the number of ICU-free and hospital-free days in the first 30 days after the start of mechanical ventilation, the rate of development of ventilator associated events in the 30 days after the start of mechanical ventilation, and mortality at 30 and 90 days after the start of mechanical ventilation. There are no safety endpoints as there is no intervention.

9) Procedures Involved

No direct procedures will be performed on patients enrolled in this study.

10) Data and Specimen Banking

Ventilator data will be stored as described above in a secure REDCap storage environment. No specimens will be collected in this study.

11) Data Management and Confidentiality

- Mechanical ventilator waveform data representing pressure, flow, and time will be collected using the standard data export functionality of the mechanical ventilators. Exported data will be encrypted at the time of export and sent wirelessly to a central server using a commercially available, USB-based, wireless data storage device and a state of the art wireless data transfer encryption protocol. Wireless data transmission will occur over a dedicated, secure research wireless network to ensure that there is no interference with the health system's standard wireless network. Waveform data files will be coded at the time of collection using a unique subject identifier. Our data export and research wireless network protocols have been developed in conjunction with the UC

Davis Research IT division (contact Kent Anderson, Director of UC Davis Research IT, for additional questions) and with Dr. Sean Peisert, PhD, an expert in data privacy and security. The safety and security of our data export and research wireless network protocols have been vetted through the standard UCDMC IT Evaluation of New Technologies protocol. Research IT has approved our protocol.

- In addition to ventilator waveform data, limited PHI will be collected such as date of birth, dates of admission/discharge/death in order to perform statistical tests to minimize the effects of confounding given the observational nature of the study. Medical record numbers (MRNs) will be collected to allow the use of unique patient identifiers and de-identified (coded) collection of PHI and non-PHI predictor variables. The code key linking unique identifiers to MRNs will be kept in an encrypted, password-protected file on the primary investigator's University computer that is protected behind the University's extensive, standard electronic security measures. PHI will not be inappropriately reused or disclosed to any other person or entity. All PHI will be deleted from the study database when all statistical analyses are completed. No materials will be used to recruit patients. Patients will not be contacted at any time before, during, or after data collection. Based on the above, signed informed consent will not be necessary. HIPAA authorization for the secondary use of routinely collected clinical data for research purposes will not be necessary in the setting of a waiver of informed consent (see Section 5 above).
- All ventilator data files will be maintained initially on a local secure server, with weekly backups onto Iron-key secure USB drives. Files will then be moved to a research analysis database in REDCap maintained by the CTSC. The local server will only be accessible to the study research staff named in this application. Re-linkage of ventilator waveform data to subject data will only occur in the secure REDCap environment through the use of coded unique identifiers at the time of subject data retrieval from the EHR.
- The REDCap application will be used as the database platform. In this case, the Biomedical Informatics Program of the UC Davis Clinical and Translational Science Center will be used as a central location for data management. REDCap (Research Electronic Data Capture) data collection projects rely on a thorough study-specific data dictionary defined in an iterative self-documenting process by all members of the research team with planning assistance from the Biomedical Informatics Program. The REDCap system provides secure, web-based applications that are flexible enough to be used for a variety of types of research, provides an intuitive interface for users to enter data and has real time validation rules (with automated data type and range checks) at the time of entry. *REDCap offers easy data manipulation with audit trails for reporting, monitoring and querying patient records, and an automated export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus). REDCap servers are housed in a local data center at UC Davis Health System and all web-based information transmission is encrypted. REDCap was developed specifically around HIPAA-Security guidelines. REDCap has been disseminated for use locally at other institutions and currently supports 240+ academic/non-profit consortium*

partners on six continents and over 26,000 research end-users (www.project-redcap.org).

- Access to the database will be controlled by the principal investigator and limited to those research personnel listed in this IRB application. Access to the database by investigators of other studies will not be permitted without separate, specific IRB approval to access this database for related research.

12) Provisions to Monitor the Data to Ensure the Safety of Subjects

Given the minimal risk nature of the study, no specific data monitoring provisions are necessary. The study involves scientific research only and will not evaluate the safety or effectiveness of the software algorithms we develop. Data from subjects will be used for research purposes only and will not be submitted to, or held for inspection by the FDA.

13) Withdrawal of Subjects

Withdrawal from the study will be allowed at any juncture. Our consent form includes contact information for the primary investigator, who can be contacted at any time. Withdrawal from the study will in no way bias further patient care or interactions with the health care system. If a subject requests that his/her health information be removed from the registry, the subject's information will be deleted immediately (within 24 business hours from receiving notification).

14) Risks to Subjects

There is no additional risk involved to the patient beyond the standard risk inherent in a retrospective analysis derived from reviewing PHI in the EHR. Mechanical ventilator waveform data do not contain PHI/PII and cannot be used to re-identify subjects. The treating physicians and staff will have no access to the information we collect, therefore our study will not influence the care received by the patient.

15) Potential Benefits to Subjects

There is no direct benefit to the patient from enrollment in the study.

16) Vulnerable Populations

This study will not include patients under the age of 18, pregnant women, or prisoners.

17) Multi-Site Research

This is a single-site study.

18) Community-Based Participatory Research

Due to the inherent necessity of mechanical ventilation, our subjects will all be in an intensive care setting, hence community involvement will not be necessary or applicable.

19) Sharing of Results with Subjects

The results of our study will not be made available to the treating ICU team and the patient's primary care provider to prevent any type of interference with the patient's care. Contact information will be made available on the consent form for the patient or their surrogates to have access to learn the results of the study.

20) Setting

All patients will be mechanically ventilated at UC Davis Medical Center in a critical care setting. Patients will be recruited as described above. Once subjects have been found appropriate for inclusion, data export from mechanical ventilators will proceed unobtrusively via wireless data transfer to a secure central server as described above.

21) Resources Available

Jason Adams, MD, UCD Pulmonary and Critical Care Medicine, Principle Investigator : study design, data analysis, clinical coordinator and study oversight
Sub-Investigators: coordinating software development, study design, data analysis
Research Assistants: data acquisition, data analysis, study/research coordination
Computer Specialists: software design
Database Specialists: database design and administration
Statistician: study design and data analysis

The MICU team at UC Davis sees a large volume of critically ill patients, a number of whom require mechanical ventilation. There are approximately 80-90 patients admitted per month to the MICU service, with approximately 25% requiring mechanical ventilation. With this large volume of potential patients, an enrollment rate of 75% would lead to approximately 16 patients per month.

As this study requires multiple phases (algorithm development, recruitment/data collection, analysis), we expect to take approximately 12 months before a publication focused on algorithm develop would be feasible.

We will be utilizing critical care units at the UC Davis Center for Virtual Care, the informatics resources of the UC Davis Clinical and Translational Science Center and UC Davis Tethered Meta Registry (https://myhs.ucdmc.ucdavis.edu/web/tethered-meta-registry). We have received pilot funding from the Center for Information Technology Research in the Interest of Society (CITRIS; http://citris-uc.org/).

This study does not involve direct intervention on subjects, so no medical or psychological resources will be made available.

To assure that all persons assisting with the research are adequately informed about the protocol, the research procedures, and their duties and functions, we will write comprehensive standard practices for the various aspects of our study including data acquisition, data analysis, EHR access/PHI information gathering. All research personnel involved in the study will be required to read and review these protocols.

22) Prior Approvals

None.

23) Provisions to Protect the Privacy Interests of Subjects

While study-specific informed consent will not be collected due to the observational, minimal risk nature of the study, subjects' privacy interests will be respected. As described above, efforts will be taken to assure the de-identification (coding) and security of the data collected.

Patients and/or families will not be directly engaged by research personnel due to the observational nature of the study protocol. We do not anticipate any anxiety or unease on the part of study subjects.

The research team will be accessing the EHR for the purposes of extracting both PHI and non-PHI information pertinent to statistical testing. The physicians on the team have access to the EHR and the MICU service master list. Mechanical ventilator waveform data contain no PHI/PII and will be stored using unique study subject identifiers only. All ventilator and EHR

data will be acquired and stored securely as described above through the use of data encryption, password protection, and unique identifiers.

24) Compensation for Research-Related Injury

As there is no potential risk for injury to the patient, compensation is not necessary to arrange.

25) Economic Burden to Subjects

There is no economic burden for patients and families participating in this study.

26) Consent Process

We are requesting a waiver of written consent. Given the high proportion of patients unable to consent, surrogate decision makers will often be approached. Informed consent will be obtained either in person or via telephone as feasible. The consent process will be carried out in accordance to HRP SOP 090.

Subjects will be assessed on their abilities to understand and to express a reasoned choice concerning:

- the nature of the research and the information relevant to his/her participation;
- consequences of participation for the subject's own situation, especially concerning the subject's health condition; and
- consequences of the alternatives to participation

If all three criteria can not be met, the patient will be judged as not having capacity and a surrogate will be approached.

Identification of the surrogate will be performed in accordance with the UCOP Guidance on Surrogate Consent for Research and will be consistent with the intent of the Common Rule (45 CFR 46, Subpart A) and all other federal and state laws and regulations pertaining to protecting human subjects participating in research.

Process for obtaining consent in person:
Subjects and their surrogates who are able and willing to travel to the UCDMC will be approached for consent. The subject will be given ample time to review the consent and ask questions about the study. If the subject or their surrogate are interested in enrolling, a signature will be obtained in person after a designated study staff person has reviewed the entire consent document with the subject and the subject has had all of his/her questions answered. The subject will be given a copy of the signed consent document.

Process for obtaining consent by telephone:
A study staff person will contact the surrogate (obtained via the patient demographics in the electronic medical record). The study staff person will review the entire consent with the subject over the telephone and the subject will be encouraged to ask any questions he/she may have about the trial and informed of risks and alternatives. If the subject is interested in enrolling, a study staff person will document the name, date, and decision in a telephone encounter in the

electronic medical record. This note will then be printed and kept in a physical registry of all enrolled patients, which will be kept in a locked office by the primary investigator.

HIPAA Authorization for Research form will be discussed at the time of consent and documented in the aforementioned EMR telephone encounter.

27) Process to Document Consent in Writing

As above, we request written consent be waived. Documentation of verbal consent via telephone on personal encounter will be written in the EMR and filed in a secure location by the PI.

28) Drugs or Devices

There are no drugs involved in this study and there are no devices being used in any diagnostic/therapeutic capacity. We are using standard data export capabilities built into the mechanical ventilators by the manufacturers for this expressed purpose, and are using commercially available products and industry standard, state of the art data security measures to allow exported data to be sent un-obtrusively and securely to a secure central server. The process of data collection will not interfere with the ventilator, the patient, or the healthcare team and therefore does not constitute a medical device, as defined by Section 201(h) of the FD&C Act. The algorithms developed for mechanical ventilator waveform analysis will only be used for research purposes and will not affect the ventilator, patient care, or the healthcare team, nor will they be evaluated for safety or effectiveness. Data from subjects will be used for research purposes only and will not be submitted to, or held for inspection by the FDA.