The APS Phenotyping Study Protocol B (alteration protocol)

Protocol Full Title:	The ARDS, Pneumonia, and Sepsis (APS) Consortium: A Prospective Observational Study to Evaluate Phenotypes (Protocol B – alteration protocol)
Protocol Short Title:	The APS Phenotyping Study Protocol B (alteration protocol)
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Network:	The ARDS, Pneumonia, and Sepsis (APS) Consortium
Funders:	(1) National Heart, Lung, and Blood Institute (NHLBI) (2) National Institute for General Medical Sciences (NIGMS)
Clinical Center Hub Institutions:	(1) University of California, San Francisco (2) Intermountain Medical Center (3) University of Colorado (4) Vanderbilt University Medical Center (5) University of Michigan (6) University of Pennsylvania
Coordinating Center & Single IRB:	Vanderbilt University Medical Center
Investigators:	See section 1
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Purpose:	This protocol outlines study procedures for participants entering the APS Consortium Study with alteration of informed consent procedures. It describes the alteration of informed consent process and the minimal risk procedures that can be completed with a patient participating under alteration of informed consent. This protocol (APS Protocol B) is a companion protocol accompanying APS Consortium Study Protocol A (full protocol), which fully describes the APS Consortium Study. Protocol B will only be run at sites that are also conducting Protocol A. Participants entering the study with alteration of informed consent on Protocol B will be converted to Protocol A when informed consent for study participation is obtained.

Contents

1. Investigators

Table 1. APS Consortium investigators

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2. Protocol Notes

2.1 Protocol Revision History

Protocol Version Number	Protocol Version Date	Summary of Revisions
1.0	March 18, 2024	Original protocol submitted to sIRB
1.1	March 18, 2024	(1) Revised protocol language to make it clear that participants without informed consent will not undergo an interview for collection of study data. (2) Revised section 12.2.3 to change the time frame of reporting adverse events to the sIRB from within 14 days to within 7 days of site awareness of event.
2.0	April 13, 2024	Protocol version used to initiate study enrollment (approved by single IRB at Vanderbilt University Medical Center).
2.1	June 6, 2024	Throughout the document, especially section 11, language was revised to more precisely outline the use of identifiable information. Enrolling sites will enter identifiable information, such as date of hospital admission and date of birth, into the study's database. These data will be visible by APS coordinating center personnel. De-identified datasets will be created for long-term storage of data outside the APS Consortium.
2.2	July 13, 2024	- Section 1: Added Xiaoli Zhao as a consortium investigator. - Section 6.1.3: Section added outlining rationale for eligibility criteria, including the inclusion of pregnant people.
3.0	August 5, 2024	- Section 7.2: Language added to clarify that aliquots of biospecimens collected on this research protocol may be used for clinical laboratory testing if the local team judges such tests to be potentially beneficial for the patient.
4.0	October 23, 2024	- Section 6.1.2: Exclusion criterion #4 changed to: The clinical team has initiated transfer of the patient to a lower level of care that does not meet inclusion criterion #2 (such as placement of a transfer order out of the ICU). - Section 7.2.1: This sentence was added: Additionally, if residual volumes of biospecimens collected clinically meet the volume and collection time needed to fulfill biospecimens outlined in protocol schedule of events of this protocol, those residual samples may be used for research purposes in this protocol.

2.2 Abbreviations

Table 2. Abbreviations

Abbreviation	Full term
AE	Adverse Event
AESI	Adverse events of special interest
APS	ARDS, Pneumonia, and Sepsis
ARDS	Acute Respiratory Distress Syndrome
AUDIT-C	Alcohol Use Disorder Identification Test – Concise
CC	Clinical Center
CCC	Consortium Coordinating Center
COPD	Chronic Obstructive Pulmonary Disease
CPT	Cell Preparation Tube
CT	Computed Tomography
CXR	Chest X-Ray
DNA	Deoxyribonucleic acid
EDTA	Ethylenediaminetetraacetic acid
EHR	Electronic Health Record
EQ-5D-5L	EuroQol 5 Dimensions 5 Level
HME	Heat Moisture Exchanger
ICAP-Revised	Inventory for Client and Agency Planning-Revised
ICU	Intensive Care Unit
IQ-CODE	Informant Questionnaire on Cognitive Decline in the Elderly
IRB	Institutional Review Board
Katz ADL	Katz Index of Independence in Activities of Daily Living
LAR	Legally Authorized Representative
Lawton IADL	Lawton Instrumental Activities of Daily Living scale
lpm	liters per minute
NBBAL	Non-Bronchoscopic Bronchoalveolar Lavage
NHATS	National Health and Aging Trends Study
NHLBI	National Heart, Lung, and Blood Institute
NIGMS	National Institute of General Medical Sciences
NIH	National Institutes of Health
OSMB	Observational Study Monitoring Board

Abbreviation	Full term
P:F ratio	Partial pressure of oxygen: Fraction of inspired oxygen ratio
PFT	Pulmonary function testing
PRC	Protocol Review Committee
RALE score	Radiographic Assessment of Lung Edema score
RNA	Ribonucleic acid
SAE	Serious Adverse Event
sIRB	Single IRB
SIRS criteria	Systemic Inflammatory Response criteria
SOFA score	Sequential Organ Failure Assessment score
UP	Unanticipated Problem
WHODAS-12	World Health Organization Disability Assessment Schedule 12-item version

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3. Purpose of this Protocol / Program Overview

3.1 Scope of Study Protocol B

This study protocol – APS Consortium Study Protocol B (alteration protocol) – describes the process by which participants for whom informed consent for study participation cannot be obtained before study entry may enter the study with an alteration of informed consent, and the minimal risk study procedures that may be completed under alteration of informed consent. This is a companion protocol to APS Consortium Study Protocol A (full protocol), which details the APS Consortium Study at length, including the rationale for the study and how data and biospecimens will be used.

Only sites that are running Protocol A will be eligible to open Protocol B. The goal is to convert participants from Protocol B to Protocol A as soon as completion of written informed consent is possible. Protocol B will only govern study procedures for participants who enter the study using alteration of informed consent until informed consent for study participation is obtained.

3.2 Protocol Documents

The APS Consortium study is governed by two study protocols:

- Protocol A (full protocol): Protocol A is a separate document that describes all study procedures that a participant may complete during the course of the APS study and governs study procedures for participants who have completed informed consent for research participation. Protocol A contains two parts:
    - Master protocol: Study procedures that govern enrollment, data collection, and biospecimen collection. The master protocol is described in the main text of this document.
    - Consortium-wide science: specific analyses that will use data and biospecimens collected in this study and will be undertaken by the APS Consortium investigators collaboratively across the entire consortium. Consortium-wide science is described in appendices to this document.

- Protocol B (alteration protocol): Protocol B is this document. It describes a procedure for participation in the APS Consortium study with alteration of informed consent. Protocol B will be used for participants for whom informed consent for research cannot be obtained via the participant or a legally authorized representative prior to initiation of study procedures. Minimal risk procedures within the APS study may be completed using alteration of informed consent. Protocol B outlines the minimal risk procedures that may be completed without informed consent for research. Identical minimal risk procedures are also included in Protocol A.

Participants who have provided informed consent will complete study procedures described in Protocol A (a separate document), and participants who have not provided informed consent will complete study procedures described in Protocol B (this document). Protocol B includes a subset of study procedures in

Protocol A and does not include any study procedures not in Protocol A. Hence, participants without informed consent for research will complete a subset of study procedures (Protocol B) completed by participants with informed consent for research (Protocol A). Participants who enter the study on the alteration of informed consent protocol (Protocol B) will be iteratively approached for consent; if and when informed consent for participation in the APS Study is obtained, the participant will be moved from Protocol B to Protocol A. Greater than minimal risk procedures may be completed after informed consent is obtained and are governed by Protocol A. Data and biospecimens collected under Protocol A and Protocol B will be pooled for storage and analysis.

4. Introduction

Please see APS Consortium Study Protocol A (full protocol) for a description of study background, rationale, and objectives. In brief, the overarching goal of the APS Consortium is to support the development of deeper mechanistic understandings of critical illness syndromes to facilitate precision-based therapies that will curtail the devastating morbidity and mortality caused by ARDS, pneumonia and sepsis. The goals of the APS Consortium were established by the NIH/NHLBI in the request for applications (RFA) soliciting applications for the clinical centers and are described in detail at (https://grants.nih.gov/grants/guide/rfa-files/RFA-HL-23-001.html).[1] The Consortium seeks to understand the heterogeneity and underlying mechanisms of critical illness syndromes and recovery in adults with ARDS, pneumonia, and/or sepsis, as well as the relationship and biological overlap among these syndromes, through a prospective, longitudinal observational study with common data and biospecimen collection. The scientific focus of the consortium is on identifying novel phenotypes of critical illness, describing the clinical and biological features that define these phenotypes, establishing their prognostic and clinical value, and identifying their fundamental mechanisms; in addition, as set out in the RFA, the Consortium will generate a richly characterized clinical dataset and biobank for future investigations.

The Consortium will conduct a cohort study of approximately 4,000 adults hospitalized in the United States with ARDS, pneumonia and/or sepsis, and collect multidimensional data and biospecimens for up to one year from the time of index hospitalization. These data and biospecimens will be used both within the Consortium and by others to enhance our understanding of the mechanistic underpinnings of ARDS, pneumonia and sepsis.

5. Study Design

Please see APS Consortium Study Protocol A (full protocol) for a full description of study design. In brief, the APS Consortium study is a multicenter observational cohort study enrolling participants with acute cardiovascular or pulmonary organ dysfunction in the context of ARDS, pneumonia, sepsis, or a condition at high risk to progress to one of these syndromes. Targeted sample size for enrollment is 4,000 participants. Biospecimens including blood, respiratory samples, circulating blood cells, urine, stool, and

oral, nasal, and rectal swabs will be collected. Rich clinical data will be collected from the medical record. These data will be used to phenotype multiple domains of health.

6. Participant Enrollment

6.1 Eligibility Criteria

Eligibility criteria for Protocol B (alteration protocol) are identical to Protocol A (full protocol). These eligibility criteria are shown below.

6.1.1 Inclusion Criteria

To be eligible for enrollment, a patient must meet all the following inclusion criteria at the time of the first study-specified biospecimen collection (Time 0):

1. Age ≥ 18 years old.

2. Admitted (or planned to be admitted) to an ICU or other in-patient hospital location where IV vasopressors or advanced respiratory support (invasive mechanical ventilation, non-invasive ventilation, or high flow nasal cannula) are routinely provided (referred to as an "eligible unit.")

3. Acute cardiovascular or pulmonary organ dysfunction defined by meeting at least one of the two criteria below:
    i) New receipt of invasive mechanical ventilation, non-invasive ventilation, high flow nasal cannula, or supplemental oxygen at a flow rate of ≥ 6 lpm for acute hypoxemia.
        → Patients who use chronic oxygen therapy are eligible to participate if they are receiving at least 6 lpm higher than their baseline oxygen requirement (e.g., a patient on 3 lpm O2 at baseline is eligible if they require ≥9 lpm for hypoxemia) or are started on advanced respiratory support (invasive mechanical ventilation, non-invasive ventilation, or high flow nasal cannula).
    ii) Receipt of intravenous infusion of a vasopressor medication for at least one hour.

4. Acute cardiovascular or pulmonary organ dysfunction (inclusion criterion #3) is attributed to an acute inflammatory condition, including but not limited to any of the following:
    i) Any infection including pneumonia.
    ii) Aspiration pneumonitis.
    iii) Pancreatitis.
    iv) Auto-inflammatory condition such as:
        a. Hemophagocytic lymphohistiocytosis.
        b. Suspected acute rheumatologic or auto-immune disease with pulmonary or cardiovascular manifestations.
        c. Suspected cryptogenic organizing pneumonia presenting acutely.
        d. Suspected diffuse alveolar hemorrhage.
        e. Suspected acute anaphylaxis.
        f. Suspected acute pulmonary drug toxicity.

6.1.2 Exclusion Criteria

To be eligible for enrollment, a patient must not meet any of the following exclusion criteria at the time of the first study-specified biospecimen collection (Time 0):

1. Patient/LAR declines participation.

2. Acute cardiovascular or pulmonary organ dysfunction (inclusion criterion #3) has been present for > 48 hours.

3. Patient has been in an eligible unit (inclusion criterion #2) for more than 120 hours (five days).

4. The clinical team has initiated transfer of the patient to a lower level of care that does not meet inclusion criterion #2 (such as placement of a transfer order out of the ICU).

5. Patient desires comfort measures only.

6. Patient is a prisoner.

7. Patient had out-of-hospital cardiac arrest leading to this hospitalization.

8. Residence immediately before this hospitalization in a long-term acute care facility.

9. Presence of tracheostomy for respiratory failure.

10. Home invasive mechanical ventilation or non-invasive ventilation (except patients with non-invasive ventilation prescribed as a treatment for a sleep disorder may participate).

11. Suspected cause of the patient's acute cardiovascular and/or pulmonary dysfunction (inclusion criterion #3) is an alternative condition (not ARDS, pneumonia, or sepsis), including but not limited to the list below:

    i) Drug overdose (without aspiration, lung injury, pneumonia, or infection).
    ii) Trauma (without aspiration, pneumonia, or infection).
    iii) Chronic lung disease without suspected infection, aspiration, or inflammation.
    iv) Asthma, COPD, sarcoidosis, interstitial lung disease, neuromuscular respiratory failure.
    v) Status epilepticus.
    vi) Acute pulmonary embolism.
    vii) Acute decompensated heart failure.
    viii) Diabetic ketoacidosis.
    ix) Acute stroke or intracranial hemorrhage.
    x) Acute bleeding (GI bleeding, post-procedural bleeding, hemolysis).
    xi) Cytokine release syndrome due to chemotherapy.

12. Inability or unwillingness to complete study-specified blood draws, for example, due to local policies about hemoglobin thresholds for research blood draws.

6.1.3 Rationale for eligibility criteria

The goal is to enroll patients with acute cardiopulmonary dysfunction that is due to either (a) ARDS, pneumonia, or sepsis, or (b) an acute inflammatory condition that places patients at high risk for short-term development of ARDS, pneumonia, or sepsis. Patients with common critical care conditions that may result in acute cardiopulmonary dysfunction, but which have established pathophysiologic mechanisms distinct from ARDS, pneumonia, and sepsis will be excluded. This approach will optimize the ability to understand the pathophysiology of ARDS, pneumonia, and sepsis, whereas an approach that limited enrollment to patients who meet the historical syndrome definitions would limit our ability to identify new, meaningful phenotypes. In addition, this approach recognizes the difficulty in making definitive clinical diagnosis of historical syndromes (ARDS, pneumonia, and sepsis) at the time of enrollment among critically ill patients. By taking this approach to inclusion criteria, the APS Consortium is expected to further improve our ability to make diagnoses in real time.

Potential participants of all sexes, genders, races, ethnicities, language proficiencies, and nationalities are invited to participate. Enrollment in the cohort will not be limited by the language(s) spoken by the participant. All adult patients across the age span are invited to participate; pediatric participants are not the focus of this project and will not be enrolled.

Pregnant individuals are eligible to participate in the APS cohort because pregnant patients experience APS syndromes at rates higher than the general population of similar age, and there is no strong rationale to exclude such participants. The risks of the procedures in this study are not greater for pregnant participants than for other participants.

Prisoners are excluded because there is concern that their participation may not be fully voluntary.

Pediatric participants <18 years old are excluded because they are frequently admitted to different, specialized pediatric hospitals, the tools for assessing organ dysfunction and molecular phenotyping are different for children, and the focus of this study is on adults.

6.2 Definition of Enrollment Time Zero

The calendar day of the first study-specified biospecimen collection is defined as “Day 0.” The study schedule of events follows “study day” nomenclature, with enrollment day (the day of the first biospecimen collection) identified as Day 0. Study Day 1 is the calendar day following enrollment. Study Day -1 is the calendar day before enrollment. In some circumstances, consent for participation may be obtained after Day 0 (such as on Day 1) or prior to Day 0 (such as Day -1).

Time zero for enrollment is defined as the time of the first biospecimen collection for the study, regardless of the timing of hospital admission, and development of ARDS, pneumonia, or sepsis. A patient is considered enrolled when the first study-specified biospecimen collection occurs. Time stamps will be collected for key events, such as hospital admission, meeting study eligibility criteria, and collection of biospecimens, so that analyses can evaluate the time between these events.

7. Study Procedures During Index Hospitalization

This section describes study procedures during the index hospitalization for patients participating in the study under alteration of informed consent.

7.1 Data collection during index hospitalization

7.1.1 Data collected by direct observation or medical record review

Patients participating in the study under alteration of informed consent (Protocol B) are unlikely to be able to answer interview questions for collection of study data. For participants unable to answer interview questions, below are domains of data that may be collected by direct observation from study personnel or medical record review. If a patient later consents for study participation and converts to study Protocol A, the research team may collect these data at that time via participant and/or surrogate interview.

- Contact information of patient and family members
- Skin color (Monk skin tone scale)
- Smoking status
- Alcohol use
- Employment status
- Education
- Current/former opioid misuse

7.1.2 Medical record data abstraction

Medical record data abstraction may occur at varying times during the hospitalization based on operationalization at a given site. These data, whether extracted at the time of a given study visit or near or after hospital discharge, will be tied to the schedule of events. Features of data abstraction will be extracted to correspond with the baseline visit as well as subsequent visits. Domains of data collection via medical record review include:

- Contact information of patient and family members, including home address and type of residence
- 9-digit zip code. This allows for linkage to other datasets to capture measures of social vulnerability (e.g., Social Vulnerability Index, Social Deprivation Index, Area Deprivation Index), as well as healthcare availability and rurality. Note: to avoid risk of re-identification of study subjects, zip code will be stripped from shared datasets; data on social vulnerability, healthcare availability, rurality, and other factors obtained by linkage to 9-digit zip code will be retained as categorial variables in shared datasets.
- Demographics

- Home medications
- Biometrics (height, weight)
- Language fluency
- Place of residence
- Chronic health conditions (including tobacco use, alcohol misuse, and opioid misuse)
- Health insurance status
- Prior hospitalizations
- Clinical laboratory results, medications, and vital signs, including SOFA score elements
- Therapies administered (including respiratory support therapies)
- Discharge disposition

7.1.3 Acute Respiratory Distress, Pneumonia, and Sepsis Syndrome Classification

Enrolled participants will be evaluated for ARDS, pneumonia, and sepsis utilizing detailed, investigator driven review and application of published and accepted clinical criteria for each syndrome. To evaluate for ARDS, pneumonia, and sepsis, investigators will evaluate data and the clinical record for each participant for Study Day -2 through Day 7 while the patient is hospitalized (the phenotyping observation window). Individual criteria for each syndrome will be collected and recorded separately allowing for patients to be classified as ARDS, Sepsis, and/or Pneumonia using multiple published criteria (e.g., for sepsis using both "sepsis-2" and "sepsis-3" criteria). These data will then be used to code variables in our dataset that classify patients according to syndrome definitions. Standard operating procedures will be provided to each site to ensure accuracy and consistency of syndrome adjudication.

ARDS will be identified based on the Berlin Definition with the additional modifications proposed in the New Global Definition of ARDS.[2,3] Trained physician investigators will determine the presence of potential precipitating factors for ARDS (e.g., sepsis, aspiration, pancreatitis). Chest radiographs and chest computed tomography scans conducted for clinical purposes during the observation window will be reviewed by trained physician investigators for bilateral infiltrates consistent with ARDS. The type of chest imaging, time and date of imaging acquisition, and bilateral infiltrates present, absent, or equivocal will be recorded in case report forms. The presence or absence of pleural effusions will also be recorded. Arterial blood gas (ABG) values drawn for clinical purposes and corresponding fraction inspired oxygen percentage (FiO2) will also be recorded in case report forms. If an ABG is unavailable on a given day, SpO2 and corresponding FiO2 will be recorded to calculate the S/F ratio. Invasive and non-invasive oxygenation and ventilation parameters will also be extracted from the medical record. We will apply strict physiologic criteria in ARDS definitions to determine the presence or absence of ARDS daily, timing when ARDS criteria are met, and the severity of ARDS based the level of hypoxemia (P:F and S:F ratios).

Participants will be assessed for the presence of pneumonia based on radiographic, clinical, and laboratory criteria, including those published by CDC and the Infectious Disease Society of America/American Thoracic Society.[4,5] Chest imaging conducted for clinical purposes during the phenotyping observation window will be reviewed by trained physician investigators for new/persistent/progressive infiltrates, consolidation, or cavitation consistent with a pneumonia event.

Clinical signs and symptoms potentially indicating a respiratory infection will be identified, including vital signs, laboratory results, and clinical status. Assessment of clinical status will include: 1) new onset purulent sputum or change in character of sputum, increasing respiratory sections, or increasing suctioning requirements, 2) new onset or worsening cough, dyspnea, or tachypnea, 3) rales or bronchial breath sounds, and 4) worsening gas exchange. These data will form the core dataset for classifying the presence and absence of pneumonia.

Sepsis will be identified based on the Sepsis-2 and Sepsis-3 definitions of sepsis, severe sepsis and septic shock.[6,7] Trained physician investigators will review the medical record to determine if an infection is confirmed, suspected, not suspected, or unknown daily for the observation window. The presence of positive culture will not be required to identify the confirmed or suspected presence of an infection; however, positive cultures can be used to help determine the presence of sepsis. Suspected sources of infection will be adjudicated by the physician investigators. The physiology of sepsis and septic shock will be classified based on the change in Sequential Organ Function Assessment (SOFA) scores, the presence or absence of the systemic inflammatory response (SIRS) criteria, the presence or absence of vasopressors, and values for lactate. These data will be used to facilitate sepsis classification by the investigator adjudicators.

7.2. Biospecimen collection during index hospitalization

7.2.1 Interplay between clinical and research procedures for biospecimen collection

Aliquots of biospecimens collected on this research protocol may be sent for clinical laboratory testing if such testing is judged to be of potential benefit to the patient. Clinical laboratory testing is optional and may be completed at the discretion of the local site team. If clinical laboratory testing is completed, results may be delivered to clinicians caring for the patient according to local practice patterns.

Additionally, if residual volumes of biospecimens collected clinically meet the volume and collection time needed to fulfill biospecimens outlined in protocol schedule of events of this protocol, those residual samples may be used for research purposes in this protocol.

7.2.2 Blood specimen collection during index hospitalization

During the index hospitalization, blood will be collected from patients at multiple timepoints, collected in EDTA or sodium citrate tubes (for protein or metabolite measurements), PAXgene tubes (for nucleic acids), CPT tubes (for peripheral blood mononuclear cells), and sodium heparin tubes (for whole blood CyTOF and flow cytometry). Blood will be collected at the timepoints indicated in the schedule of events for biospecimen collection and will be coordinated with blood draws for clinical purposes as much as possible.

7.2.3 Respiratory specimen collection during index hospitalization

During the index hospitalization, the following respiratory specimens will be collected: 1) nasal swabs to facilitate both microbiome profiling and pathogen detection, 2) oral swabs, 3) tracheal aspirate (TA) from patients receiving invasive mechanical ventilation, 4) heat moisture exchanger (HME) filter fluid from patients receiving invasive mechanical ventilation.

7.2.4 Other specimens during the index hospitalization

Participants will have rectal swabs and stool samples serially collected for the primary purpose of microbiome profiling and urine collected for future use.

7.3. Imaging studies during index hospitalization

During the index hospitalization, investigators will review chest imaging completed clinically during the observation window for clinical phenotyping (Study Day -2 through Day 7) and enter key findings into the study data collection forms. Additionally, as detailed in the schedule of events section, serial chest x-ray (CXRs) and CT scan images that were performed as part of the participant's clinical care will be collected and uploaded to a common, secure site, with eventual deposition into BioData Catalyst. The initial goal is to upload up to 3 CXRs and one CT scan (chest CT preferred, abdominal CT acceptable when no chest CT is available) completed during the index hospitalization as part of clinical care. The number of images uploaded per patient may change over time. These stored images will be used by the APS investigators and will be available in the APS databank for future work.

8. Schedule of Events

Study procedures, including collection of data, biospecimens, and radiographic images, are detailed in tables within this section.

Table 3. Schedule of Events: Data collection (Protocol B - alteration protocol)

Event [a]	Time Point							
	Study Day (in-hospital only)					At Discharge	Hospital Summary	3-months by telephone (Study Day window: Day 85-135)
	-2	-1	0[b]	1 - 7	8-14			
A. Eligibility and Baseline Data								
Eligibility Criteria			X					
Attempts to obtain informed consent				X	X			X
Baseline History			X					
Demographics			X					
Chronic Medications			X					
Admitting Diagnoses			X					
B. Observation or Medical Record Review [c]								
Contact Information			X					
Skin Color			X					
Alcohol Use			X					
Smoking Status			X					
C. Data Collection								
Daily Data								
- Vital Signs	X	X	X	X				
- Laboratory Values	X	X	X	X		X		
- Ventilator Data	X	X	X	X				
- Select Medications	X	X	X	X		X		
- Fluid Balance	X	X	X	X				
- Cumulative IV Sedation[d]	X	X	X	X				
- Sedation/Delirium	X	X	X	X				
- Blood Products	X	X	X	X				
APS Classification	X	X	X	X				
Outcome Data								
- Mortality							X	
- Discharge location						X		
- Organ Failures	X	X	X	X		X	X	
- ECMO / Prone position							X	

Table 3 Footnotes

a. The data collection schedule of events displays the study days from which data will be collected. The collected data will reflect patient status on those study days. The data may be collected later in a respective fashion.

b. Study Day 0 is anchored on when the first study-specific biospecimen is collected. The time of first biospecimen collection is termed Time 0 and denotes the time a patient is enrolled into the study. Per study eligibility criteria, enrollment must occur within 48 hours of meeting inclusion criteria.

c. Due to the patient's status, an interview will not be possible while a patient is participating in the study under alteration of informed consent. Contact information, skin color, smoking status, and alcohol use status will be collected as possible through direct observation and medical record review.

d. Cumulative amounts of continuous IV administration of select sedation agents will be collected from Study Day -2 to 7.

Table 4. Schedule of Events: Biospecimens collected during index hospitalization (Protocol B – alteration protocol)

Event	Index Hospitalization (Study Day)				
	Day 0[a]	**Day 2**	**Day 4[b,c]**	**Day 6[c]**	**Day 14[c]**
Acceptable study days for collection	Day 0-1	Day 2-3	Day 3-5	Day 6-8	Day 14-17
Max Total Blood Volume (ml)[d]	33.2	15.2			
- EDTA tubes (total mL)	2x 6ml (12)	1x 10ml (10)			
- Extra EDTA tube if CPT not collected (total ml)[d]	1x6ml (6)				
- RNA Paxgene tubes (total mL)	1x 2.5ml (2.5)	1x 2.5ml (2.5)			
- CPT tubes (total mL)[e]	2x 8ml (16)				
- Na citrate tubes (total mL)	1x 2.7ml (2.7)	1x 2.7ml (2.7)			
- Buffy coat from EDTA	From EDTA				
- RBCs	From EDTA				
Urine tubes (total mL)	1x 5ml (5)				
Oral swab	x	x		x	
Nasal swab	x	x		x	
Rectal swab	x	x		x	
Stool	x	x		x	
HME filter fluid[f]	x	x	x	x	x
Tracheal aspirate[f]	x	x	x	x	x

Table 4 Footnotes

a. Study Day 0 is anchored as the calendar day when the first study-specified biospecimen is collected. By study eligibility criteria, this must occur within 48 hours of the patient meeting eligibility criteria. The first biospecimen collected will, by definition, be collected on Day 0. Other biospecimens scheduled for collection on Day 0 can be collected as late as Day 1.

b. Day 4 specimens are only collected from participants on invasive mechanical ventilation (IMV). Day 4 specimen collection is preferred on Study Day 4 or 5 but may be collected on Day 3 if Day 2 specimens were collected on Day 2 (instead of Day 3).

c. Patient participating in the study under alteration of informed consent will not have blood collected for study Day 4, Day 6, or Day 14. This ensures that research blood draws for participants without informed consent for study participation will not be completed more than 2 times in a week and that total blood volume for this research study will not exceed 50 ml in 8 weeks (criteria used by the Office of Human Research Protections to define minimal risk for adults who are not healthy).[8]

d. Participants who do not have blood collected for cellular analyses (CPT tubes) will have an additional 6 ml tube of EDTA collected at the study visit on Day 0. Participants who do have blood collected for cellular analyses (CPT) will not have this extra tube of EDTA collected.

e. During processing of CPT tubes, plasma will be saved and stored when possible.

f. HME filter fluid and tracheal aspirate fluid only collected from participants on invasive mechanical ventilation (IMV).

Table 5. Schedule of events: Storage of clinically-obtained radiology images (Protocol B – alteration protocol)

Images from the following radiographic studies performed as part of clinical care will be collected by study personnel and uploaded into the study database.

Imaging type	Procedures
In-hospital clinically obtained CXRs	Upload up to 3 CXRs per participant. Details of which CXRs to upload will be outlined in study operating procedures. Initially, CXRs targeted for uploading will be CXRs completed closest to 8:00am on Day 0, Day 2, and Day 6.
In-hospital clinically obtained CT scans	Upload up to 1 scan per participant. If multiple scans are available, select the scan completed closest to 8:00am on Day 0. Chest CT preferred, abdominal CT acceptable if no chest CT performed during hospitalization.
Post-discharge clinically obtained CT scans	Upload up to 1 scan per participant. If multiple scans are available, select the scan closest to 6 months. Chest CT preferred, abdominal CT acceptable if no chest CT performed between hospital discharge and 12 months.

Table 6. Study procedures in Protocol A (full study completed with informed consent for study participation) that will not be performed on Protocol B (this protocol with alteration of informed consent).

Study procedures that will <u>not</u> be completed with alteration of informed consent. **These study procedures may only be initiated after informed consent for study participation and transition to Study Protocol A.**
Day 4 blood collection
Day 6 blood collection
Day 14 blood collection
Non-bronchoscopic bronchioalveolar lavage (NBBAL)
Long-term outcome surveys, including: - 3-month surveys - 6-month surveys - 12-month surveys
Long-term outcome in-person visits, including: - 3-month visit - 6-month visit - 12-month visit (which includes pulmonary function tests and chest CT)

9. Use of Data and Biospecimens

Data, biospecimens, and radiographic images collected in the APS Consortium will be used for 3 purposes:

1. Completion of APS Consortium-wide science as outlined in appendices to Protocol A (funded by the APS Consortium budget).

2. Completion of APS Clinical Center-specific science as outlined in grants proposals from Clinical Centers investigators and selected for funding via the NIH peer review process (funded by the APS Consortium budget).

3. Banking for use in future ancillary studies conducted by investigators both inside and outside the APS Consortium (biobanking is funded by the APS Consortium budget but ancillary studies for use of bio-banked data and specimens is not funded by the APS Consortium budget).

During conduct of the APS Consortium study procedures, data, biospecimens, and radiographic images will be collected by enrolling sites and transmitted to the APS Consortium Coordinating Center at Vanderbilt University Medical Center. Data and biospecimens will be organized and catalogued at the coordinating center. The coordinating center will distribute data and biospecimens as needed to complete Consortium-wide science and Clinical Center-specific science. Additionally, the coordinating center will periodically transmit data and biospecimens to repositories managed by the National Heart, Lung, and Blood Institute (NHLBI) -- BioData Catalyst (data repository) and BioLINCC (biospecimen repository).

During the period of performance for the APS Consortium, requests for data and/or biospecimens for use in ancillary studies will be reviewed for approval by the APS Steering Committee. After the completion of the APS Consortium period of performance, requests for data and/or biospecimens for use in ancillary studies will be governed by NHLBI through the BioData Catalyst and BioLINCC programs.

10. Terminology and Statistical Considerations

A complete description of the terminology the APS Consortium will use to describe phenotypes and the statistical approaches is available in APS Consortium Study Protocol A (full protocol). In brief, the Consortium will be evaluating historical syndromes (e.g., ARDS, pneumonia, sepsis), previously defined phenotypes (e.g., hyper- vs hypo-inflammatory, SRS1 vs SRS2, high elastance vs low elastance), and novel phenotypes discovered within the science of the Consortium itself. Analyses of Consortium-wide science will be led by the APS Consortium Coordinating Center. Analyses of Clinical Center Specific studies will be led by the Clinical Center driving that study. Ancillary studies will be analyzed by the investigative team running the ancillary study.

11. Human Subjects

11.1 Risks and benefits

The APS Consortium Study is an observational prospective cohort study with collection of data and biospecimens with methods routinely used in current routine medical practice. This protocol (Protocol B – alteration protocol) describes the study procedures that will be completed while a patient is participating under alteration of informed consent. While participating under alteration of informed consent, patients will undergo study procedures that are minimal risk. The US Code of Federal Regulations (CRF 46.102(j)) defines minimal risk as "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests" (https://www.ecfr.gov/on/2018-07-19/title-45/subtitle-A/subchapter-A/part-46#46.102).[9]

Table 7 details each study procedure for patients participating with alteration of informed consent and the rationale for each being minimal risk. These study procedures are consistent with guidance from the Office of Human Research Protections on research procedures that present no more than minimal risk to human participants (https://www.hhs.gov/ohrp/regulations-and-policy/guidance/categories-of-research-expedited-review-procedure-1998/index.html).[8]

The primary risks of study participation are related to the potential of disclosure of private health information and complications from biospecimen collection procedures. These risks will be minimized by using a secure REDCap data collection system for data entry and storage, maintaining good clinical practice procedures at all sites for handling of private health data, de-identifying data and specimens prior to long-term storage outside the consortium, training study teams on best practices for biospecimen collection, and collecting biospecimens at times that clinical labs are already being collected when possible.

Samples taken as part of this study may be used to evaluate human genetics in the future. Genetic testing results will not be linked to identifiable patients nor placed in the medical record. Inadvertent disclosure of genetic testing results could influence insurance policies or future employment. Genetic research that produces data that could result in identification of the patient will not be pursued with biospecimens collected under alteration of informed consent without consent ever being obtained except for patients known to have died prior to the end of the 3-month study time window (Study Day 85-135).

Participants are not expected to receive direct personal benefits for participating in the APS Consortium study. On a societal level, benefits of participants joining the APS Consortium study include contributing to increased knowledge about ARDS, pneumonia, and sepsis, which could lead to medical advances that ultimately decrease morbidity and mortality from these syndromes.

Table 7. Potential risks to participants enrolled in the APS Consortium study by study procedure that will be completed with alteration of informed consent (Protocol B – alteration protocol).

Study procedure	Potential risks	Study methods to minimize risks	Rationale for completing study procedure with alteration of informed consent
Collection of personal data	Inappropriate disclosure of private health information (loss of confidentiality/privacy).	Only study personnel trained in good clinical practice for clinical research studies will be involved in data handling. Each enrolling site will maintain appropriate training and certification in protection of human participants for all study personnel involved in interacting with patients and/or handling data. Data will be entered into and stored within REDCap, a secure internet-based data collection tool with multiple layers of security, including authentication of end-users, automatic user logout after 30 minutes of inactivity, a time-stamped audit trail, encrypted information transmission, and firewall protection of documents. Additional information on REDCap is available at: www.project-redcap.org.	Data collection will be noninvasive and rely on extraction from the medical record. Data will be stored in secure REDCap tools. Only deidentified data will be placed in long-term storage outside the consortium. The probability of harm anticipated from this research procedure is not greater than that from the routine in-hospital experience of adults hospitalized with ARDS, pneumonia, or sepsis.
Blood collection (phlebotomy)	Pain at phlebotomy site, infection at the phlebotomy site, bleeding, damage to surrounding nerves, transient light-headedness, fainting/syncope.	Only study or clinical personnel trained in phlebotomy will collect blood for this study. Patients will be positioned in a safe location for phlebotomy, such as supine in a bed. When possible, blood will be collected from pre-existing vascular catheters and timed with blood draws for clinical care to avoid additional phlebotomy.	Patients participating under alteration of informed consent will have a maximum of 2 blood draws and <50 ml blood collected, consistent with guidance from the Office of Human Research Protections for minimal risk blood collection research procedures.[8] Patients in this population typically have pre-existing vascular catheters in place, providing a convenient and clean point of collection. Blood for research will be collected at the same time as blood collection for clinical purposes whenever possible.
Urine collection	No plausible risks identified.	Only study or clinical personnel trained in the collection of urine will collect urine for this study. Urine will be collected via patient voiding or collection from pre-existing urinary catheters. No invasive procedures will be initiated in the study to collect urine.	No plausible risk identified. Patients within the study population routinely have urine collected while they are in the hospital. Invasive procedures will not be used to collect urine in this study. The probability of harm or discomfort anticipated from this research procedure is not greater than that from the routine in-hospital experience of adults hospitalized with ARDS, pneumonia, or sepsis.
Collection of oral, nasal, and rectal swabs	Localized transient irritation, pain, and/or bleeding may occur at the swab site.	Only study or clinical personnel trained in the collection of oral, nasal and rectal swabs will collect swabs for this study. Personnel will be trained to hold pressure on the swab site if it bleeds.	These types of swabs are routinely collected from hospitalized adults. The probability of harm or discomfort anticipated from this research procedure is not greater than that from the routine in-hospital experience of adults hospitalized with ARDS, pneumonia, or sepsis.

Study procedure	Potential risks	Study methods to minimize risks	Rationale for completing study procedure with alteration of informed consent
Stool collection	No plausible risks identified.	Stool will only be collected via participants freely stooling or via stool collection systems in place for clinical care (e.g., rectal tube, fecal incontinence bag). No invasive procedures will be initiated by the study to collect stool.	No plausible risk identified. The probability of harm or discomfort anticipated from this research procedure is not greater than that from the routine in-hospital experience of adults hospitalized with ARDS, pneumonia, or sepsis.
HME (ventilator) filter collection	Inadvertent disconnection of ventilator tubing for longer than necessary to collect the filter, which could rarely result in low oxygen levels, organ damage, and death if not recognized. The risk of patient injury from HME (ventilator) filter collection is considered very low.	Only study or clinical personnel trained in the collection of HME (ventilator) filters will collect the filters. Ventilators at all study sites have alarms that alert clinical teams when ventilator tubing is disconnected. HME filters are routinely used for clinical care. Patients receiving invasive mechanical ventilation are routinely disconnected from the ventilator in clinical care daily. When possible, HME filters will be collected during a disconnection of the ventilator that is occurring as part of clinical care.	Ventilator filters are routinely changed as part of clinical care of patients on invasive mechanical ventilation. The collection of HME filter fluid is a non-invasive procedure that entails capturing filters that would otherwise be discarded. The probability of harm or discomfort anticipated from this research procedure is not greater than that from the routine in-hospital experience of adults on invasive mechanical ventilation.
Tracheal aspirate fluid collection	Bleeding, localized pain, drop in oxygen levels (hypoxemia), and dislodgement of the tracheal tube. A drop in oxygen levels from tracheal aspirate collection is very unlikely to cause patient harm.	Only study or clinical personnel trained in the collection of tracheal aspirate fluid will collect this specimen. Tracheal suctioning is a routine clinical procedure.	Tracheal aspirate collection is a routine clinical procedure for adults on invasive mechanical ventilation. Tracheal aspirate collection for this protocol will be done at times that tracheal aspirates are being collected as part of clinical care, whenever possible. The probability of harm or discomfort anticipated from this research procedure is not greater than that from the routine in-hospital experience of adults on invasive mechanical ventilation.
Storage of biospecimens for future testing	Biospecimens will be placed in long-term storage, where they may be retrieved for future studies. Inadvertent disclosure of testing results could cause loss of privacy.	Biospecimens for future testing will be deidentified before they are stored. These biospecimens will be labeled with a study number and the link between that study number and the patient's identity will not be provided to long-term storage facilities. Thus, the risk of inadvertent disclosure of identifiable information is judged to be very low. Results of testing will not be placed in the medical record.	Stored specimens will not have any patient identifiers. Thus, the probability of harm is judged to be very low and not greater than the normal experience of adults hospitalized with ARDS, pneumonia, or sepsis. Genetic research that produces data that could result in identification of the patient will not be pursued with biospecimens collected under alteration of informed consent without consent ever being obtained except for patients known to have died prior to the 3-month study time point.

11.2 Alteration of Informed Consent

11.2.1 Approach to informed consent for this study

This protocol (APS Study Protocol B – alteration protocol) describes study procedures that will be completed by patients participating in the study through an alteration of informed consent procedure and without written informed consent for study participation. This protocol will only govern study conduct for patients participating under alteration of informed consent.

A companion protocol (APS Study Protocol A – full protocol) governs study conduct for patients participating with written informed consent for study participation.

11.2.2 Description of and Rationale for two study protocols (Protocol A and Protocol B)

A key objective of this study is to rigorously phenotype ARDS, pneumonia, and sepsis, among severely and critically ill patients as early as possible after onset of these diseases. To achieve this objective, patients must be enrolled as early as possible in their course of illness. Early biospecimens are crucial for the objectives of the APS Consortium. Up to 75% of patients in the ICU experience delirium or altered mental status prohibiting their ability to provide informed consent.[10] Frequently, LARs/surrogates for critically ill adults are not available to provide written informed consent for research participation in a timely fashion. For example, prior work has shown that at a publicly funded hospital, 18% of eligible patients for ARDS clinical trials were not enrolled due to the patient not having capacity for consent and no LAR/surrogate being available.[11]

We have an option for participants to enter the study with alteration of informed consent for a subset of study procedures that involve minimal incremental risk above ongoing clinical care, because obtaining written informed consent at the time of enrollment would be impracticable in a significant subset of the population eligible for the study, and conducting the study without that subset would result in detrimental selection bias. Requiring written informed consent prior to study enrollment would compromise the integrity of the study by biasing the enrolled sample toward a less severely ill population (those who can consent for themselves). For example, in the Etiology of Pneumonia in the Community (EPIC) Study, eligible patients not enrolled were twice as likely to receive invasive mechanical ventilation compared to eligible patients who were enrolled.[12] Furthermore, requiring informed consent prior to enrollment could result in systemic exclusion of patients from minoritized groups. For example, in an ARDS Network trial that enrolled patients with ARDS, non-enrollment due to lack of an available LAR/surrogate was 18-times more likely at a publicly-funded hospital compared to a nearby academic medical center.[11]

When a study team identifies a patient as eligible for the study, if the patient can consent for research, or, in the case of the patient not having capacity for consent, if an LAR/surrogate is available, the study team will pursue informed consent for research participation before initiation of study procedures. If consent is obtained, study conduct will be governed by Study Protocol A (separate document).

Alternatively, when a study team identifies a patient as potentially eligible for the study, if the patient lacks capacity for consent and no LAR/surrogate is available, the patient may enter the study under Study Protocol B described in this document using an alteration of informed consent. This protocol includes only minimal risk procedures. The minimal risk study procedures in Protocol B correspond to identical study procedures in Protocol A. Protocol B contains a subset of study procedures from Protocol A that are minimal risk. Protocol B has no informed consent document.

Participants who enter the study using the alteration of informed consent protocol (Protocol B) will be iteratively approached for consent; if and when informed consent for participation in the APS Study is obtained, the participant will be moved from Protocol B to Protocol A (Figure 1). Greater than minimal risk procedures may be completed after informed consent is obtained among participants who started study participation under alteration of informed consent procedures. Patients who move from Protocol B to Protocol A will seamlessly continue on the APS Study schedule of events and maintain the same "study day" structure initiated at study entry. Study days continue through the transition from Protocol B to Protocol A; that is, if a patient provides informed consent on Day 4, study procedures completed on Protocol B for Day 0 through Day 3 will remain unchanged and Study Day 4 procedures will pick up on Protocol A.

For participants who enter the study with alteration of informed consent, study team members will attempt to obtain informed consent while the patient is in the hospital through Study Day 14 and at the 3-month time point.

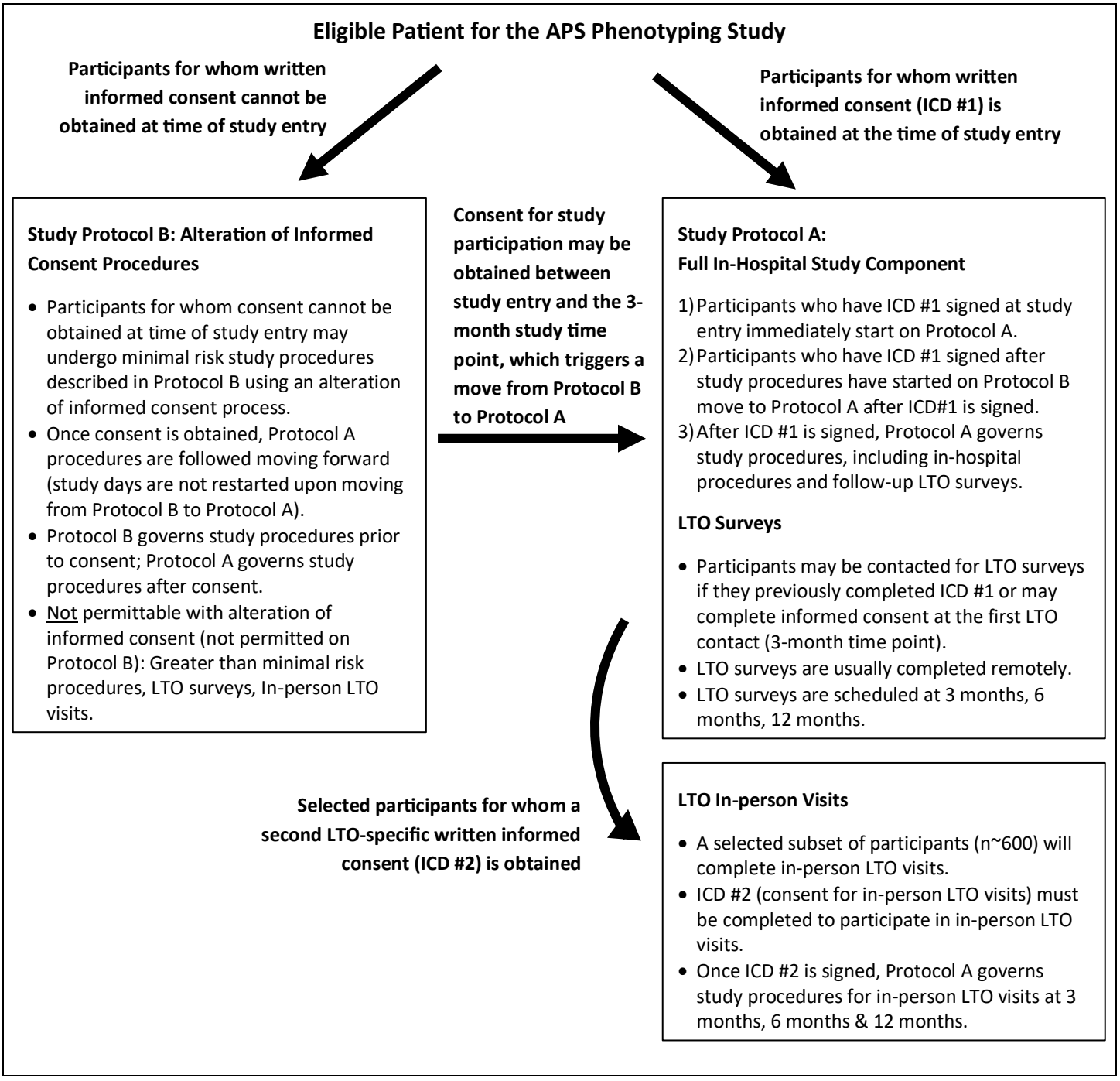
Data and biospecimens collected under Protocol A and Protocol B will be pooled for storage and analysis.

An approach of using two protocols to enroll participants – one that governs consented patients (Protocol A) and one that governs patients participating under alteration of informed consent (Protocol B) – is being utilized to minimize selection bias that would occur if only patients who were able to immediately provide written informed consent were enrolled. Outlining minimal risk procedures from the APS Study schedule of events in a separate protocol (Protocol B) enables participants without consent to begin minimal risk study procedures using an alteration of informed consent process. Meanwhile, participants with consent completed may engage in all study procedures, including both minimal risk procedures and greater than minimal risk procedures. Completion of greater than minimal risk procedures enables more rigorous scientific evaluation.

Goals of the study team include:

- Early enrollment of a population that represents the patient population of those suffering from ARDS, pneumonia, and sepsis, including those who are critically ill and often unable to rapidly consent for research.
- Obtain informed consent for study participation prior to initiation of study procedures for as many participants as possible.
- For participants who enter the study with alteration of informed consent, obtain subsequent written informed consent as soon as possible.

Figure 1. Flow diagram of informed consent procedures.



11.2.3 Alteration of informed consent process

When a patient does not possess medical decision-making capacity for consent, and an LAR/surrogate is not available for informed consent discussions despite good faith efforts to reach an LAR/surrogate, written informed consent is considered impracticable and the study team may enroll the patient using an alteration of informed consent approach.

To enter a participant into the study without written informed consent for study participation using the alteration of informed consent process, the study team must complete each of the following before study procedures begin:

i. Confirm the patient lacks decision making capacity to consent for study participation. This assessment is completed by a study team member trained in good clinical practice for the conduct of clinical research who is in direct contact with the patient. If the patient cannot meaningfully engage with the study team member (such as, a state of intubation, chemical sedation, and/or not responsive to verbal stimuli), the study team member may consider the patient to lack decision making capacity for consent. If the patient can meaningfully engage with the study team member, the study team member will explain the APS study to the patient and review the informed consent document with the patient. After this explanation, if the patient cannot describe the basic elements of the study, including risks and benefits of study participation, the study team member may consider the patient as not possessing decision making capacity for consent. The study team member will document the process and outcome of capacity assessment in the APS Study Electronic Data Capture instrument.

ii. Confirm no LAR/ surrogate is available to discuss consent for study participation. The study team will make a good faith effort to identify an LAR/surrogate, including at a minimum:

    a. searching for family or other people accompanying the patient in the hospital;
    b. calling phone numbers for the patient, patient's family, and patient's decision makers listed in the medical record;
    c. asking the clinical care team for information on the whereabouts of the patient's family and/or other decision makers.

iii. Confirm with the clinical care team that they believe participation in the study is not in opposition of the patient's best interests.

iv. Confirm that study team will continue to seek consent for study participation from the patient or an LAR/surrogate iteratively while the patient is in the hospital through Study Day 14, and if needed, at 3-months (typically via telephone).

v. Place a participant notification document at the patient's bedside. The participant notification document states that the patient was entered into a research study, provides a description of the study in lay language, states that the research team would like to talk about the study with family and/or medical decision makers for the patient, and provide contact information for the study team. The goals of the participant notification document are to immediately make information about the study available to people who visit the patient in the hospital and facilitate communication between the patient's family/decision maker and the study team as soon as possible. The informed consent document for Protocol A (ICD #1) will be appended to the participant notification document.

Once the steps above have been completed, the study team should document completion of each step in the APS Study Electronic Data Capture instrument. Thereafter, the study team may begin study procedures described in APS Study Protocol B.

11.2.4 Informed consent after study initiation with alteration of informed consent

The study team will assess the patient for capacity to provide consent for study participation and, if the patient does not possess capacity, search for an LAR/surrogate on at least 4 calendar days per week while the patient is in the hospital through Study Day 14. The study team will consult with the clinical team to identify any individuals who are making medical decisions for the patient during this time period and will attempt to contact these individuals. If consent is not obtained prior to the 3-month study time point for telephone contact (Study Day 85 through Study Day 135), the study team will attempt to obtain consent via telephone contact at that time. The study team will document these efforts to obtain informed consent in the study electronic data capture instrument.

The possible outcomes of the process for seeking informed consent after study entry and the implications of each outcome are detailed below and in Figure 2.

i. Category 1: Participant is enrolled with alteration of informed consent and later has written informed consent for study participation completed (either by the participant or an LAR/surrogate).

    Action for Category 1: Participant may complete minimal risk procedures described in Protocol B before consent is obtained. At the time of written informed consent, the participation moves from Protocol B to Protocol A. After informed consent is obtained, the participant may complete the study procedures described in Protocol A, including both minimal risk study procedures and greater than minimal risk study procedures. The study days remain continuous during the transfer from Protocol B to Protocol A, meaning that study days do not start over at Day 0 upon conversion from Protocol B to Protocol A, but rather Day 0 remains the same after conversion and Protocol A picks up on the Study Day on which consent was obtained. For example, if consent is obtained on Study Day 3, only minimal risk procedures may be done for Study Days 0, 1, and 2; then after consent is completed on Day 3, greater than minimal risk procedures may start on Day 3 for study procedures scheduled for Day 3 and later.

ii. Category 2: Participant is enrolled with alteration of informed consent and later the patient or LAR/surrogate is available for a decision about consent and declines full study participation moving forward but agrees to use of data and biospecimens already collected.

    Action for Category 2: Study procedures that involve direct contact between the study team and participant will cease. Medical record data collection will continue. Collected data and biospecimens will be retained in the study and available for use in the future.

iii. Category 3: Participant is enrolled with alteration of informed consent and later the patient or LAR/surrogate is available for a decision about consent and declines study participation moving forward and also declines use of data and biospecimens already collected.

Action for Category 3: All study procedures will cease. Data with information and biospecimens stored at the enrolling site and coordinating center will be destroyed. This will be considered a study withdrawal. A record of a patient enrolling and then withdrawing will be maintained. The study team will attempt to collect the reason for withdrawal and record it in the APS Electronic Data Capture instrument. The study team will not attempt to contact the participant after the 3-month study window. If a participant contacts the study team after the 3-month study window to withdraw from the study, the study team will honor that request for withdrawal. If the participant withdraws from the study long after enrollment, some data and biospecimens may have already been used. In that case, deidentified data and biospecimens that have been transferred to NIH repositories or to laboratories for analysis may not be able to be destroyed. Completed works, such as manuscripts, that used the participant's data and/or biospecimens will not be revised or retracted and data to support those works will be retained.

iv. Category 4: Participant is enrolled with alteration of informed consent and informed consent is never obtained nor declined (the study team never discussed consent for study participation with the patient at a time when the patient had capacity or with an LAR/surrogate).

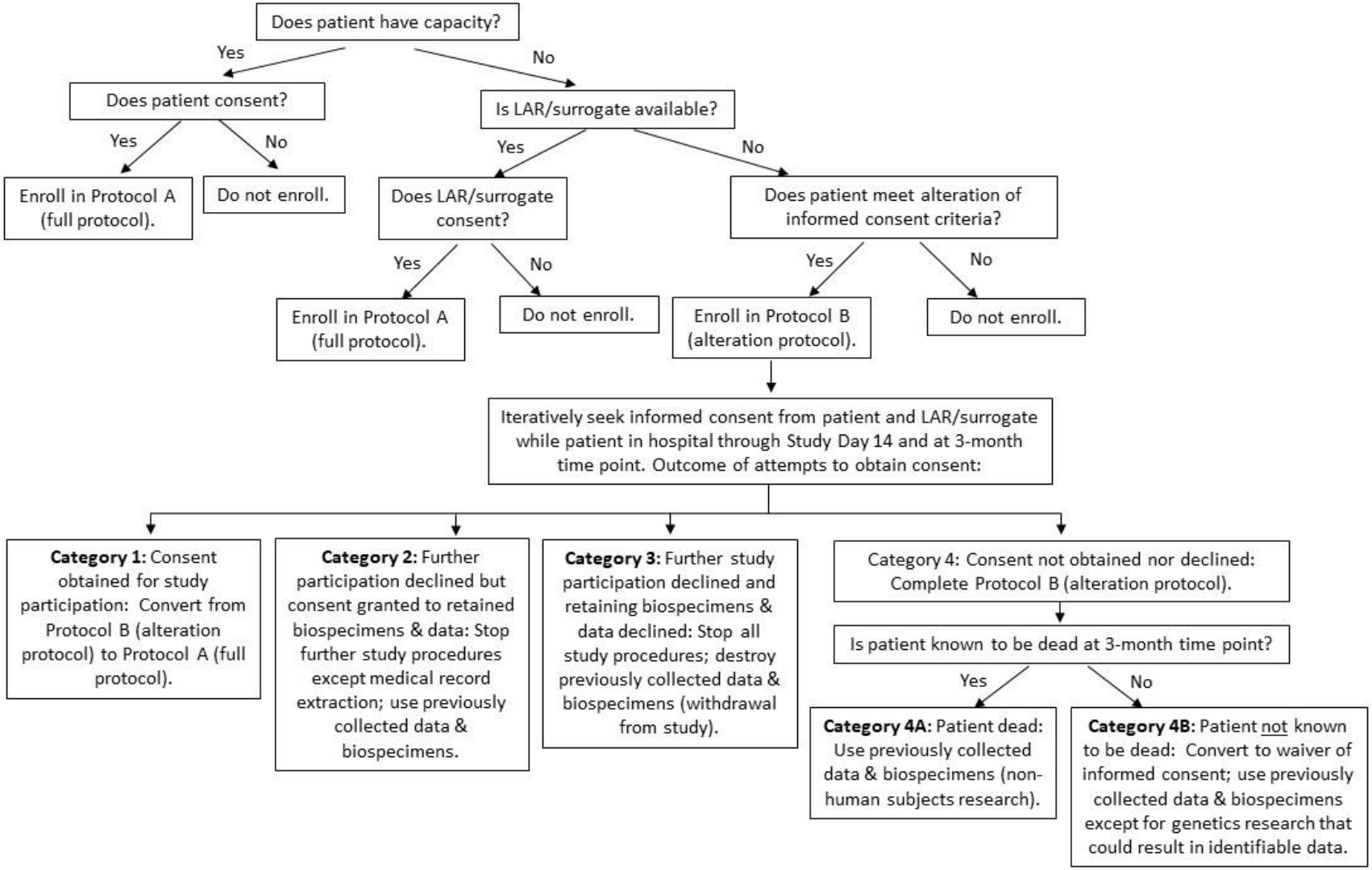
a. Category 4A: Consent was never obtained and the patient is known to be dead at or before the 3-month study time point for telephone contact (Study Day 85 through Study Day 135). The patient can be confirmed to be dead through several mechanisms, including but not limited to: death in the hospital, family member reports patient death at the 3-month telephone call, obituary for the patient identified.

Action for Category 4A: Participant completed Protocol B. At the time of death, use of data and biospecimens previously collected moves to a non-human subjects paradigm. Previously collected data and biospecimens may be used for future research under a non-human subjects paradigm.

b. Category 4B: Consent was never obtained and the patient is not known to be dead through the 3-month study time point for telephone contact (through Study Day 135). This scenario applies to participants who participated in the study under alteration of informed consent, never had informed consent obtained, and are either known to be alive at Study Day 135 or vital status is unknown at Study Day 135.

Action for Category 4B: Participant completed Protocol B. At Study Day 135, after consent has been shown to be impracticable by consent not being obtained despite a good faith effort to obtain consent while the patient was in the hospital and via telephone calls during the 3-month study window, the patient's participation converts to a waiver of informed consent paradigm. Only minimal risk study procedures will have been completed. Previously collected data and biospecimens may be used for future research under a waiver of informed consent paradigm. Genetic research that produces data that could result in identification of the patient will not be pursued with biospecimens collected from participants in this category.

Figure 2. Approach to informed consent and alteration of informed consent after a patient has been confirmed as eligible for the study.



11.3 Human subjects considerations for data and biospecimen banking and sharing

11.3.1 Storage of data and biospecimens

Data collected as part of the Consortium-wide study, including those captured from the EHR and other hospital databases, will be transferred into the study database via standardized electronic case report forms (eCRFs), which will reside in a centralized database located on secure servers. Study data will be entered and accessed via a secure, password-protected REDCap database website wherein all web-based information is encrypted. REDCap was developed specifically around HIPAA Security guidelines and is recommended by both the Vanderbilt University Privacy Office and Institutional Review Board. REDCap is available to all sites participating in the APS Consortium.

Data transferred to the APS Coordinating Center will include dates (for example, hospital admission date, and date of birth) and contact information to facilitate post-hospital follow-up visits. Biospecimens will be labeled with a study identification number without patient name, medical record number, or date of birth Access to personal health information in study databases will be limited to only those individuals requiring that level of access.

Study data and biospecimens will be stored for an indefinite period of time for future use. Deidentified data and biospecimens will be shared with researchers outside the APS Consortium. For long-term storage of data, personal identifiers will be removed once quality assurance has been confirmed and prior to data lock. All research records will be accessible for inspection by authorized representatives of the IRB, federal regulatory agency representatives, and NIH representatives.

11.3.2 Sharing data and biospecimens

The APS Consortium will develop data management and sharing plans consistent with NIH policies (https://sharing.nih.gov/).

APS Consortium investigators will be permitted to access and use data and biospecimens for the purpose of achieving the Consortium-wide and center-specific project aims directly from the Consortium Coordinating Center. Consortium-wide biospecimens and data will be sent to the central biorepository and study database housed at the Consortium Coordinating Center. Investigators seeking to perform approved ancillary studies with data and/or biospecimens collected by the APS Consortium may request data and biospecimens from the Consortium Coordinating Center before data and biospecimens are deposited in BioData Catalyst and BioLINCC.

Ultimately, the Consortium Coordinating Center will deposit de-identified data and biospecimens in BioData Catalyst and BioLINCC. Once data and biospecimens reach BioData Catalyst and BioLINCC, they will be available to investigators through the governance of BioData Catalyst and BioLINCC without involvement of the Consortium Coordinating Center.

11.3.4 Co-enrollment with other studies

The APS Consortium steering committee, OSMB, and NHLBI will agree on co-enrollment procedures before participants in the APS study are co-enrolled with other studies. Principles for co-enrollment will include the following:

- Co-enrollment should not affect the scientific goals of the APS Consortium. Co-enrollment will not be permitted if it compromises the scientific integrity and/or statistical power of APS Consortium studies.
- Co-enrollment will be compliant with NIH and NHLBI guidelines and policies.
- Co-enrollment will only be allowed when study procedures for the APS Consortium studies can be achieved. Co-enrollment in the APS Consortium will not be permitted when study procedures in a co-enrolled study would prevent completion of data or biospecimen collection for the APS Consortium study.
- Safe blood collection procedures for critically ill patients will be followed as detailed by the PETAL Network Investigators.[13]

12. Adverse Events and Safety Monitoring

The procedures for conducting safety monitoring and reporting adverse events are identical between APS Study Protocol A (full protocol) and APS Study Protocol B (alteration protocol).

12.1 Overview of Safety Monitoring

In this observational study that uses routine techniques for data and biospecimen collection, substantial numbers of serious, study-related adverse events are not anticipated. The study will not be overseen by the US Food and Drug Administration (FDA). Safety monitoring will be performed by the investigators, the study's single IRB at Vanderbilt University Medical Center, and an NHLBI-appointed Observational Safety Monitoring Board (OSMB).

12.2 Adverse Events

12.2.1 Paradigm for collecting Adverse Events

In this study, investigators will collect and report adverse events (AEs) that are classified as serious and related to study procedures, those prespecified as adverse events of special interest (AESIs), and those that potentially change the risk: benefit balance for patient participation (Unanticipated Problem (UP)). AEs that meet at least one of the following three criteria will be collected in this study:

1) both serious and study related;
2) AESI;
3) UP.

AEs that do not meet any of these criteria will not be collected.

Events that meet criteria for an AE in the population enrolled in this study will be numerous due to the severe medical conditions these patients have. The proportion of AEs experienced by the study population that are related to study procedures is anticipated to be extremely small. Thus, the paradigm of AE collection and reporting in this study was designed to capture all the events that could potentially represent a safety concern for the study while avoiding overly burdensome AE monitoring for participants, study teams, the IRB, and OSMB.

12.2.2 Definitions for Adverse Events

(i) Adverse Event

An AE is defined as any untoward medical occurrence.

(ii) Serious Adverse Event (SAE)

A serious AE (SAE) is an untoward medical occurrence that directly causes at least one of the following in the judgement of the study team:

- Death
- Life-threatening condition that places the participant at immediate risk of death
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions or a congenital anomaly/birth defect.
- An important medical event not meeting the criteria for one of the outcomes above but, based on medical judgment, jeopardized participant safety or required medical or surgical intervention to prevent one of the outcomes listed in this definition.

(iii) Relatedness of SAEs

SAEs will be evaluated for relatedness to study procedures using the definitions below:

- Definitely Related: The adverse event meets all three of the following criteria: (a) a temporal sequence from study procedure to the adverse event suggests relatedness, (b) the event cannot be explained by the known characteristics of the participant's clinical state or therapies, and (c) evaluation of the participant's clinical state indicates to the study team the experience is definitely related to study procedures.

- Possibly Related: In the study team's opinion, the adverse event has a reasonable possibility of being related to study procedures but one or more of the above criteria for "Definitely Related" are not met.

- Probably Not Related: The adverse event occurred at a time when it could have been caused by study procedures but, in the opinion of the study team, can reasonably be explained by the known characteristics of the participant's clinical state or therapies.

- Definitely Not Related: The adverse event was definitely produced by the participant's clinical state or therapies and not by the study procedures.

- Uncertain Relationship: The adverse event does not meet any of the criteria outlined above and the study team cannot ascertain enough information to classify relatedness of the event.

For the purposes of this study, an adverse event is considered related to study procedures if there is a "reasonable possibility" of a causal relationship between a study procedure and the adverse event or the relationship cannot be determined; this includes events that are classified as definitely related, possibly related, or of uncertain relationship.

(iv) Adverse events of special interest (AESIs)

An adverse event of special interest (AESI) is defined as a pre-specified event of scientific or medical concern that has the potential of being related to study procedures and is important to understand regardless of investigator classifications. There are no AESI for this protocol (Protocol B).

(v) Unanticipated Problem (UP)

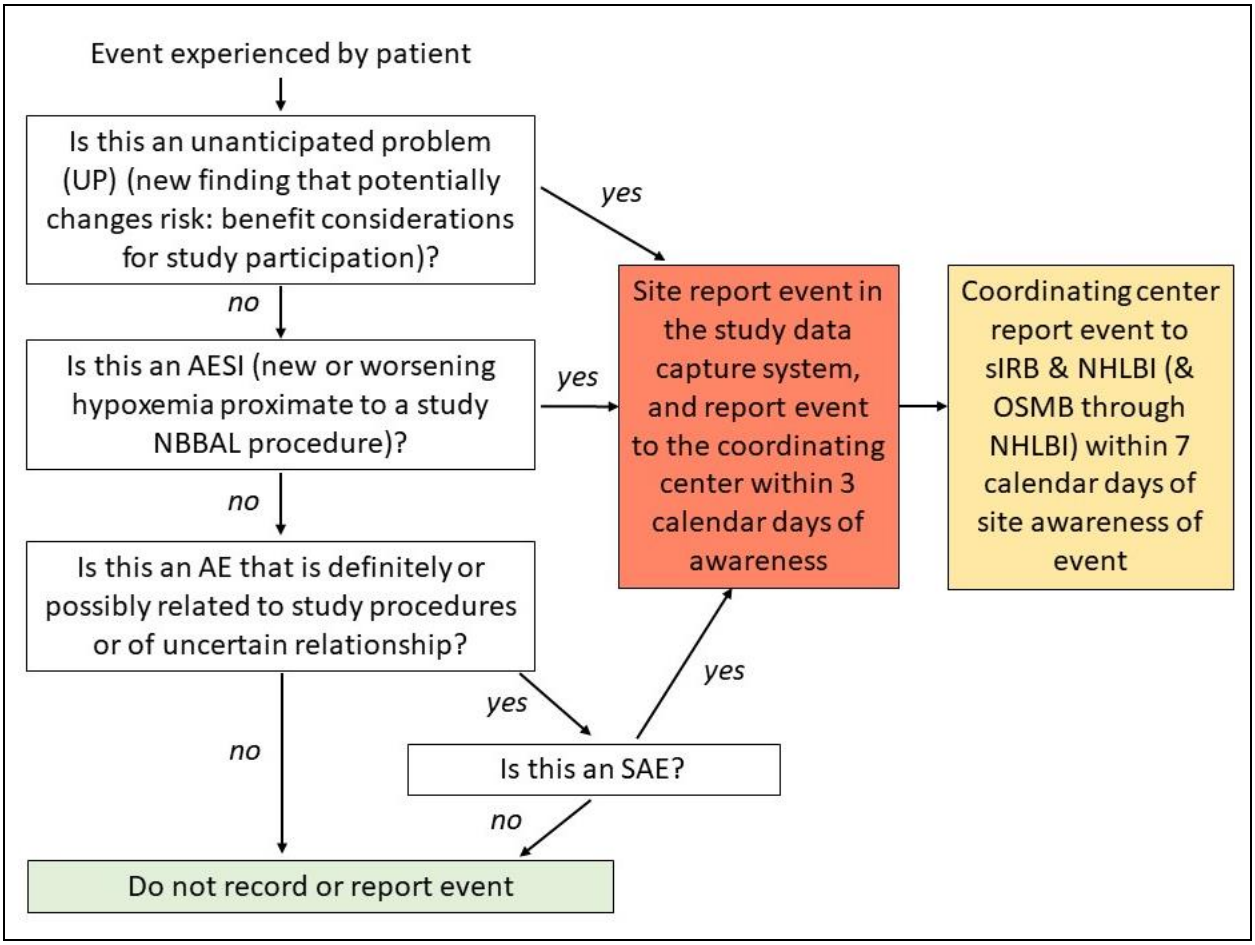
An unanticipated problem is a finding discovered during the conduct of the study that suggests participation in the study may have more risk than was anticipated at the time of study initiation. UPs have the potential to change the risk: benefit balance of the study compared to what was known at the time of study launch.

12.2.3 Reporting Adverse Events

AEs that meet criteria for reporting should be entered into the study's electronic data collection system within 3 calendar days of the study team becoming aware of the AE. Reporting an AE will include a clinical narrative explaining the context of the AE and rationale for the investigator's classification of the event as serious and related, an AESI, or an UP. The study team should also alert the Consortium Coordinating Center for reported events. The coordinating center will report the AE to the sIRB and OSMB within 4 calendar days of receiving the report of an AE (thus, within 7 calendar days of site awareness of the event). Reported events will be followed until resolution.

Figure 3 is a summary flow diagram to assist study teams with deciding which adverse events to report in this study.

Figure 3. Flow diagram to assist with decisions about AE recording and reporting.



12.3 Observational Study Monitoring Board (OSMB)

The OSMB will be comprised of experts in APS syndromes and fields relevant for this study. The OSMB is appointed by NHLBI. The principal role of the OSMB is to evaluate the safety and integrity of the study. Full details of the OSMB structure and function will be provided in an OSMB charter, which will be reviewed with the OSBM at its first meeting with the study team.

Prior to initiation of study enrollment, the OSMB will review the study protocol and informed consent documents. OSMB meetings will be scheduled regularly in accordance with the OSMB charter. Additionally, the NIH, OSMB, and investigators may call ad hoc OSMB meetings.

The OSMB will regularly monitor several aspects of the study, including the safety, enrollment rates, protocol compliance, cohort demographics and geographic distribution, and data quality and completeness.

Recommendations to end, modify, or continue aspects of the study will be communicated by the OSMB, through the OSMB executive secretary, to the Consortium Coordinating Center.

12.4 Institutional Review Boards (IRBs)

This is a multi-center cohort study for which a single IRB will be used for the ethical review of the proposed research per NIH policy (https://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-094.html). Vanderbilt University Medical Center will serve as the single IRB of record. Local context will be reviewed by local IRBs for each participating site.

This protocol (Protocol B) does not have an accompanying informed consent document; all patients participating in this protocol will be participating under alteration of informed consent.

Processes of obtaining informed consent and use of alteration of informed consent should be reviewed during local context review to ensure study procedures are consistent with local laws and standards.

13. References

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