UM IRB No.: 20211211 **NCT05545735**
Protocol Date: November 14, 2023
Principal Investigator: Jonathan P. Meizoso, M.D., M.S.P.H.
Study Title: The Duration of Antibiotic Therapy for Early VAP (DATE) Trial

Cover Page for Protocol

Sponsor name:	None
ClinicalTrials.gov ID#	NCT05545735
University of Miami IRB#	20211211
Brief title:	The Duration of Antibiotic Therapy for Early VAP (DATE) Trial
Official title of study:	The Duration of Antibiotic Therapy for Early VAP (DATE) Trial: A Surgical Infection Society Multicenter Randomized Clinical Trial of 4 vs. 7 Days of Definitive Antibiotic Therapy for Early Ventilator-Associated Pneumonia in the Surgical Intensive Care Unit
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I. Protocol Title

The Duration of Antibiotic Therapy for Early VAP (DATE) Trial: A Surgical Infection Society Multicenter Randomized Clinical Trial of 4 vs. 7 Days of Definitive Antibiotic Therapy for Early Ventilator-Associated Pneumonia in the Surgical Intensive Care Unit

II. IRB Review History

Not applicable

III. Hypothesis and Specific Aims

The **hypothesis** of this randomized controlled trial (RCT) is that 4 days of antibiotic therapy, as compared to 7 days, is non-inferior regarding the primary outcome of ventilator-associated pneumonia (VAP) recurrence and superior in decreased antibiotic exposure among surgical intensive care unit (ICU) patients with early (within 2 – 7 days of intubation via endotracheal or tracheostomy tube) VAP. Our **specific aim** is to determine whether 4 days of antibiotic therapy is non-inferior to 7 days of antibiotic therapy for the treatment of early VAP with regards to recurrence and superior with regards to antibiotic exposure time.

IV. Background

The prevalence of multidrug resistant (MDR) pathogens in ICUs worldwide has reached epidemic proportions (1, 2). In some cases, the choice of potential therapy is limited or even nonexistent (3). Antibiotic prescription, through selection pressure, represents the main mechanism by which resistance emerges (4). Limitations in the development of new antibiotics (5) underscores the importance of adherence to the principles of antibiotic stewardship (6).

VAP is the most common serious infection in mechanically ventilated critically ill patients (7). Approximately one half of antibiotic prescription in the ICU is related to VAP, including prophylactic, empiric, and definitive therapy (8). The development of evidence-based

algorithms for the rational use of antibiotics in the management of patients with both suspected and confirmed VAP is pivotal to decreasing the emergence of MDR pathogens.

Shortening the duration of antimicrobial therapy for VAP represents one strategy to curtail the emergence of MDR pathogens. Although prior guidelines recommended a treatment course of 8 – 14 days (9), newer guidelines recommend a treatment course of 7 days (10, 11) and data show that both clinical and microbiological resolution of infection typically occur much sooner (12, 13). In one study of ICU patients ventilated for > 5 days who developed VAP, 8 days of antimicrobial therapy was equally as effective as 15 days, provided VAP was not caused by a non-lactose fermenting gram negative bacillus (14). Favorable results following courses of therapy < 8 days have been reported, albeit in small uncontrolled series (15).

One subset of patients for whom a decreased duration of antimicrobial therapy may be particularly effective is those who develop VAP ≤ 7 days after intubation (i.e., early VAP). Early VAP comprises the majority of cases of pneumonia diagnosed in the ICU (16). Furthermore, as compared to patients who develop late VAP, patients who develop early VAP are more likely to be infected with community-acquired pathogens sensitive to narrow spectrum antibiotics (16).

Finally, nearly all cases of early VAP caused by sensitive pathogens demonstrate microbiological resolution after relatively short (i.e., 3 – 5 day) courses of therapy (12). Therefore, we have designed this multicenter randomized controlled trial in partnership with the Surgical Infection Society to determine whether a shorter course of antibiotic therapy (i.e., 4 days) is non-inferior as longer therapy (i.e., 7 days) for the treatment of early VAP in critically ill surgical patients regarding recurrences and superior regarding antibiotic exposure.

V. Inclusion and Exclusion Criteria

A) Inclusion Criteria

- **a.** Surgical patient
- **b.** Early VAP, defined as VAP occurring within 2 – 7 days of intubation (via endotracheal or tracheostomy tube) (9). VAP will be defined according to local institutional protocol.
- **c.** Hospital length of stay (LOS) ≤ 10 days at the time of VAP diagnosis.
- **d.** Patients are willing to provide informed consent or their Legally Authorized Representative (LAR) is willing to provide informed consent on their behalf when the patient is unable (i.e., cognitively impaired from sedation on a ventilator).

B) Exclusion Criteria

- **a.** Age < 18 years
- **b.** Prior episode of VAP for the index admission
- **c.** VAP caused by any of the following pathogens:
  - **i.** Methicillin-resistant *Staphylococcus aureus* (MRSA)
  - **ii.** Vancomycin-intermediate *Staphylococcus aureus* (VISA)
  - **iii.** *Pseudomonas aeruginosa*
  - **iv.** Vancomycin-resistant *Enterococcus* (VRE)
  - **v.** *Acinetobacter baumanii*
  - **vi.** *Stenotrophomonas maltophilia*
  - **vii.** Carbapenem-resistant *Enterobacteriaceae* (CRE)
  - **viii.** Extended-spectrum beta lactamase-producing gram-negative bacilli
- **d.** Causative pathogen not sensitive to choice of initial empiric antibiotic
- **e.** Antibiotic therapy for ≥ 5 of the last 10 days preceding VAP diagnosis
- **f.** Septic shock, defined as evidence of tissue hypoperfusion after adequate volume expansion, due to infection, and requiring ≥ 1 vasopressor (17)

g. Current or recent (within 30 days) use of immunosuppressive medications

h. LOS $\geq$ 72 hours at a transferring facility

i. Pregnancy or lactation

j. Legal arrest or incarceration

k. Moribund state in which death is imminent

l. ECMO (Extracorporeal membrane oxygenation)

m. Extubation prior to randomization

VI. Number of Subjects

The total required sample size for this study is **458 patients**. Assumptions for the power analysis include non-inferiority for VAP recurrence and superiority for antibiotic-free days in the intervention group, 3 planned analyses of the data with O'Brien-Fleming spending function with binding futility boundaries, 25% recurrence rate in the control group (14), and 6 enrolling centers with an average cluster size of 10. To detect a 10% difference in outcomes between groups with 80% power and assuming a 10% dropout rate, a total sample size of 458 patients is required for this study. Sample size will be recalculated at each interim analysis with better estimates based on accrued patients. The planned analyses will take place after enrollment of 150, 300, and all patients.

VII. Study-Wide Recruitment Methods

This is a multicenter randomized controlled trial. We have partnered with the Surgical Infection Society to aid in recruitment of interested centers for participation in the study. The recruitment methods for individual subjects to participate in the study will be uniform across all centers. A member of the research team at each center will screen all patients in their respective surgical ICUs by reviewing the medical record of each patient in the ICU for eligibility based on the inclusion and exclusion criteria listed in *Section V* (above). Screening will occur daily during the study period. We will be requesting a waiver of the requirement for written authorization

from patients to access their health records due to the nature of the study. Please see further documentation in *Section XXXII* (below).

VIII. Study Timeline

Each individual patient enrolled in the study will be followed for 30 days or until hospital discharge, whichever occurs first. We will also review patient charts at hospital discharge to determine overall hospital length of stay and overall mortality, in addition to 30-day outcomes. We expect all subjects to be enrolled within the first 2 years of study across all centers, with full data analysis completed at 3 months after study completion.

IX. Study Endpoints

A) Primary Outcomes

- **a.** VAP recurrence within 30 days
  - **i.** VAP recurrence = VAP occurring 2 – 14 days following completion of initial therapy
- **b.** Antibiotic-free days within 30 days

B) Secondary Outcomes

- **a.** Antibiotic exposure
  - **i.** Days of antibiotics
  - **ii.** Antibiotic days (defined as the product of days of antibiotics and number of antibiotics per day)
- **b.** Clinical improvement, measured using daily $CPIS_{clinical}$ score while enrolled in the study
- **c.** VAP relapse = recurrent VAP caused by initial pathogen (if culture data available), occurring 2 – 14 days following completion of initial therapy
- **d.** 30-day Ventilator-free days

e. Empyema

f. Need for tracheostomy

g. Non-pulmonary infections

h. 30-day ICU-free days

i. Hospital LOS

j. In-hospital Mortality

X. Procedures Involved

This is a multicenter, randomized, clinical trial. The trial will be reported in accordance with the recommendations of the CONSORT statement (18). IRB approval will be obtained. All subjects, or their legally authorized representatives, will provide written consent for study participation. The trial is registered with the US National Institutes of Health (ClinicalTrials.gov Identifier #NCT05545735).

Screening will occur daily by study personnel. Eligible patients will be approached as soon as possible after inclusion criteria are met (i.e., 1 – 3 days prior to randomization). Randomization will occur using a computer-generated block pattern no later than the end of the fourth day of appropriate antibiotic therapy. Randomization will occur at the hospital level in blocks of 20.

Empiric antibiotic therapy will be instituted as soon as possible following diagnosis of suspected pneumonia by the clinical team. The default antibiotic will be based on the local institutional antibiogram and practice. Pre-existing treatment for a non-pulmonary infection with at least one antibiotic that has appropriate activity against the VAP pathogen may be substituted for the default antibiotic. Once sensitivity data become available, therapy may be de-escalated to a more narrow-spectrum agent, as indicated.

The default duration of antibiotic therapy will be determined by study group assignment; the treatment team will be asked to adhere to study group assignment whenever possible. However, the treatment team may choose to extend the duration of antibiotic therapy based on

clinical circumstances, such as deterioration in hemodynamic or respiratory status that is believed to be related to incompletely treated VAP, or continued treatment of a non-pulmonary infection. The treatment team may also decide to extend the duration of antibiotic therapy based on the results of procalcitonin measurements, if obtained. Clinical decisions will take precedence over study group assignment.

Patients will be followed for 30 days or until hospital discharge, whichever occurs first. Please see the attached data collection tool for detailed information.

Adverse event monitoring will occur daily at each individual institution. Any adverse event will trigger notification to the site PI per local IRB regulations. The safety of the study will be monitored by an independent Data Safety Monitoring Board (DSMB). The DSMB has been formed by the Surgical Infection Society and will consist of Drs. Sebastian Schubl, Rondi Gelbard, and Christopher Guidry. The committee will meet after each planned interim analysis (see *Sections VI* and *XII*) and submit a written report to the overall study PI (Dr. Meizoso), who will submit to the IRB (see attached "*DSMB Charter*").

Disease Related Adverse Events: It is recognized that this patient population who require critical care support will experience a number of common aberrations in laboratory values, signs, and symptoms due to the severity of the underlying disease and the impact of standard therapies. These will not necessarily constitute an AE unless they:

- require significant intervention,
- lead to discontinuation of study procedures,
- felt to be related to study procedures
- or are considered to be of concern, in the Investigator's clinical judgment.

Examples of the type of AEs that may be associated with the patient population are acute respiratory failure; respiratory distress; acute lung injury; acute respiratory distress syndrome (ARDS); acute renal failure; fever, bacteremia; sepsis, septic shock; hypotension; metabolic acidosis, pleural effusion; mineral or electrolyte imbalance. For purposes of this study, deaths

will be captured as clinical outcomes and do not need to be reported as SAEs unless felt related to study procedures.

XI. Data and Specimen Banking

There will be no specimen banking for this study.

XII. Data Management

All data will be collected on the attached case report form (CRF) and then input by study personnel at each individual site into the University of Miami REDCap electronic data management system. Each site PI will be responsible for keeping a secure file linking the patient medical record number (MRN) to their study ID in the event that additional information is required for study analysis, which will be destroyed at the conclusion of the study. All data will be entered into REDCap in a de-identified manner, using only the study ID, without including any personal identifying information. Data analysis will be performed by Angela Sauaia, MD, PhD. Dr. Sauaia is a tenured Professor of Surgery and Public Health at the University of Colorado Denver and the Colorado School of Public Health, where she is also the Associate Director of the NIH-funded T32 postdoctoral research fellowship in trauma surgery, and statistical consultant to the Ernest E. Moore Shock Trauma Center at Denver Health Medical Center. Additionally, she is the former Statistical Editor for the *Journal of Trauma and Acute Care Surgery*, with over 30 years' experience in injury-related research, particularly in critically ill and injured patients.

Three equally spaced analyses (two interim and one final) will be conducted for all outcomes, using the O'Brien-Fleming alpha spending function. Data analyses will be performed using SAS v9.4 (SAS Inc., Cary, NC). Randomization will occur at the hospital level in blocks of 20. Data will be analyzed using an intention-to-treat strategy (i.e., data of patients randomized to receive 4 days of antibiotic therapy will be analyzed as belonging to this group even if they receive longer courses) and a per-protocol strategy (i.e., crossovers and protocol violations

excluded). Data will be expressed as median (interquartile range) or frequency (%). Normality of continuous variables will be assessed by visual inspection of histograms. Differences in the means of continuous normally distributed variables will be assessed using Student's t-test or ANOVA. Differences in the medians of non-normally distributed continuous variables will be assessed using the Wilcoxon rank sum or Kruskal-Wallis tests. Proportions will be compared using the chi-squared or Fischer's exact test, as appropriate. Univariate analysis of categorical outcomes will be expressed as the relative risk with 95% confidence intervals, with standard errors adjusted for intra-center clustering. A generalized estimating equation or linear mixed model (with appropriate transformation of outcome variables to approximate normality, if needed) will be fit to address possible confounding if randomization fails to assure equitable distribution. Baseline variables associated with randomization status at the $p<0.25$ level by univariate analysis will be added to the model using a stepwise selection method. The overall contribution of the fitted model to predicting variability in the outcome of interest will be assessed using the likelihood ratio chi-squared test. The alpha error level is defined at 0.05, with statistical significance at $p < 0.05$. No adjustment for multiplicity of outcomes will be done as this is an exploratory (rather than confirmatory) trial, and all hypotheses are pre-planned. Adjustment for multiple comparisons in pre-planned hypotheses leads to more type II errors (19, 20).

XIII. Provisions to Monitor the Data to Ensure the Safety of Subjects

As mentioned previously (see *Section X*), a DSMB will be convened. The DSMB will meet after each planned interim analysis, review data collected across all sites, and submit a written report to the overall study PI, who will submit the report to the IRB. Data analysis will be performed by Dr. Sauaia, as mentioned above (see *Section XII*).

Data will be monitored daily at each site and any adverse events will be reported to the site PI per local IRB regulations. Efficacy and safety data will be collected on CRFs and inputted into REDCap by study personnel at each site. The study will be terminated early if there are

unacceptably high rates of adverse events or if there is a clear benefit noted in either study group, as deemed by the DSMB.

XIV. Withdrawal of Subjects

Subjects, or their legally authorized representatives, can withdrawal from the study at any time. If a subject wishes to withdraw from the study, we will request their permission to allow us to continue collecting data to use in the intention-to-treat analysis. As previously mentioned (see *Section X*), the clinical team may choose to continue antibiotic therapy despite the subject's study group allocation. Clinical decision-making will supersede any study procedures or protocols.

XV. Risks to Subjects

There is a risk that a default of 4 days of antibiotic therapy will be too short. In order to mitigate this risk, clinical endpoints will be followed daily during treatment. If any of these endpoints suggest inadequate therapy, the treatment team may choose to extend the duration of treatment. This decision will take precedence over study group assignment.

XVI. Potential Benefits to Subjects

The most significant potential direct benefit to subjects enrolled in this study is the possibility of limiting days of antibiotic exposure. Limiting the number of days receiving antibiotic therapy may decrease the subjects' individual risk of developing *Clostridium difficile* colitis, a common and potentially life-threatening consequence of antibiotic exposure. Similar multicenter randomized controlled trials aimed at limiting antibiotic days in patients with intra-abdominal infections have recently been published, with the University of Miami as a participating center, and have shown a benefit to shorter antimicrobial therapy, including less antibiotic days without increase in infectious complications (21).

XVII. Vulnerable Populations

Our research does not involve pregnant women, neonates, children, or prisoners. In potential subjects being mechanically ventilated and cognitively impaired, their LAR will be approached to provide informed consent.

XVIII. Multi-Site Research

This is a multicenter randomized controlled trial. The University of Miami will serve as the coordinating center for the study and Dr. Jonathan P. Meizoso, Assistant Professor of Surgery in the Divisions of Trauma and Surgical Critical Care, DeWitt Daughtry Family Department of Surgery, University of Miami Miller School of Medicine, will serve as the lead investigator. Ronald J. Manning, ARNP, MSPH, will serve as the study coordinator.

Prior to enrollment of the first study participant, we will coordinate a meeting of all site PIs and coordinators to review the study protocol and answer any questions. This meeting will occur via a virtual meeting platform (e.g., Zoom). During this meeting, we will ensure that all sites have the current protocol. We will also ensure that all appropriate safeguards are in place, including a location for CRFs to be stored in a locked office. Prior to this meeting, we will ensure that all sites have received IRB approval from their local IRB. We will plan to meet with all sites via virtual meeting platform from 1 – 4 times per month, as appropriate, at which time we will ensure study compliance, timely reporting of adverse events, and answer additional questions. Prior to the implementation of any study modification, we will contact all sites, ensure that the modification has been submitted to their local IRBs, and ensure that approval has been attained from their local IRBs. DSMB reports will be furnished to each site via either email or during one of these study meetings. Any problems with the study and closure of the study will also be reported as outlined above.

XIX. Community-Based Participatory Research

This study does not involve community-based participatory research.

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XX. Sharing of Results with Subjects

Results of the study will not be shared with individual subjects. The findings of the study will be presented at the Annual Scientific Meeting of the Surgical Infection Society and published in a peer-reviewed journal upon study completion.

XXI. Setting

Locally, patients will be recruited from the Surgical Intensive Care Unit at Jackson Memorial Hospital and/or the Trauma Intensive Care Unit at the Ryder Trauma Center. CRFs will be stored in the Trauma Research Office, located in the Ryder Trauma Center, Suite T-242. Security measures include a locked door to enter Suite T-242 and an additional locked door to enter the Trauma Research Office. Across all other sites, measures to ensure compliance and security of protected health information will be subject to the local IRB policies. Currently, sites that have expressed interest in participating in this multicenter study include:

Denver Health Medical Center (Denver, CO)
PI: Fredric Pieracci, MD, MPH
Texas Health Harris Methodist Hospital (Fort Worth, TX)
PI: Therese Duane, MD, MBA
MetroHealth (Cleveland, OH)
PI: Vanessa P. Ho, MD, MPH
Weill Cornell Medical Center (New York, NY)
PI: Philip S. Barie, MD, MBA

XXII. Resources Available

The University of Miami and overall study PI will be Jonathan P. Meizoso, MD, MSPH. Dr. Meizoso is Assistant Professor of Surgery in the Divisions of Trauma and Surgical Critical Care of the DeWitt Daughtry Family Department of Surgery at the University of Miami Miller

School of Medicine. Dr. Meizoso has extensive experience in clinical research with over 15 years of involvement in the design, conduct, implementation, analysis, and dissemination of studies involving trauma, surgical critical care, and burns. He has over 50 peer-reviewed publications in high-impact journals, including the *Journal of the American College of Surgeons*, *Journal of Trauma and Acute Care Surgery*, and *Surgical Infections*, with an h-index of 19 and over 800 citations of his published work. During residency, he completed a two-year postdoctoral research fellowship in trauma and surgical critical care, at which time he also obtained a Master of Science in Public Health degree to further his understanding and enhance his skills in study design, epidemiology, and biostatistics.

Dr. Nicholas Namias, Co-Investigator for this study, Chief of Trauma and Acute Care Surgery, and Vice Chair of the DeWitt Daughtry Family Department of Surgery at the University of Miami, also has extensive research experience of over 30 years. Additionally, he has experience in the management and conduct of multicenter randomized controlled trials, including the recent STOP-IT trial, which investigated the use of an abbreviated antibiotic course for patients with intra-abdominal infections, that was published in the *New England Journal of Medicine* (21).

Ronald J. Manning, ARNP, MSPH, will serve as the study coordinator. He is currently the Research Coordinator for the Divisions of Trauma, Surgical Critical Care, and Burns at the University of Miami Miller School of Medicine and has led the coordination efforts for numerous studies during his decades-long position.

Finally, the Trauma Research Office at the Ryder Trauma Center is composed of 4 general surgery residents who have taken two years off from residency in a dedicated postdoctoral research fellowship in trauma and surgical critical care investigation. Along with the PI and study coordinator, they lead the day-to-day efforts of the several voluntary and paid research assistants employed by our Office. All personnel are trained using the CITI Course for the Protection of Human Research Subjects and are current with all certifications, per IRB requirements.

XXIII. Prior Approvals

We will ensure all study sites have their local IRB approval prior to beginning the study. In addition, the study was presented to the Surgical Infection Society and they have decided to endorse the study as a Surgical Infection Society multicenter trial.

XXIV. Recruitment Methods

See *Section VII* (above).

XXV. Local Number of Subjects

Local enrollment of subjects will not exceed 458 patients, as this is the total number of subjects that will be accrued across all study sites.

XXVI. Confidentiality

All data will be collected on the attached case report form (CRF) and then input by study personnel at each individual site into the University of Miami REDCap electronic data management system. Each site PI will be responsible for keeping a secure file linking the patient medical record number (MRN) to their study ID in the event that additional information is required for study analysis, which will be destroyed at the conclusion of the study. Individual patient MRNs will not be entered into REDCap; the individual subjects will be identified using their study ID. Protected Health Information (PHI) that will be entered into REDCap include hospital admission and discharge dates, ICU admission and discharge dates, date of death (if applicable), and age. The dates entered into REDCap will be used to calculate ICU and hospital lengths of stay, however the exact dates will be removed from the report used for statistical analysis using the feature in REDCap to extract de-identified data only. Data analysis will be performed by Angela Sauaia, MD, PhD (see *Section XII*).

CRFs will be stored in the Trauma Research Office, located in the Ryder Trauma Center, Suite T-242. Security measures include a locked door to enter Suite T-242 and an additional locked door to enter the Trauma Research Office. Across all other sites, measures to ensure compliance and security of protected health information will be subject to the local IRB policies.

The de-identified data report will be used by Dr. Sauaia to perform statistical analyses. No elements of PHI will be included in the file for statistical analysis. The only information sent from our site to Dr. Sauaia for analysis will be what is contained in the de-identified report. Our data will not be shared with any other entity.

The de-identified data from the study will be maintained on the REDCap database for use for future secondary analyses using the trial data. Interested investigators may contact the PI with a request for the de-identified data and access may be granted if an appropriate study design is proposed.

XXVIa. Will the research collect protected health information or personally identifiable information from the EMR or from subjects at UHealth and/or JHS?

Yes

XXVIb. Check the box next to the correct statement below:

[ ] Research subjects will sign a HIPAA Authorization before the research will collect this data.

[X] Research subjects will not sign a HIPAA Authorization for this data collection and the research is requesting a waiver of HIPAA Authorization from the IRB.

XXVIc. How will the research store the data?

University of Miami REDCap

XXVId. Select one of the following:

[ ] The Principal Investigator (and/or Study Team members) will record (e.g., write down, abstract) data acquired in a manner that does not include any indirect or direct identifiers and the recorded data will not be linked to the individuals' identity.

[X] The Principal Investigator (and/or Study Team members) will record (e.g., write down, abstract) the data collected in a manner that does not include any direct identifiers of any subject. Instead, the Principal Investigator and/or Study Team members will assign a code (that is not derived in whole or in part from any direct or indirect identifiers of the individual) to each study subject and link the code to the study subject's identity. The link to each subject's identity and/or other identifiable information will be maintained on a document separate from the research data.

XXVII. Biospecimens

Not applicable. No biospecimens will be collected.

XXVIII. Provisions to Protect the Privacy Interests of Subjects

The research team will access patient health records via daily screening of the electronic health record, as described above. The only contact with the patient and/or legally authorized representative will be to obtain consent for participation in the study. No additional screenings or procedures will be performed as a result of this study, thereby protecting the privacy interests of the subjects.

XXIX. Compensation for Research-related Injury

There is no compensation for research-related injury. We do not anticipate any injury to result directly as a consequence of the proposed research study.

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XXX. Economic Burden to Subjects

Subjects will not be responsible for any additional costs as a result of participation in this research study. Rather, they may experience decreased costs as it relates to less days of antibiotic therapy.

XXXI. Consent Process

We will be obtaining consent for participation in this study as outlined by the SOP: Informed Consent Process for Research (HRP-090). Consent will take place at the patient bedside and/or via telephonic witnessed consent. In the majority of cases, patients will be on the ventilator and sedated, thus not able to participate in the consent process. Therefore, their legally authorized representative will be asked to provide consent. This is the only practical approach as, by nature of the disease process being studied, the patients will generally be unable to participate in the informed consent process themselves. Ongoing consent will be implied unless the patient or their representative requests to be withdrawn from the study. If the patient becomes liberated from the ventilator during the study, and the treating clinical team determines the subject has the capacity for consent, they will then have the ability to re-consent or withdraw consent. Non-English-speaking patients will be eligible to participate as well, and the informed consent process will be conducted using a certified interpreter as provided by the hospital.

REMOTE CONSENTING for a participant's LAR that is unavailable for in-person consenting may include the following:

1. Send a copy of the consent document to the participant's LAR before the discussion.
2. Arrange a video conference meeting or a conference call (if you cannot use Zoom) that includes:
    a. Person obtaining consent

   b. Participant's LAR
   c. Additional people requested by the LAR (e.g., relative, friend)
   d. If you are not able to use a video conference system or if the participant will not be able to provide an electronic signature, include an impartial witness
   e. Video conferencing via Zoom for Healthcare will be used for remote consent whenever it is possible.
3. Identify everyone on the call or video conference
4. Confirm the identity of the LAR by viewing their driver's license or another form of identification. If you can confirm the identity visually, document that you recognized the individual. Another alternative is to create and provide a passcode to the potential participant via text or email and ask them for the passcode during the meeting.
5. Review and explain the information in the consent document.
6. Answer any questions the LAR has about the study
7. Ask the LAR questions about the study to confirm their comprehension
8. Ask the LAR if they consent to participate
9. If the LAR agrees, ask them to sign and date the consent document electronically (i.e. REDCap)
10. If you are unable to obtain an electronic signature, ask the LAR to:
    a. Sign and date the consent document;
    b. Take a picture of the signed copy of the consent document; and
    c. Forward the images to you.
11. If there is a witness to the procedure, have the witness sign and date a copy of the document (electronically or with wet ink) and provide a copy of the signed and dated document to you.
12. Sign and date the consent document as the individual obtaining consent
13. Repeat and/or include the same process for HIPAA Authorization

14. If the LAR signed electronically, explain how they will receive a copy of the signed documents.

Documenting remote consent process:

1. Explain the rationale for obtaining remote consent and HIPAA Authorization
2. Document the date and time you obtained the participant's consent
3. Document the list of attendees by name and role
4. Document whether you obtained consent via a Zoom meeting or phone call
5. Document the electronic platform used to obtain consent (REDCap)
6. Document how you confirmed the participant's identity
7. Document that you answered all of the LAR's questions.
8. Document that you assessed comprehension by asking the participant/LAR questions, and the LAR was able to answer the questions correctly and apparently understood.
9. Document that the LAR verbally agreed to participate or permit the participant to participate.
10. Print the signed and dated copies or images and maintain a copy in the research record and upload to the electronic medical record, if applicable. If you are using an electronic platform as a regulatory binder, transfer the images and documents electronically into the electronic platform and follow requirements for certified copies
11. Document how you provided a copy of the signed and dated consent form and HIPAA authorization to the LAR if you obtained an electronic or wet signature and date. You may use email to send the consent document if you include "SECURE" in the subject line.
12. Document the circumstances if you were unable to obtain a signature and date

Example: Informed consent was obtained on Date at Time. The participant was not able to come to the site because personal reasons. A copy of the consent document was emailed to the

prospective participant before the consent discussion. REDCap was used for electronic documentation of obtaining consent. The consent process was performed by phone/ZOOM. The individuals attending the discussion were: (list the names of the individuals). The identity of the LAR was confirmed via passcode or viewing their drivere's license. The person obtaining consent explained the research to the participant and answered the participant's questions. The person obtaining consent asked the participant questions to ascertain whether the s/he understood the study, and the participant was able to answer the questions. The participant/LAR voluntarily agreed to participate. The subject/LAR signed and dated the consent document. A copy of the signed documets were placed in the research record and another given to the LAR via email. After signing the consent document, the participant took a picture and sent it to the research team/ OR The participant was unable to send a picture of the document because of certain circumstances. An impartial witness observed the entire process.

XXXII. Process to Document Consent in Writing

We will be following "SOP: Written Documentation of Consent (HRP-091)" to obtain written consent and when applicable HRP-093 SOP – Electronic Signatures for Documentation of Consent. Please see the attached informed consent form.

XXXIII. Authorization for Use and Disclosure of Protected Health Information

Type of Request: Waiver of Authorization for access to medical record for subject identification/recruit and Waiver of Authorization for access to medical record to obtain data for research.

I confirm that I will destroy the Protected Health Information (PHI) I and/or my Study Team receive from JHS and/or UHealth at the earliest opportunity.

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Study Title: The Duration of Antibiotic Therapy for Early VAP (DATE) Trial

I confirm that the Protected Health Information (PHI) I acquire from JHS and/or UHealth will not be re-used or disclosed to any other person or entity, except as required by law or for authorized oversight of the research study or for other research for which the use or disclosure of PHI is permissible.

Notwithstanding the preceding "I confirm" statements above, I agree that neither I nor any member of the study team listed on the IRB submission for this Protocol shall ever re-use or re-disclose any other information acquired from Jackson Health System in any format, whether **identified or de-identified**, to any individual or entity without first obtaining written permission from Jackson Health System, even if such re-use or re-disclosure is permissible by law (e.g., HIPAA).

Jonathan P. Meizoso, M.D., M.S.P.H. 11/3/2023

PI Signature Date

XXXIV. Drugs or Devices

Not applicable

XXXV. References

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