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Complete List of Authors:	FOUCRIER, Arnaud; Hospital Beaujon, Department of Anaesthesiology and Critical Care, Beaujon Hospital, DMU Parabol, AP-HP Nord, Université de Paris Roquilly, Antoine; CHU Nantes, Pôle anesthésie réanimations, CIC Immunologie et infectiologie, Service d'Anesthésie Réanimation chirurgicale, Hôtel Dieu, Nantes, F-44093 France Bachelet, Delphine; Hopital Bichat - Claude-Bernard, Département d'épidémiologie, Biostatistiques et Recherche Clinique, Hôpital Bichat, AP-HP Nord, Université de Paris, 75018, Paris, France Martin-Loeches, Ignacio; University of Dublin Trinity College, Multidisciplinary Intensive Care Research Organization (MICRO), Department of Intensive Care Medicine, St. James's University Hospital,; IDIBAPS, Hospital Clinic,Universidad de Barcelona, CIBERes, Barcelona, Spain Bougle, Adrien; APHP, Department of Anesthesiology and Critical Care Medicine, Cardiology Institute, Sorbonne University, GRC 29, Pitié-Salpêtrière Hospital, 47-83 Boulevard de l'Hôpital, 75013, Paris, France. Timsit, Jean-François; Hôpital Bichat - Claude-Bernard, Medical and Infectious Diseases ICU (MI2), F-75018 Paris, France; University of Paris, IAME, INSERM, F-75018 Paris, France Montravers, Philippe; CHU Bichat-Claude Bernard, Université Paris-Diderot, APHP, Département d'anesthésie-réanimation, université Paris VII Sorbonne Cité, CHU Bichat-Claude-Bernard Zahar, Jean-Ralph; Hopital Avicenne, Service de Microbiologie Clinique et Unité de Contrôle et de Prévention Du Risque Infectieux, Eloy, Philippine; Hôpital Bichat Claude-Bernard, Département d'épidémiologie, Biostatistiques et Recherche Clinique, Hôpital Bichat, AP-HP Nord, Université de Paris, 75018, Paris, France Weiss, Emmanuel; Hôpital Beaujon, Anesthesiology and Intensive Care
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Antimicrobial Stewardship for Ventilator Associated Pneumonia in Intensive Care (the ASPIC trial): study protocol for a randomized controlled trial

Arnaud FOUCRIER[1], Antoine ROQUILLY[2], Delphine BACHELET[3], Ignacio MARTIN-LOECHES[4,5], Adrien BOUGLE[6], Jean-François TIMSIT[7], Philippe MONTRAVERS[8], Jean-Ralph ZAHAR[9], Philippine ELOY[3], Emmanuel WEISS[1], ASPIC study group

[1] Department of Anaesthesiology and Critical Care, Beaujon Hospital, DMU Parabol, AP-HP Nord, Université de Paris, 100 Boulevard du Général Leclerc, 92110, Clichy, France

[2] Nantes Université, CHU Nantes, Pôle anesthésie réanimations, CIC Immunologie et infectiologie, Service d'Anesthésie Réanimation chirurgicale, Hôtel Dieu, Nantes, F-44093 France

[3] Département d'épidémiologie, Biostatistiques et Recherche Clinique, Hôpital Bichat, AP-HP Nord, Université de Paris, 75018, Paris, France

[4] Multidisciplinary Intensive Care Research Organization (MICRO), Department of Intensive Care Medicine, St. James's University Hospital, Trinity Centre for Health Sciences, Dublin, Ireland

[5] Hospital Clinic, IDIBAPS, Universidad de Barcelona, CIBERes, Barcelona, Spain

[6] Department of Anesthesiology and Critical Care Medicine, Cardiology Institute, Sorbonne University, GRC 29, AP-HP, Pitié-Salpêtrière Hospital, 47-83 Boulevard de l'Hôpital, 75013, Paris, France. adrien.bougle@aphp.fr

[7] AP-HP, Bichat Hospital, Medical and Infectious Diseases ICU (MI2), F-75018 Paris, France; University of Paris, IAME, INSERM, F-75018 Paris, France

[8] Département d'anesthésie-réanimation, université Paris VII Sorbonne Cité, CHU Bichat-Claude-Bernard, AP-HP, 46, rue Henri-Huchard, 75018 Paris, France

[9] Service de Microbiologie Clinique et Unité de Contrôle et de Prévention Du Risque Infectieux, Groupe Hospitalier Paris Seine Saint-Denis, AP-HP, 125 Rue de Stalingrad, 93000, Bobigny, France

Corresponding author :

Dr Arnaud FOUCRIER

Department of Anaesthesiology and Critical Care, Beaujon Hospital, DMU Parabol, AP-HP Nord, Université de Paris, 100 Boulevard du Général Leclerc, 92110, Clichy, France

email: arnaud.foucrier@aphp.fr

Abstract (233 words)

Introduction: Ventilator associated pneumonia (VAP) remains the leading cause of infections treated in the Intensive Care Units (ICU). Reducing antibiotic consumption in (ICU) is one factor in reducing the emergence of resistance. In a personalized care approach, we hypothesize that the duration of treatment of VAP can be reduced in function of the response to treatment.

Methods and analysis: The ASPIC trial is a pragmatic prospective national multicenter, phase III, non-inferiority, comparative randomized (1:1) single-blinded clinical trial. Five hundred ninety adult patients hospitalized in 24 french ICU with a microbiologically confirmed first episode of VAP that received appropriate empiric antibiotic therapy will be included. They will be randomly allocated to standard management with duration of appropriate antibiotic fixed for 7 days according to international guidelines or antimicrobial stewardship based on daily clinical assessment of clinical cure. The assessment of clinical cure will be repeated daily until at least 3 criteria of clinical cure are met, allowing the discontinuation of antibiotic therapy in experimental group. The primary endpoint is a composite endpoint combining of all-cause mortality measured at day 28, treatment failure or new episode of microbiologically confirmed VAP until day 28.

Discussion: Demonstrate that a strategy to reduce the duration of antibiotic therapy for VAP based on clinical assessment is safe could lead to changes in practice as part of a personalized therapeutic approach, by reducing exposure to antibiotics and their side effects.

Ethics and dissemination: The ASPIC trial has been approved by the French regulatory agency (Agence Nationale de Sécurité du Médicament et des Produits de Santé, ANSM; EUDRACT number 2021-002197-78, 19 August 2021) and an independent ethics committee the Comité de Protection des Personnes (CPP) Ile-de-France III (CNRIPH : 21.03.25.60729, 10 Ocotber 2021) for the study protocol (version ASPIC−1.3; 03 September 2021) for all study centers. Participant recruitment is scheduled to begin in 2022. Results will be published in international peer-reviewed medical journals.

Trial registration number: NCT05124977, first posted November 18, 2021

Protocol version identifier N°1-3, 03 September 2021

Strengths and limitations of this study

- High quality methodology using randomized controlled trial (RCT) design that will provide a high-level of evidence on antimicrobial stewardship for management of ventilator-associated pneumonia (VAP) antibiotic strategy

- First RCT conducting in Europe assessing the value of clinical cure criteria ('STOP criteria') supported by an international expert panel to develop an antimicrobial stewardship strategy

- Class of antibiotics prescription not imposed by the protocol, in a pragmatic approach and in order to maximize the external validity of the results

- Risk of poor adherence of investigator team to experimental strategy, which could lead to absence of antibiotic discontinuation even if 'STOP' criteria are met.

INTRODUCTION

Reduction of use of antibiotics is a major point in the war against antimicrobial resistance in ICU (1). VAP is the first cause of healthcare-associated infections in ICU and more than half of antibiotics prescriptions in ICU are due to respiratory tract infections (2,3). The association between increase in antibiotic consumption and resistance emergence has been well documented for all patients admitted to the ICU who received antibiotic treatment and for patients treated for VAP (4).

In the last few years, the concept of antimicrobial stewardship (ASP) has been developed. It refers to programs, education, interventions that aim to optimize antibiotic use (5). In a recent review by Dyar et al. reports different definitions of ASP used in the literature (6). Antimicrobial stewardship refers to the responsible use of antimicrobials by healthcare professionals, and more specifically, to selection of the most appropriate antibiotic, duration, dose and route of administration for a given patient with a demonstrated or suspected infection (7,8).

For VAP treatment, international guidelines (9–11) strongly recommend a 7-day course of antibiotic therapy rather than a longer duration but underline that "there are situations in which a shorter or longer duration of antibiotics may be indicated, depending upon the rate of improvement of clinical, radiologic, and laboratory parameters". In the absence of very specific situations (severe immunodepression, abscessed pneumonia, necrotizing pneumonia), it is recommended not to exceed the duration of antibiotic therapy by more than 7-8 days. These recommendations are based on the concordant results of two meta-analyses that compared two treatment durations: 7-8 days vs. longer durations (12,13).

Recently, Weiss et al. (14) poled a panel of international experts to develop consensus criteria to evaluate the clinical response to antibiotic treatment for hospital-acquired pneumonia (HAP)

and VAP. In this work, various innovative concepts are developed. First, the experts agree that the criteria usually used in the literature to characterize the suspicion of VAP are weighted differently. According to the experts, among 9 selected criteria, the first 4 criteria with the most significant impact were: 1. Worsening of gas exchange, 2. Hypotension / vasopressor requirement, 3. Temperature abnormalities (fever or hypothermia), 4. Purulent tracheal secretions (rated ex-aequo with temperature abnormalities). Logically, less specific signs (hyperleukocytosis, encephalopathy, auscultatory abnormalities) were ranked lower. More surprisingly, the CPIS (Clinical Pulmonary Infection Score) was ranked 6th while it is no longer considered a determinant for initiating antibiotic treatment.

According to the experts, these criteria, when they regress or disappear, are therefore considered associated with clinical cure of VAP. Considering the small differences in the relative weights of each criterion, it seems reasonable to consider that the association of at least 3 of these criteria is necessary to consider a clinical cure. To date, no prospective evaluation of the robustness of these criteria to guide antimicrobial treatment duration has been performed.

The ASPIC study aims at investigating whether an antimicrobial stewardship for microbiologically proven VAP based on daily assessment of clinical cure and antimicrobial discontinuation, if it is obtained, would be non-inferior to standard management in terms of all-cause mortality, treatment failure or occurrence of new episode of VAP before day 28.

METHODS AND ANALYSIS

Study design

This study is a pragmatic, national, multicenter, phase III, single-blinded, non-inferiority comparative randomized clinical trial (RCT) comparing two therapeutic strategies for microbiologically proven VAP on the basis of two parallel arms:

- Experimental group: Antimicrobial stewardship based on daily clinical assessment of clinical cure. Discontinuation of appropriate antibiotic therapy is made if clinical cure (daily assessment) criteria of VAP are met.
- Control group: Standard management: Fixed duration of 7 days of appropriate antibiotic therapy according to VAP guidelines. In the control group, clinical cure assessment will be performed daily by the intensivist in charge of the patient but the antibiotic therapy will not be discontinued until 7 days whatever the clinical cure.

The trial overview is summarized in Figure 1. We report here the study protocol according to the SPIRIT (Standard Protocol Items: Recommendations for interventional Trials) statement (15).

Definitions

Appropriate empiric antibiotic therapy: the empiric antibiotic therapy is defined as appropriate if all the VAP causative pathogens are susceptible (*in vitro*) to at least one molecule of the empirical treatment. Empiric antibiotic therapy is defined as inappropriate if at least one causative bacteria is resistant (*in vitro*) to the empirical treatment.

Definitive diagnosis of VAP is defined, in accordance with international guidelines, by the association of:

- Mechanical ventilation requirement for more than 48 hours
- New pulmonary infiltrate of strongly suspected infectious origin
- Worsening oxygenation
- Purulent tracheal secretions and at least 1 of the following criteria within the 24 hours prior to the first dose of antibiotic therapy: (i) fever (body temperature >38,3°C) or hypothermia (body temperature <35°C) , (ii) white blood cell (WBC) count >10,000 cells/mm^3 or <4,000 cells/mm^3
- microbiological criteria (positive quantitative culture of a lower respiratory tract (LRT): bronchoalveolar lavage fluid (BAL) (positivity threshold $\geq 10^4$ colony-forming units/mL) or plugged telescopic catheter (PTC) (threshold $\geq 10^3$ colony-forming units/mL) or quantitative endotracheal aspirate (ETA) distal pulmonary secretion samples (significant threshold $\geq 10^5$ colony-forming units/mL)

Clinical cure (Figure 2)

- complete resolution of at least 3 the 4 clinical signs and/of symptoms of VAP, according the STOP algorithm (items: purulent Secretions, body Temperature, Oxygenation, systolic blood Pressure) AND

- No additional antibiotic therapy required for VAP treatment AND
- Patient is alive

Treatment failure defined by signs of VAP within 72 hours after the end antibiotic treatment at the test of cure visit

Superinfection: Isolation of a pathogen, other than the causative baseline pathogen, from a LRT specimen obtained in a subject with signs and symptoms of VAP developed during antibiotic treatment

Persistence: Continued presence of the original causative baseline pathogen(s) from a LRT culture obtained between EOT and 72 after EOT

New VAP: New episode of microbiologically documented VAP from 72h after the EOT to day 28

VAP-Recurrence: New VAP due to at least one of the original causative pathogen(s) found at baseline

Definitions of treatment failure, persistence, superinfection, persistence, VAP recurrence and new VAP are summarized in Figure 3.

Setting

This will be a French multicenter study involving 24 centers. Participants will be recruited in ICU wards during their hospital stay.

Study population

Participants in ICU wards will be eligible if they fulfilled following criteria:

Inclusion criteria:

- Aged 18 years or more
- Patient under mechanical ventilation (MV)
- Microbiologically confirmed diagnosis of first episode of VAP (see definition section)
- Initial appropriate empiric antibiotic therapy (see definitions section)
- Written informed consent from the patient or a legal representative if appropriate. If absence of a legal representative the patient can be included following an emergency procedure

Exclusion criteria:

- Patient under selective bowel decontamination
- Concomitant extra-respiratory infection requiring antibiotic therapy at inclusion
- Inclusion in another experimental study on antimicrobial stewardship
- Moribund at admission (IGS II>80)
- Thoracic trauma with Abbreviated Injury Scale (AIS) thorax ≥ 3
- Severely immunocompromised patients: congenital immunodeficiency, neutropenia (<0.5 G/l), leukopenia (<1 G/l), acute hematologic malignancy or stem cell transplant, HIV infection with CD4 count below 200/mm^3, immunosuppressive therapy or long term corticosteroid therapy > 0.5 mg/kg

- VAP due to: *Pseudomonas aeruginosa*, Carbapenem-resistant *Acinetobacter* spp, Carbapenem-resistant *Enterobacterales*
- Bacterial VAP occurring in the context of superinfection of COVID-19 or other viral VAP (confirmed by RT-PCR)
- Patients with empyema, necrotizing and abscessed pneumonia
- Pregnant women
- No health insurance coverage

Recruitment

The screening will aim at identifying patients hospitalized in ICU who underwent a lower respiratory tract sample because a VAP was suspected. During this period, management of patients is similar to usual care with clinical, biological and radiological assessments. After microbiological diagnosis confirmation and reception of Antibiotic Susceptibility Testing (AST) proving that the initial empiric antibiotic therapy was appropriate, eligible patient will be offered participation in the trial. Written informed consent would be obtained by the investigator or by a physician representing the investigator, from all patients, their next of kin, as appropriate, accordingly to French regulatory agencies authorization (see section Methods for obtaining information and consent from research participants).

Treatment allocation and randomization

Participants will be randomized (Day 1) with a 1:1 ratio to either antimicrobial stewardship-guided antibiotic therapy strategy (experimental group) or standard management (control group) using a computer-generated randomization scheme of various-sized blocks, through an internet centralized randomization service running 24hrs/24hrs. Randomization will be stratified by center. The randomization scheme will be generated by a statistician who is not

involved in any other aspect of the study, and all researchers will be blinded to block size(s) and randomization list to avoid prediction of future patient's allocation. Allocation concealment will be ensured, as the service will not release the randomization code until the patient has been recruited into the trial.

Blinding

This study will be single-blinded. Participants will not be informed of their group allocation. Blinding will be ensured as most patients will be either sedated (within standard of care) or unable to have appropriate discussions with investigational team for the duration of the experimental at study. The statistician conducting the data analysis will also be blinded to group allocation. The medical staff cannot be blinded to the randomization arm due to the nature of experimental design and our choice to evaluate this strategy in real-life clinical practice conditions. If the patient is transferred to another clinical ward or leave the hospital during the 3-month follow-up, other healthcare professionals involved in their management will not be made aware of the randomization arm.

Study procedures

The general flowchart of the study is shown in Figure 1. A pragmatic approach will be followed and usual patient management recommended by international guidelines (9–11) will be provided in participating ICUs. In particular the choice of antibiotic therapy will be left at investigator discretion.

In the experimental group, the ICU physician will discontinue the antibiotic therapy as soon as clinical cure criteria of VAP are met. Minimal duration of appropriate antibiotic treatment will be 3 days (including empirical antibiotic therapy). After 72 hours (delay to receive AST results)

of appropriate antibiotic treatment, the assessment of clinical cure will be performed daily on the basis of 4 criteria:

- Regression or the decreased abundance of purulent tracheal secretions
- Absence of fever or hypothermia
- Improvement of oxygenation (assessed by increase of PaO_2/FiO_2 ratio)
- Absence of hypotension (hypotension is defined by mean arterial pressure < 70 mmHg(16,17)) or decreased need for epinephrine or norepinephrine by at least 0,1 µg/kg/mn compared to baseline (day of inclusion)

This assessment will be repeated daily until at least 3 of the 4 criteria are met, i.e. the patient is considered clinically cured, thereby allowing the discontinuation of antibiotic therapy (Figure 2).

A daily phone hotline, provided by coordinating investigator's team, will be accessible to investigators for multidisciplinary validation of antibiotic discontinuation in patients included in the experimental group.

For control group, fixed duration of antibiotic therapy will be at least 7 full days (since the initiation of empirical antibiotic therapy), whatever clinical assessment.

For both groups, in case of non-clinical recovery after 7 full days (treatment failure) and/or in case of suspicion of new VAP during treatment (superinfection), a new lower respiratory tract sampling will be performed, and a new antibiotic therapy will be initiated. In case of new VAP, patients will be treated according to the usual practices of the center.

Following data will be collected daily from day 2 to day 28 or to ICU discharge in participants from both arms: vital status, ventilation status, PaO_2 and FiO_2 (if ventilated), temperature, tracheal secretions, blood pressure, use and dose of vasopressors, data on any infection throughout study period (infection site, bacteriological documentation, number of days of antibiotic therapy), antibiotic use (molecule; dosage; duration of treatment).

Additional data will be collected daily from Day 2 to Day 8: clinical assessment, focused pulmonary examination, laboratory assessment (usual tests, biochemical, hematological), radiological evaluation (Chest X-Ray/CT-scan), if performed as part of usual care.

Rectal swabbing for collection of data on colonization or acquisition of Multidrug Resistant (MDR) bacteria will be performed at ICU admission and weekly until ICU discharge as part as usual care.

All participants will be followed up to day 90 with vital status assessment.

Outcomes

The primary endpoint will be a composite of:

1. All-cause mortality (ACM) measured at day 28 after initiation of therapy OR

2. Treatment failure defined by signs of VAP within 72 hours after the end antibiotic treatment at the test of cure visit OR

3. New episode of microbiologically confirmed VAP from 72H after the end of antibiotic treatment to day 28 after initiation of VAP antibiotic treatment

To avoid interpretation bias for the primary outcome, clinical and microbiological records of all participants will be reviewed by adjudication committee composed with two experts in order to evaluate the presence of (i) clinical cure, (ii) treatment failure and (iii) new episode of VAP. This evaluation will be performed blindly from the randomization group and from the interpretation of the investigation team, according to predefined criteria (see Definition section). The adjudication committee will be composed of study investigators (including scientific committee of ASPIC). Each member will review the primary endpoints criteria of a subgroup of patients that were not enrolled in its center.

Secondary endpoints will be: day 28 all-cause mortality, proportion of treatment failure and of new episode of VAP; the number of antibiotic free days alive from initiation of VAP antibiotic therapy to day 28; the duration of invasive MV; the length of ICU stay, defined by the number of days between inclusion and ICU discharge or in-ICU death; the proportion of VAP recurrence assessed by the intensivist; the antibiotic related side effects; the proportion of acquisition of MDR bacteria (defined as the identification of a MDR bacteria carriage not present at admission); the proportion of protocol deviation i.e. lack of antibiotic therapy discontinuation despite a fulfillment of clinical cure definition in the experimental group ; the total cumulative costs of antibiotics and incremental cost effectiveness ratio; and the Desirability of Outcome Ranking (DOOR) and the Response Adjusted for Duration of Antibiotic Risk (RADAR) for each strategy (experimental and control groups)(18).

All trial participants will be ranked with respect to the desirability of their overall outcome and the distributions of DOORs will be compared between strategies Overall clinical outcomes at day 28 will be ranked from most to least desirable as followed:

1. Survival, clinical cure
2. Survival, new pulmonary infection
3. Death

In RADAR analyses, patients will be ranked overall clinical outcome, but in case of ex-aequo, the patient with a shorter duration of antibiotic use will receive a higher rank

Sample size justification

Assuming that 25% of the patients will encountered all-cause mortality, treatment failure or occurrence of new episode of VAP before day 28 in the control arm (19), 590 subjects (295 per arm) are needed to establish non-inferiority with the absolute difference of death, treatment failure or occurrence of new episode of VAP doesn't exceed 10% (non-inferiority margin)

between experimental and control arms with a power of 80%, a type I error (alpha) of 2.5%. Using data from Teixeira and al. (20), we derived an estimated absolute rate of 28-days survival without treatment of 50% (absolute rate of treatment failure / new episode of VAP without treatment cannot be estimated). The non-inferiority margin of 10% was chosen as the largest difference that may be potentially clinically acceptable and so that antimicrobial stewardship preserves at least half the effect of standard of care (21).

Data analysis plan

The primary analysis will be performed on the intention-to-treat population (22). The 95% confidence interval of the difference in proportions of all-cause death, treatment failure or occurrence of new episode of VAP observed between the two groups will be estimated. This confidence interval will be compared to the non-inferiority margin of 10%. If the lower limit of the confidence interval of the difference in proportions is less than or equal to -10%, then we cannot conclude that the antimicrobial stewardship-based strategy is non-inferior to the reference strategy. In the opposite case, if the lower limit of the confidence interval is strictly greater than -10%, then we will conclude that the antimicrobial stewardship-based strategy is non-inferior on all-cause mortality, treatment failure or occurrence of new episode of VAP at day 28 after inclusion. Sensitivity analysis on per-protocol population will be performed. All tests of superiority (secondary objectives) will be two-sided with type I error of 5% and tests of non-inferiority will be one-sided with type I error 2.5%. All statistical analyses will be performed using SAS software (SAS Institute Inc., Cary, NC) v. 9.4 or later, or R software (R Foundation for Statistical Computing, Vienna, Austria. http://www.r-project.org/) v. 4.0 or later.

The primary analysis will also been performed in the following subgroups of patients:

- Those whose baseline bacteriological samples were assessed by rapid microbiological technique (germ identification and antibiogram) ;
- Patients admitted to ICU for trauma vs other reasons of admission
- Patients with early onset PAVM (< 5 days after ICU admission) vs late onset PAVM (≥5 days after ICU admission).

No strategy of imputation is forecasted in case of missing data for the primary assessment criterion. Information available at time of last follow-up will be taken into account.

Data collection and management

Data collection will be performed in electronic format. The statistical software used for data entry will be CleanWeb™; it will fulfill the regulatory requirements and security norms. Data will be handled according to the French law. All original records (including consent forms, reports of suspected unexpected serious adverse reactions and relevant correspondences) will be archived at trial sites for 15 years. The cleaned trial database file will be anonymized and maintained for 15 years. Data on primary and secondary endpoints, will be collected, as detailed in Study procedures section and Table 1. The data of this study will be available upon reasonable request from the corresponding author but it will not be publicly available due to privacy or ethical restrictions.

Table 1. Chronology of the study and procedures

Actions		D-2 to D1	D1	D2 to D8	D9 to D27 or discharge of hospital	D28	D90
Inclusion visit			X_R				
Verification of inclusion and non-inclusion criteria			X_R				
Information			X_R				
Written Informed consent			X_R				
Randomization			X_R				
Pregnancy test			X_R				
Medical history		X_C	X_C				
Physical examination		X_C	X_C	X_C	X_C	X_R	
Phone call							X_R
Chest X-Ray/CT-scan		X_C	X_C	X_C			
PaO_2/FiO_2 ratio		X_C	X_C	X_C	X_C		
Assessment of clinical symptoms of VAP		X_C	X_C				
Assessment of clinical recovery of VAP				Xc			
Start antibiotics			X_C				
Antibiotics			X_C	X_C	X_C		
Rectal swab				X_C	X_C		
Serum creatinin and calculated creatinin clearance			X^b_C				
White blood count		X_C	X_C	X_C	X_C		
SCORE	ISS	X_C					
	SOFA	X_C	X_R				
	IGS	X_C					
Assessment of rate of treatment failure and new episode of VAP						X_R	
Antibiotic free days						X_R	
Vital status						X_R	X_R
Adverse events			X_R	X_R	X_R	X_R	X_R
Hospital admissions				X_C	X_C	X_R	X_R

* length of antibiotic therapy depends on the clinical response. In the control group, predictable length is 7 days.

b creatinin clearance may be performed (Cl_{cr}= (urinary creatinin/serum creatinin)*urine $volume_{24h}$) as frequently as clinically indicated to guide appropriate antibiotic therapy in subjects with renal impair

X_C : made in usual care

X_R : acts added for research

TRIAL STATUS

Not yet recruiting. Participant recruitment is scheduled to begin in 2022 and the recruiting period will last 36 months.

ETHICS AND DISSEMINATION

Legal obligations and approval

Sponsorship has been agreed by Assistance Publique—Hôpitaux de Paris (AP-HP, Clinical Research and Innovation Department) for this interventional research protocol involving human participants concerning a health product. AP-HP has obtained the approval of the French medicine regulatory agency (Agence Nationale de Sécurité du Médicament et des Produits de Santé, ANSM; EUDRACT number 2021-002197-78, 19 August 2021) and of the ethics comitee (Comité de Protection des Personnes (CPP) Ile-de-France III (CNRIPH : 21.03.25.60729, 10 October 2021)) for the study protocol (version ASPIC−1.3; 03 September 2021). The trial will be carried out in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines. Any substantial modification to the protocol will be sent to the sponsor, and then to the ANSM and the CPP for approval before the amendment can be implemented. The information sheet and the consent form can be revised if necessary, particularly if there is a substantial amendment to the study or if adverse reactions occur. AP-HP is the owner of the data. The data cannot be used or disclosed to a third party without its prior permission.

Methods for obtaining information and consent from research participants

In accordance with Article L.1122-1-1 of the French Public Health Code, no research will be carried out without patient free and informed consent, obtained in writing after the person has been given the information specified in Article L.1122-1 of said Code. Written informed consent will be obtained from all patients, their next of kin, as appropriate. If patients are unable to provide informed consent and if neither their next of kin nor other designated person is available, a procedure for inclusion in the study in emergency situations would be applied. A definitive post hoc consent form would be ultimately obtained from patients who survived but had been initially treated on the basis of the emergency consent. These procedures have been approved for the ASPIC trial by the french Commission nationale de l'informatique et des libertés (CNIL, ref MLD/MFI/AR2111748, 18 October 2021).

Patient and public involvement

The patient's (or next of kin's) free and informed written consent will be obtained after a reflection period of at least 15 minutes after information, by the investigator, or by a doctor representing the investigator, before enrollement in the trial, during the baseline visit.

The investigator will specify in the research participant's medical file the methods used for obtaining their consent as well as the methods used for providing information with a view to obtaining consent. The investigator will retain the original signed and dated consent form.

Subjects may exit the study at any time and for any reason.

Data deposition, quality control and curation

The persons responsible for the quality control of clinical matters will take all necessary precautions to ensure the confidentiality of information related to the study participants. These persons, as well as the investigators themselves, are bound by professional confidentiality. During or after the research, all data collected about the participants and sent to the sponsor by

the investigators (or any other specialized collaborators) will be anonymized. Under no circumstances should the names, addresses and other protector identifiers of the subjects involved be shown.

In any case of premature withdrawals and exits, the investigator must provide their reason(s) and try to collect primary endpoint, secondary endpoints and safety assessment, if the participant agrees. If a participant exits the study prematurely or withdraws consent, any data collected prior to the date of premature exit may still be used excepted if the participant refuses it in writing.

The research data will be collected and monitored using an eCRF through CleanWEB™ Electronic Observation Book and will be centralized on a server hosted by the AP-HP Operation Department.

Research staff of the Clinical Trial Unit will work with local investigators to obtain data that are as complete and accurate as possible. An independent Clinical Research Associate appointed by the sponsor will be responsible for the proper running of the study, for collecting, documenting, recording and reporting all handwritten data, in accordance with the Standard Operating Procedures applied within the Clinical Research and Innovation Department of AP-HP. The investigators agree to accept the quality assurance audits carried out by the sponsor as well as the inspections carried out by the competent authorities. All data, documents and reports may be subject to regulatory audits. These audits and inspections cannot be refused on the grounds of medical secrecy. An audit can be carried out at any time by independent individuals appointed by the sponsor, aiming at ensuring the quality of the study, the validity of the results and compliance with the legislation and regulations in force. The persons who manage and monitor the study agree to comply with the sponsor's audit requirements. The audit may encompass all stages of the study, from the development of the protocol to the publication of

the results and the storage of the data used or produced as part of the study. Sponsor is responsible for access to the study database.

The investigator will assess the seriousness of each adverse event, report all serious and non-serious adverse events in the case report form and assess the causal relationship of serious adverse events with the study procedures according to the WHO method.

A data monitoring committee is not needed for this trial as the expected risk for the participant is minimal.

Publication plan

Results will be published in international peer-reviewed medical journals. Scientific presentations and reports will be written under the responsibility of the coordinating investigator of the study with the agreement of the principal investigators and the methodologist. The co-authors of the reports and publications will be the investigators and clinicians involved, on a pro rata basis of their contribution in the study, as well as the biostatistician and associated researchers. Rules on publication will follow international recommendations (23).

Authors' contributions: AF and EW contributed to the conception and design of the research protocol, assisted by DB and PE. AR, IM-L, PM, J-FT and J-RZ provided critical input pertaining to the design of the trial interventions and procedures. AF wrote the first draft of the protocol and this manuscript. DB and PE designed the statistical analysis plan. All authors critically revised and modified the protocol and the article. They all approved the final version to be published.

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Competing interests statement :

AF, DB, AB, PE: declare no competing interest

AR: grants from bioMerieux and Merck

IM-L: board on PFIZER, MSD, GILEAD

J-FT directly related to the protocol: none, participation to scientific advisory boards: Pfizer, Gilead, Merck, BD, Shionoghi; readings: Merck, Biomerieux, Pfizer, Shionogi; research grants to my research unit: thermofischer, Pfizer, Merck

J-RZ: consulting fees from MSD, Pfizer, speaker fees fom MSD, Pfizer, Shionogi, Correvio and Eumedica

EW: Speaker fees from MSD, Akcea therapeutics and LFB, support for attending meeting/travel: LFB and Akcea therapeutics

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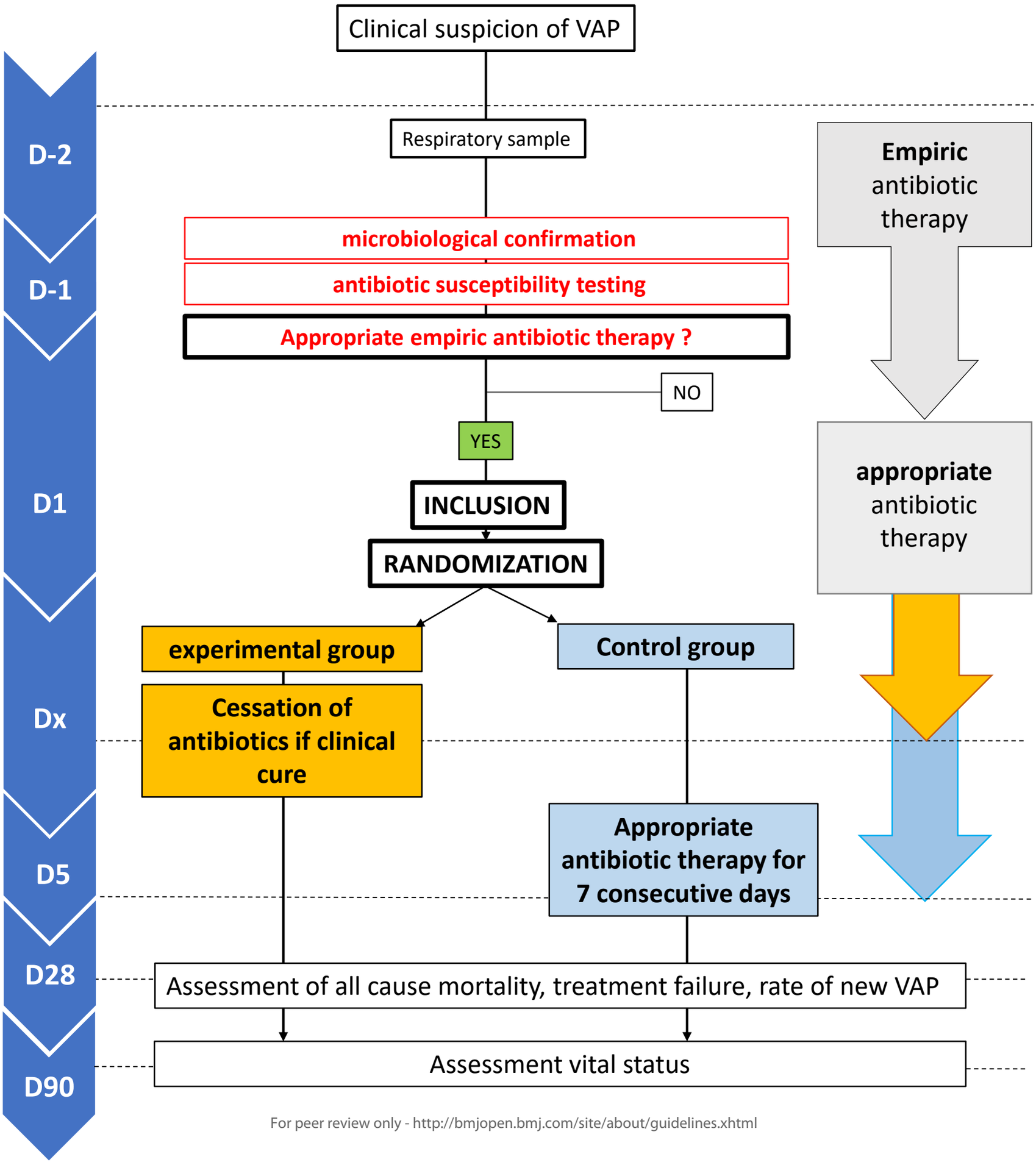
Figures and Table legends

Figure 1: General flowchart of the study

Figure 2: Criteria of clinical cure and criteria for discontinuation of antibiotic therapy in experimental arm

Figure 3: Description of microbiological categories of outcomes in relation to time of occurrence of new episode of VAP after inclusion adapted from(24)

Table 1: Chronology of the study and procedures


Clinical suspicion of VAP
D-2
Respiratory sample
Empiric antibiotic therapy
D-1
microbiological confirmation
antibiotic susceptibility testing
Appropriate empiric antibiotic therapy ?
NO
YES
D1
INCLUSION
RANDOMIZATION
appropriate antibiotic therapy
experimental group
Control group
Dx
Cessation of antibiotics if clinical cure
D5
Appropriate antibiotic therapy for 7 consecutive days
D28
Assessment of all cause mortality, treatment failure, rate of new VAP
D90
Assessment vital status

Experimental group

- Antimicrobial stewardship based on daily clinical assessment of clinical cure of confirmed pnemonia are met. Intensivists will perform clinical assessment daily in order to decide on the pursuit or discontinuation of antibiotic therapy.
- Antibiotherpay is stopped if signs of **clinical cure** of pneumonia are met (minimum 3 days)

CLINICAL CURE

STOP antibiotics if ≥ 3 criteria are met

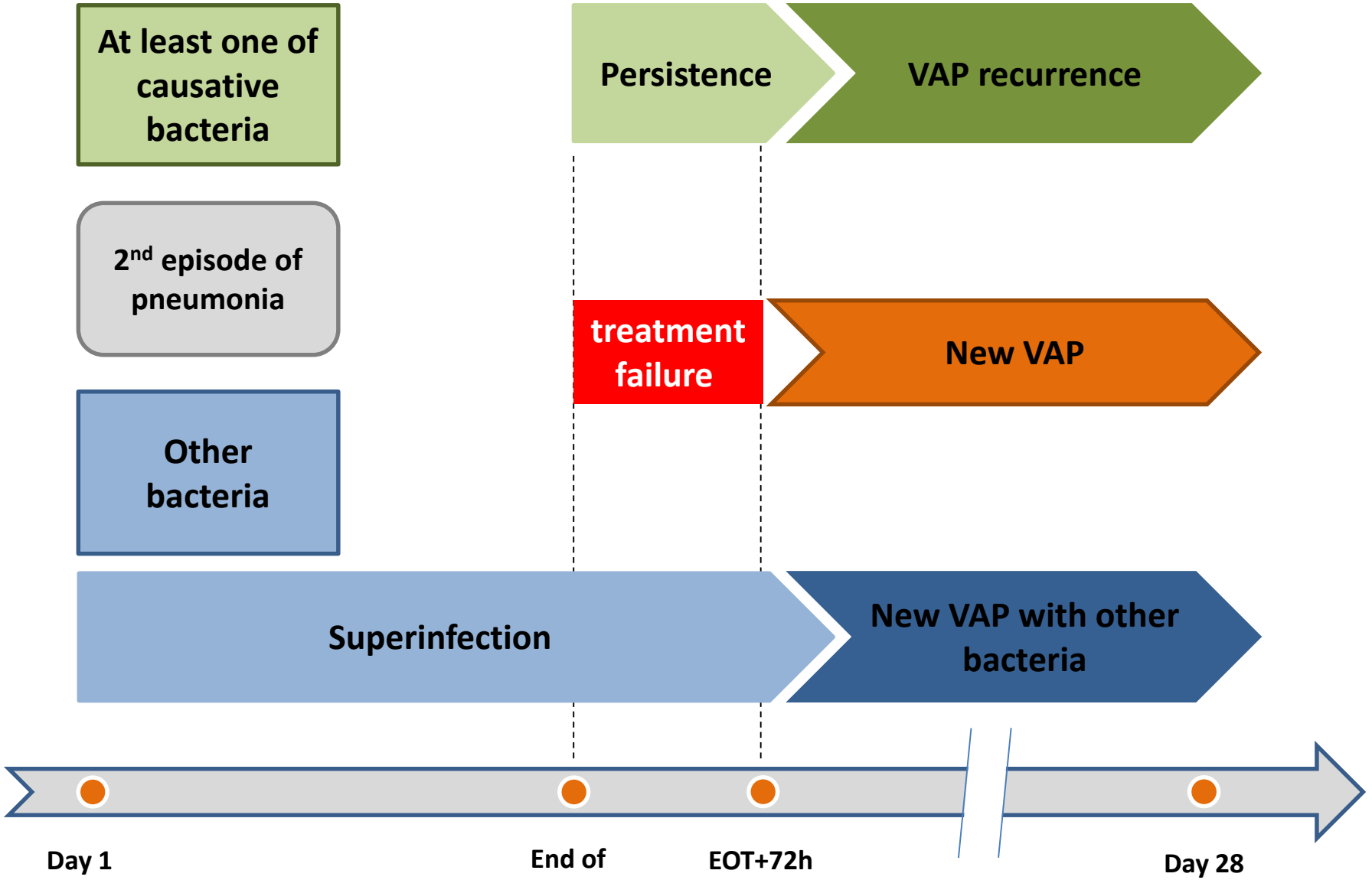
1. Regression* of purulent trachael **S**ecretions

2. Normo**T**hermia
36°C < T < 38.3°C

3. Improved*
Oxygenation, measured by an increase in the of the PaO2/FiO2 ratio

4. Absence of hy**P**otension

* compared to the day of initiation of antibiotic therapy



SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	3
Funding	4	Sources and types of financial, material, and other support	25
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	25
	5b	Name and contact information for the trial sponsor	
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	18
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	14
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
	6b	Explanation for choice of comparators	
Objectives	7	Specific objectives or hypotheses	

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	10
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	10
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	12,13
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	14
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	14
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	14,15
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Fig 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	15
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	15
Methods: Assignment of interventions (for controlled trials)			
Allocation:			

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	11
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	11
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	11,12
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	12
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	17
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Table 1
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	17
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16,17
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	17,18

Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	21
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	21
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	22
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	18
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	18
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	19
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	19
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	NA
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18, 21
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	20,21
	31b	Authorship eligibility guidelines and any intended use of professional writers	22
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	yes
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Antimicrobial Stewardship for Ventilator Associated Pneumonia in Intensive Care (the ASPIC trial): study protocol for a randomized controlled trial

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Complete List of Authors:	FOUCRIER, Arnaud; Hospital Beaujon, Department of Anaesthesiology and Critical Care, Beaujon Hospital, DMU Parabol, AP-HP Nord, Université de Paris Roquilly, Antoine; CHU Nantes, Pôle anesthésie réanimations, CIC Immunologie et infectiologie, Service d'Anesthésie Réanimation chirurgicale, Hôtel Dieu, Nantes, F-44093 France Bachelet, Delphine; Hopital Bichat - Claude-Bernard, Département d'épidémiologie, Biostatistiques et Recherche Clinique, Hôpital Bichat, AP-HP Nord, Université de Paris, 75018, Paris, France Martin-Loeches, Ignacio; University of Dublin Trinity College, Multidisciplinary Intensive Care Research Organization (MICRO), Department of Intensive Care Medicine, St. James's University Hospital,; IDIBAPS, Hospital Clinic,Universidad de Barcelona, CIBERes, Barcelona, Spain Bougle, Adrien; APHP, Department of Anesthesiology and Critical Care Medicine, Cardiology Institute, Sorbonne University, GRC 29, Pitié-Salpêtrière Hospital, 47-83 Boulevard de l'Hôpital, 75013, Paris, France. Timsit, Jean-François; Hôpital Bichat - Claude-Bernard, Medical and Infectious Diseases ICU (MI2), F-75018 Paris, France; University of Paris, IAME, INSERM, F-75018 Paris, France Montravers, Philippe; CHU Bichat-Claude Bernard, Université Paris-Diderot, APHP, Département d'anesthésie-réanimation, université Paris VII Sorbonne Cité, CHU Bichat-Claude-Bernard Zahar, Jean-Ralph; Hopital Avicenne, Service de Microbiologie Clinique et Unité de Contrôle et de Prévention Du Risque Infectieux, Eloy, Philippine; Hôpital Bichat Claude-Bernard, Département d'épidémiologie, Biostatistiques et Recherche Clinique, Hôpital Bichat, AP-HP Nord, Université de Paris, 75018, Paris, France Weiss, Emmanuel; Hôpital Beaujon, Anesthesiology and Intensive Care
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Antimicrobial Stewardship for Ventilator Associated Pneumonia in Intensive Care (the ASPIC trial): study protocol for a randomized controlled trial

Arnaud FOUCRIER[1], Antoine ROQUILLY[2], Delphine BACHELET[3], Ignacio MARTIN-LOECHES[4,5], Adrien BOUGLE[6], Jean-François TIMSIT[7], Philippe MONTRAVERS[8], Jean-Ralph ZAHAR[9], Philippine ELOY[3], Emmanuel WEISS[1], ASPIC study group

[1] Department of Anaesthesiology and Critical Care, Beaujon Hospital, DMU Parabol, AP-HP Nord, Université de Paris, 100 Boulevard du Général Leclerc, 92110, Clichy, France

[2] Nantes Université, CHU Nantes, Pôle anesthésie réanimations, CIC Immunologie et infectiologie, Service d'Anesthésie Réanimation chirurgicale, Hôtel Dieu, Nantes, F-44093 France

[3] Département d'épidémiologie, Biostatistiques et Recherche Clinique, Hôpital Bichat, AP-HP Nord, Université de Paris, 75018, Paris, France

[4] Multidisciplinary Intensive Care Research Organization (MICRO), Department of Intensive Care Medicine, St. James's University Hospital, Trinity Centre for Health Sciences, Dublin, Ireland

[5] Hospital Clinic, IDIBAPS, Universidad de Barcelona, CIBERes, Barcelona, Spain

[6] Department of Anesthesiology and Critical Care Medicine, Cardiology Institute, Sorbonne University, GRC 29, AP-HP, Pitié-Salpêtrière Hospital, 47-83 Boulevard de l'Hôpital, 75013, Paris, France.

[7] AP-HP, Bichat Hospital, Medical and Infectious Diseases ICU (MI2), F-75018 Paris, France; University of Paris, IAME, INSERM, F-75018 Paris, France

[8] Département d'anesthésie-réanimation, université Paris VII Sorbonne Cité, CHU Bichat-Claude-Bernard, AP-HP, 46, rue Henri-Huchard, 75018 Paris, France

[9] Service de Microbiologie Clinique et Unité de Contrôle et de Prévention Du Risque Infectieux, Groupe Hospitalier Paris Seine Saint-Denis, AP-HP, 125 Rue de Stalingrad, 93000, Bobigny, France

Corresponding author

Arnaud FOUCRIER, Department of Anaesthesiology and Critical Care, Beaujon Hospital, DMU Parabol, AP-HP Nord, Université de Paris, 100 Boulevard du Général Leclerc, 92110, Clichy, France

email: arnaud.foucrier@aphp.fr

Abstract (218 words)

Introduction: Ventilator associated pneumonia (VAP) remains the leading cause of infections treated in the Intensive Care Units (ICU). In a personalized care approach, we hypothesize that the duration of treatment of VAP can be reduced in function of the response to treatment.

Methods and analysis: The ASPIC trial is a pragmatic national multicenter, phase III, non-inferiority, comparative randomized (1:1) single-blinded clinical trial. Five hundred ninety adult patients hospitalized in 24 French ICU with a microbiologically confirmed first episode of VAP that received appropriate empiric antibiotic therapy will be included. They will be randomly allocated to standard management with duration of appropriate antibiotic fixed for 7 days according to international guidelines or antimicrobial stewardship based on daily clinical assessment of clinical cure. The assessment of clinical cure will be repeated daily until at least 3 criteria of clinical cure are met, allowing the discontinuation of antibiotic therapy in experimental group. The primary endpoint is a composite endpoint combining of all-cause mortality measured at day 28, treatment failure or new episode of microbiologically confirmed VAP until day 28.

Discussion: Demonstrate that a strategy to reduce the duration of antibiotic therapy for VAP based on clinical assessment is safe could lead to changes in practice as part of a personalized therapeutic approach, by reducing exposure to antibiotics and their side effects.

Ethics and dissemination: The ASPIC trial has been approved by the French regulatory agency (Agence Nationale de Sécurité du Médicament et des Produits de Santé, ANSM; EUDRACT number 2021-002197-78, 19 August 2021) and an independent ethics committee the Comité de Protection des Personnes (CPP) Ile-de-France III (CNRIPH : 21.03.25.60729, 10 Ocotber 2021) for the study protocol (version ASPIC−1.3; 03 September 2021) for all study centers. Participant recruitment is scheduled to begin in 2022. Results will be published in international peer-reviewed medical journals.

Trial registration number: NCT05124977, first posted November 18, 2021

Protocol version identifier N°1-3, 03 September 2021

Strengths and limitations of this study

- High quality methodology using randomized controlled trial (RCT) design that will provide a high-level of evidence on antimicrobial stewardship for management of ventilator-associated pneumonia (VAP) antibiotic strategy

- First RCT conducting in Europe assessing the value of clinical cure criteria ('STOP criteria') supported by an international expert panel to develop an antimicrobial stewardship strategy

- Class of antibiotics prescription not imposed by the protocol, in a pragmatic approach and in order to maximize the external validity of the results

- Risk of poor adherence of investigator team to experimental strategy, which could lead to absence of antibiotic discontinuation even if 'STOP' criteria are met.

INTRODUCTION

Reduction of use of antibiotics is a major point to control antimicrobial resistance in ICU (1). VAP is the first cause of healthcare-associated infections in ICU and more than half of antibiotics prescriptions in ICU are due to respiratory tract infections (2,3). The association between increase in antibiotic consumption and resistance emergence has been well documented for all patients admitted to the ICU who received antibiotic treatment and for patients treated for VAP (4).

In the last few years, the concept of antimicrobial stewardship (ASP) has been developed. It refers to programs, education, interventions that aim to optimize antibiotic use (5). In a recent review by Dyar et al. reports different definitions of ASP used in the literature (6). Antimicrobial stewardship refers to the responsible use of antimicrobials by healthcare professionals, and more specifically, to selection of the most appropriate antibiotic, duration, dose and route of administration for a given patient with a demonstrated or suspected infection (7,8).

For VAP treatment, international guidelines (9–11) strongly recommend a 7-day course of antibiotic therapy rather than a longer duration but underline that "there are situations in which a shorter or longer duration of antibiotics may be indicated, depending upon the rate of improvement of clinical, radiologic, and laboratory parameters". In the absence of very specific situations (severe immunodepression, abscessed pneumonia, necrotizing pneumonia), it is recommended not to exceed the duration of antibiotic therapy by more than 7-8 days. These recommendations are based on the concordant results of two meta-analyses that compared two treatment durations: 7-8 days vs. longer durations (12,13).

Recently, Weiss et al. (14) poled a panel of international experts to develop consensus criteria to evaluate the clinical response to antibiotic treatment for hospital-acquired pneumonia (HAP)

and VAP. In this work, various innovative concepts are developed. First, the experts agree that the criteria usually used in the literature to characterize the suspicion of VAP are weighted differently. According to the experts, among 9 selected criteria, the first 4 criteria with the most significant impact were: 1. Worsening of gas exchange, 2. Hypotension / vasopressor requirement, 3. Temperature abnormalities (fever or hypothermia), 4. Purulent tracheal secretions (rated ex-aequo with temperature abnormalities). Logically, less specific signs (hyperleukocytosis, encephalopathy, auscultatory abnormalities) were ranked lower.

According to the experts, when these criteria regress or disappear, they are therefore considered associated with clinical cure of VAP. Considering the small differences in the relative weights of each criterion, it seems reasonable to consider that the association of at least 3 of these criteria is necessary to consider a clinical cure. To date, no prospective evaluation of the robustness of these criteria to guide antimicrobial treatment duration has been performed.

The ASPIC study aims at investigating whether an antimicrobial stewardship for microbiologically proven VAP based on daily assessment of clinical cure and antimicrobial discontinuation, if it is obtained, would be non-inferior to standard management in terms of all-cause mortality, treatment failure or occurrence of new episode of VAP before day 28.

METHODS AND ANALYSIS

Study design

This study is a pragmatic, national, multicenter, phase III, single-blinded, non-inferiority comparative randomized clinical trial (RCT) comparing two therapeutic strategies for microbiologically proven VAP on the basis of two parallel arms:

- Experimental group: Antimicrobial stewardship based on daily clinical assessment of clinical cure. Discontinuation of appropriate antibiotic therapy is made if clinical cure (daily assessment) criteria of VAP are met.
- Control group: Standard management: duration of 7 full days (7 times consecutive 24h) of appropriate antibiotic therapy according to VAP guidelines. In the control group, clinical cure assessment will be performed daily by the intensivist in charge of the patient but the antibiotic therapy will not be discontinued until 7 days whatever the clinical cure.

The trial overview is summarized in Figure 1. We report here the study protocol according to the SPIRIT (Standard Protocol Items: Recommendations for interventional Trials) statement (15).

Definitions

Appropriate empiric antibiotic therapy: the empiric antibiotic therapy is defined as appropriate if all the VAP causative pathogens are susceptible (*in vitro*) to at least one molecule of the empirical treatment. Empiric antibiotic therapy is defined as inappropriate if at least one causative bacteria is resistant (*in vitro*) to the empirical treatment.

Definitive diagnosis of VAP is defined, in accordance with international guidelines, by the association of:

- Mechanical ventilation requirement for more than 48 hours
- New pulmonary infiltrate of strongly suspected infectious origin
- Worsening oxygenation
- Purulent tracheal secretions and at least 1 of the following criteria within the 24 hours prior to the first dose of antibiotic therapy: (i) fever (body temperature >38,3°C) or hypothermia (body temperature <35°C) , (ii) white blood cell (WBC) count >10,000 cells/mm^3 or <4,000 cells/mm^3
- microbiological criteria (positive quantitative culture of a lower respiratory tract (LRT): bronchoalveolar lavage fluid (BAL) (positivity threshold $\geq 10^4$ colony-forming units/mL) or plugged telescopic catheter (PTC) (threshold $\geq 10^3$ colony-forming units/mL) or quantitative endotracheal aspirate (ETA) distal pulmonary secretion samples (significant threshold $\geq 10^5$ colony-forming units/mL)

Clinical cure (Figure 2)

- complete resolution of at least 3 the 4 clinical signs and/of symptoms of VAP, according the STOP algorithm (items: purulent Secretions, body Temperature, Oxygenation, systolic blood Pressure) AND

- No additional antibiotic therapy required for VAP treatment AND
- Patient is alive

Treatment failure defined by signs of VAP within 72 hours after the end antibiotic treatment at the test of cure visit

Superinfection: Isolation of a pathogen, other than the causative baseline pathogen, from a LRT specimen obtained in a subject with signs and symptoms of VAP developed during antibiotic treatment

Persistence: Continued presence of the original causative baseline pathogen(s) from a LRT culture obtained between EOT and 72 after EOT

New VAP: New episode of microbiologically documented VAP from 72h after the EOT to day 28

VAP-Recurrence: New VAP due to at least one of the original causative pathogen(s) found at baseline

Definitions of treatment failure, persistence, superinfection, persistence, VAP recurrence and new VAP are summarized in Figure 3.

Setting

This will be a French multicenter study involving 24 centers. Participants will be recruited in ICU wards during their hospital stay.

Study population

Participants in ICU wards will be eligible if they fulfilled following criteria:

Inclusion criteria:

- Aged 18 years or more
- Patient under mechanical ventilation (MV)
- Microbiologically confirmed diagnosis of first episode of VAP (see definition section)
- Initial appropriate (see definitions section) antibiotic therapy (whether empirical or not)
- Written informed consent from the patient or a legal representative if appropriate. If absence of a legal representative the patient can be included following an emergency procedure

Exclusion criteria:

- Patient under selective bowel decontamination
- Concomitant extra-respiratory infection requiring antibiotic therapy at inclusion
- Inclusion in another experimental study on antimicrobial stewardship
- Moribund at admission (IGS II>80)
- Thoracic trauma with Abbreviated Injury Scale (AIS) thorax ≥ 3
- Severely immunocompromised patients: congenital immunodeficiency, neutropenia (<0.5 G/l), leukopenia (<1 G/l), acute hematologic malignancy or stem cell transplant, HIV infection with CD4 count below 200/mm^3, immunosuppressive therapy or long term corticosteroid therapy > 0.5 mg/kg

- VAP due to: *Pseudomonas aeruginosa*, Carbapenem-resistant *Acinetobacter* spp, Carbapenem-resistant *Enterobacterales*
- Bacterial VAP occurring in the context of co-infectionof COVID-19 or other viral VAP (confirmed by RT-PCR)
- Patients with empyema, necrotizing and abscessed pneumonia
- Pregnant women
- No health insurance coverage

Recruitment

The screening will aim at identifying patients hospitalized in ICU who underwent a LRT sample because a VAP was suspected. During this period, management of patients is similar to usual care with clinical, biological and radiological assessments. After microbiological diagnosis confirmation and reception of Antibiotic Susceptibility Testing (AST) proving that the initial empiric antibiotic therapy was appropriate, eligible patient will be offered participation in the trial. Written informed consent would be obtained by the investigator or by a physician representing the investigator, from all patients, their next of kin, as appropriate, accordingly to French regulatory agencies authorization (see section Methods for obtaining information and consent from research participants).

Treatment allocation and randomization

Participants will be randomized (Day 1) with a 1:1 ratio to either antimicrobial stewardship-guided antibiotic therapy strategy (experimental group) or standard management (control group) using a computer-generated randomization scheme of various-sized blocks, through an internet centralized randomization service running 24hrs/24hrs. Random block sizes proportional to the number of groups will be generated using a pre-specified maximum blindly

from the investigators. Permuted block technique will be used to assign treatment within the various-sized blocks. Randomization will be stratified by center. The randomization scheme will be generated by a statistician who is not involved in any other aspect of the study, and all researchers will be blinded to block size(s) and randomization list to avoid prediction of future patient's allocation. Allocation concealment will be ensured, as the service will not release the randomization code until the patient has been recruited into the trial.

Blinding

This study will be single-blinded. Participants will not be informed of their group allocation. Blinding will be ensured as most patients will be either sedated (within standard of care) or unable to have appropriate discussions with investigational team for the duration of the experimental at study. The statistician conducting the data analysis will also be blinded to group allocation. The medical staff cannot be blinded to the randomization arm due to the nature of experimental design and our choice to evaluate this strategy in real-life clinical practice conditions. If the patient is transferred to another clinical ward or leave the hospital during the 3-month follow-up, other healthcare professionals involved in their management will not be made aware of the randomization arm.

Study procedures

The general flowchart of the study is shown in Figure 1. A pragmatic approach will be followed and usual patient management recommended by international guidelines (9–11) will be provided in participating ICUs. In particular the choice of antibiotic therapy will be left at investigator discretion.

In the experimental group, the ICU physician will discontinue the antibiotic therapy as soon as clinical cure criteria of VAP are met. Minimal duration of appropriate antibiotic treatment will

be 3 days (including empirical antibiotic therapy). After 72 hours (usual delay to receive AST results) of appropriate antibiotic treatment, the assessment of clinical cure will be performed daily on the basis of 4 criteria:

- Regression or the decreased abundance of purulent tracheal secretions
- Absence of fever or hypothermia
- Improvement of oxygenation (assessed by increase of PaO_2/FiO_2 ratio and PaO_2/FiO_2>150)
- Absence of arterial hypotension (hypotension is defined by mean arterial pressure < 70 mmHg(16,17)) or decreased need for epinephrine or norepinephrine by at least 0,1 µg/kg/mn compared to baseline (day of inclusion)

This assessment will be repeated daily until at least 3 of the 4 criteria are met, i.e. the patient is considered clinically cured, thereby allowing the discontinuation of antibiotic therapy (Figure 2).

A daily phone hotline, provided by coordinating investigator's team, will be accessible to investigators for multidisciplinary validation of antibiotic discontinuation in patients included in the experimental group.

For control group, ~~fixed~~ duration of antibiotic therapy will be at least 7 full days (since the initiation of empirical antibiotic therapy), whatever clinical assessment.

For both groups, in case of non-clinical recovery after 7 full days (treatment failure) and/or in case of suspicion of new VAP during treatment (superinfection), a new lower respiratory tract sampling will be performed, and a new antibiotic therapy will be initiated. In case of new VAP, patients will be treated according to the usual practices of the center.

Following data will be collected daily from day 2 to day 28 or to ICU discharge in participants from both arms: vital status, ventilation status, PaO_2 and FiO_2 (if ventilated), temperature, tracheal secretions, blood pressure, use and dose of vasopressors, data on any infection

throughout study period (infection site, bacteriological documentation, number of days of antibiotic therapy), antibiotic use (molecule; dosage; duration of treatment).

Additional data will be collected daily from Day 2 to Day 8: clinical assessment, focused pulmonary examination, laboratory assessment (usual tests, biochemical, hematological), radiological evaluation (Chest X-Ray/CT-scan), if performed as part of usual care.

Rectal swabbing for collection of data on colonization or acquisition of Multidrug Resistant (MDR) bacteria will be performed at ICU admission and weekly until ICU discharge as part as usual care.

All participants will be followed up to day 90 with vital status assessment.

Outcomes

The primary endpoint will be a composite of:

1. All-cause mortality (ACM) measured at day 28 after initiation of therapy OR

2. Treatment failure defined by signs of VAP within 72 hours after the end antibiotic treatment at the test of cure visit OR

3. New episode of microbiologically confirmed VAP from 72H after the end of antibiotic treatment to day 28 after initiation of VAP antibiotic treatment

To avoid interpretation bias for the primary outcome, clinical and microbiological records of all participants will be reviewed by adjudication committee composed with two experts in order to evaluate the presence of (i) clinical cure, (ii) treatment failure and (iii) new episode of VAP. This evaluation will be performed blindly from the randomization group and from the interpretation of the investigation team, according to predefined criteria (see Definition section). The adjudication committee will be composed of study investigators (including

scientific committee of ASPIC). Each member will review the primary endpoints criteria of a subgroup of patients that were not enrolled in its center.

Secondary endpoints will be: day 28 all-cause mortality, proportion of treatment failure and of new episode of VAP; the number of antibiotic free days alive from initiation of VAP antibiotic therapy to day 28; the duration of invasive MV; the length of ICU stay, defined by the number of days between inclusion and ICU discharge or in-ICU death; the proportion of VAP recurrence assessed by the intensivist; the antibiotic related side effects; the proportion of acquisition of MDR bacteria (defined as the identification of a MDR bacteria carriage not present at admission); the proportion of protocol deviation i.e. lack of antibiotic therapy discontinuation despite a fulfillment of clinical cure definition in the experimental group ; the total cumulative costs of antibiotics and incremental cost effectiveness ratio; and the Desirability of Outcome Ranking (DOOR) and the Response Adjusted for Duration of Antibiotic Risk (RADAR) for each strategy (experimental and control groups)(18).

All trial participants will be ranked with respect to the desirability of their overall outcome and the distributions of DOORs will be compared between strategies Overall clinical outcomes at day 28 will be ranked from most to least desirable as followed:

1. Survival, clinical cure
2. Survival, new pulmonary infection
3. Death

In RADAR analyses, patients will be ranked overall clinical outcome, but in case of ex-aequo, the patient with a shorter duration of antibiotic use will receive a higher rank

Sample size justification

Assuming that 25% of the patients will encountered all-cause mortality, treatment failure or occurrence of new episode of VAP before day 28 in the control arm (19), 590 subjects (295 per

arm) are needed to establish non-inferiority with the absolute difference of death, treatment failure or occurrence of new episode of VAP doesn't exceed 10% (non-inferiority margin) between experimental and control arms with a power of 80%, a type I error (alpha) of 2.5%.

A non-inferiority margin of 10% was chosen taking into account the methodological data applied to the randomized controlled trials dedicated to VAP. According European medicine Agency (20), the suggested non-inferiority margin should not exceed -12.5% for clinical outcome documented at a Test-of-Cure visit. In this recommendation, the margin of 12.5% do not include mortality.

In a published study (ASPECT)(21) designed to show non-inferiority for the primary endpoint in the intention-to-treat population, with a 10% non-inferiority margin to achieve 90% power at a one-sided significance level of 0,025 (based on regulatory agency guidance (22) and assuming a 28-day all-cause mortality rate of 20% in both groups.

Data analysis plan

The primary analysis will be performed on the intention-to-treat population (23). The 95% confidence interval of the difference in proportions of all-cause death, treatment failure or occurrence of new episode of VAP observed between the two groups will be estimated. This confidence interval will be compared to the non-inferiority margin of 10%. If the lower limit of the confidence interval of the difference in proportions is less than or equal to -10%, then we cannot conclude that the antimicrobial stewardship-based strategy is non-inferior to the reference strategy. In the opposite case, if the lower limit of the confidence interval is strictly greater than -10%, then we will conclude that the antimicrobial stewardship-based strategy is non-inferior on all-cause mortality, treatment failure or occurrence of new episode of VAP at day 28 after inclusion. Sensitivity analysis on per-protocol population will be performed. All

tests of superiority (secondary objectives) will be two-sided with type I error of 5% and tests of non-inferiority will be one-sided with type I error 2.5%. All statistical analyses will be performed using SAS software (SAS Institute Inc., Cary, NC) v. 9.4 or later, or R software (R Foundation for Statistical Computing, Vienna, Austria. http://www.r-project.org/) v. 4.0 or later.

The primary analysis will also been performed in the following subgroups of patients:

- Those whose baseline bacteriological samples were assessed by rapid microbiological technique (germ identification and AST)
- Patients admitted to ICU for trauma vs other reasons of admission
- Patients with early onset VAP (< 5 days after ICU admission) vs late onset VAP (≥5 days after ICU admission).

No strategy of imputation is forecasted in case of missing data for the primary assessment criterion. Information available at time of last follow-up will be taken into account.

Data collection and management

Data collection will be performed in electronic format. The statistical software used for data entry will be CleanWeb™; it will fulfill the regulatory requirements and security norms. Data will be handled according to the French law. All original records (including consent forms, reports of suspected unexpected serious adverse reactions and relevant correspondences) will be archived at trial sites for 15 years. The cleaned trial database file will be anonymized and maintained for 15 years. Data on primary and secondary endpoints, will be collected, as detailed in Study procedures section and Table 1. The data of this study will be available upon reasonable request from the corresponding author but it will not be publicly available due to privacy or ethical restrictions.

Table 1. Chronology of the study and procedures

Actions		D-2 to D1	D1	D2 to D8	D9 to D27 or discharge of hospital	D28	D90
Inclusion visit			X_R				
Verification of inclusion and non-inclusion criteria			X_R				
Information			X_R				
Written Informed consent			X_R				
Randomization			X_R				
Pregnancy test			X_R				
Medical history		X_C	X_C				
Physical examination		X_C	X_C	X_C	X_C	X_R	
Phone call							X_R
Chest X-Ray/CT-scan		X_C	X_C	X_C			
PaO_2/FiO_2 ratio		X_C	X_C	X_C	X_C		
Assessment of clinical symptoms of VAP		X_C	X_C				
Assessment of clinical recovery of VAP				Xc			
Start antibiotics			X_C				
Antibiotics			X_C	X_C	X_C		
Rectal swab				X_C	X_C		
Serum creatinin and calculated creatinin clearance			X^b_C				
White blood count		X_C	X_C	X_C	X_C		
SCORE	ISS	X_C					
	SOFA	X_C	X_R				
	IGS	X_C					
Assessment of rate of treatment failure and new episode of VAP						X_R	
Antibiotic free days						X_R	
Vital status						X_R	X_R
Adverse events			X_R	X_R	X_R	X_R	X_R
Hospital admissions				X_C	X_C	X_R	X_R

* length of antibiotic therapy depends on the clinical response. In the control group, predictable length is 7 days.

b creatinin clearance may be performed (Cl_{cr}= (urinary creatinin/serum creatinin)*urine $volume_{24h}$) as frequently as clinically indicated to guide appropriate antibiotic therapy in subjects with renal impair

X_C : made in usual care

X_R : acts added for research

TRIAL STATUS

Not yet recruiting. Participant recruitment is scheduled to begin in 2022 and the recruiting period will last 36 months.

ETHICS AND DISSEMINATION

Legal obligations and approval

Sponsorship has been agreed by Assistance Publique—Hôpitaux de Paris (AP-HP, Clinical Research and Innovation Department) for this interventional research protocol involving human participants concerning a health product. AP-HP has obtained the approval of the French medicine regulatory agency (Agence Nationale de Sécurité du Médicament et des Produits de Santé, ANSM; EUDRACT number 2021-002197-78, 19 August 2021) and of the ethics comitee (Comité de Protection des Personnes (CPP) Ile-de-France III (CNRIPH: 21.03.25.60729, 10 October 2021)) for the study protocol (version ASPIC−1.3; 03 September 2021). The trial will be carried out in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines. Any substantial modification to the protocol will be sent to the sponsor, and then to the ANSM and the CPP for approval before the amendment can be implemented. The information sheet and the consent form can be revised if necessary, particularly if there is a substantial amendment to the study or if adverse reactions occur. AP-HP is the owner of the data. The data cannot be used or disclosed to a third party without its prior permission.

Methods for obtaining information and consent from research participants

In accordance with Article L.1122-1-1 of the French Public Health Code, no research will be carried out without patient free and informed consent, obtained in writing after the person has been given the information specified in Article L.1122-1 of said Code. Written informed consent will be obtained from all patients, their next of kin, as appropriate. If patients are unable to provide informed consent and if neither their next of kin nor other designated person is available, a procedure for inclusion in the study in emergency situations would be applied. A definitive post hoc consent form would be ultimately obtained from patients who survived but had been initially treated on the basis of the emergency consent. These procedures have been approved for the ASPIC trial by the french Commission nationale de l'informatique et des libertés (CNIL, ref MLD/MFI/AR2111748, 18 October 2021).

Patient and public involvement

The patient's (or next of kin's) free and informed written consent will be obtained after a reflection period of at least 15 minutes after information, by the investigator, or by a doctor representing the investigator, before enrollement in the trial, during the baseline visit.

The investigator will specify in the research participant's medical file the methods used for obtaining their consent as well as the methods used for providing information with a view to obtaining consent. The investigator will retain the original signed and dated consent form.

Subjects may exit the study at any time and for any reason.

Data deposition, quality control and curation

The persons responsible for the quality control of clinical matters will take all necessary precautions to ensure the confidentiality of information related to the study participants. These persons, as well as the investigators themselves, are bound by professional confidentiality. During or after the research, all data collected about the participants and sent to the sponsor by

the investigators (or any other specialized collaborators) will be anonymized. Under no circumstances should the names, addresses and other protector identifiers of the subjects involved be shown.

In any case of premature withdrawals and exits, the investigator must provide their reason(s) and try to collect primary endpoint, secondary endpoints and safety assessment, if the participant agrees. If a participant exits the study prematurely or withdraws consent, any data collected prior to the date of premature exit may still be used excepted if the participant refuses it in writing.

The research data will be collected and monitored using an eCRF through CleanWEB™ Electronic Observation Book and will be centralized on a server hosted by the AP-HP Operation Department.

Research staff of the Clinical Trial Unit will work with local investigators to obtain data that are as complete and accurate as possible. An independent Clinical Research Associate appointed by the sponsor will be responsible for the proper running of the study, for collecting, documenting, recording and reporting all handwritten data, in accordance with the Standard Operating Procedures applied within the Clinical Research and Innovation Department of AP-HP. The investigators agree to accept the quality assurance audits carried out by the sponsor as well as the inspections carried out by the competent authorities. All data, documents and reports may be subject to regulatory audits. These audits and inspections cannot be refused on the grounds of medical secrecy. An audit can be carried out at any time by independent individuals appointed by the sponsor, aiming at ensuring the quality of the study, the validity of the results and compliance with the legislation and regulations in force. The persons who manage and monitor the study agree to comply with the sponsor's audit requirements. The audit may encompass all stages of the study, from the development of the protocol to the publication of

the results and the storage of the data used or produced as part of the study. Sponsor is responsible for access to the study database.

The investigator will assess the seriousness of each adverse event, report all serious and non-serious adverse events in the case report form and assess the causal relationship of serious adverse events with the study procedures according to the WHO method.

A data monitoring committee is not needed for this trial as the expected risk for the participant is minimal.

Publication plan

Results will be published in international peer-reviewed medical journals. Scientific presentations and reports will be written under the responsibility of the coordinating investigator of the study with the agreement of the principal investigators and the methodologist. The co-authors of the reports and publications will be the investigators and clinicians involved, on a pro rata basis of their contribution in the study, as well as the biostatistician and associated researchers. Rules on publication will follow international recommendations (24).

Authors' contributions: AF and EW contributed to the conception and design of the research protocol, assisted by DB and PE. AR, IM-L, PM, J-FT, AB and J-RZ provided critical input pertaining to the design of the trial interventions and procedures. AF wrote the first draft of the protocol and this manuscript. DB and PE designed the statistical analysis plan. All authors critically revised and modified the protocol and the article. They all approved the final version to be published.

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Competing interests statement:

AF, DB, AB, PE: declare no competing interest

AR: grants from bioMerieux and Merck

IM-L: board on PFIZER, MSD, GILEAD

J-FT directly related to the protocol: none, participation to scientific advisory boards: Pfizer, Gilead, Merck, BD, Shionoghi; readings: Merck, Biomerieux, Pfizer, Shionogi; research grants to my research unit: thermofischer, Pfizer, Merck

J-RZ: consulting fees from MSD, Pfizer, speaker fees fom MSD, Pfizer, Shionogi, Correvio and Eumedica

EW: Speaker fees from MSD, Akcea therapeutics and LFB, support for attending meeting/travel: LFB and Akcea therapeutics

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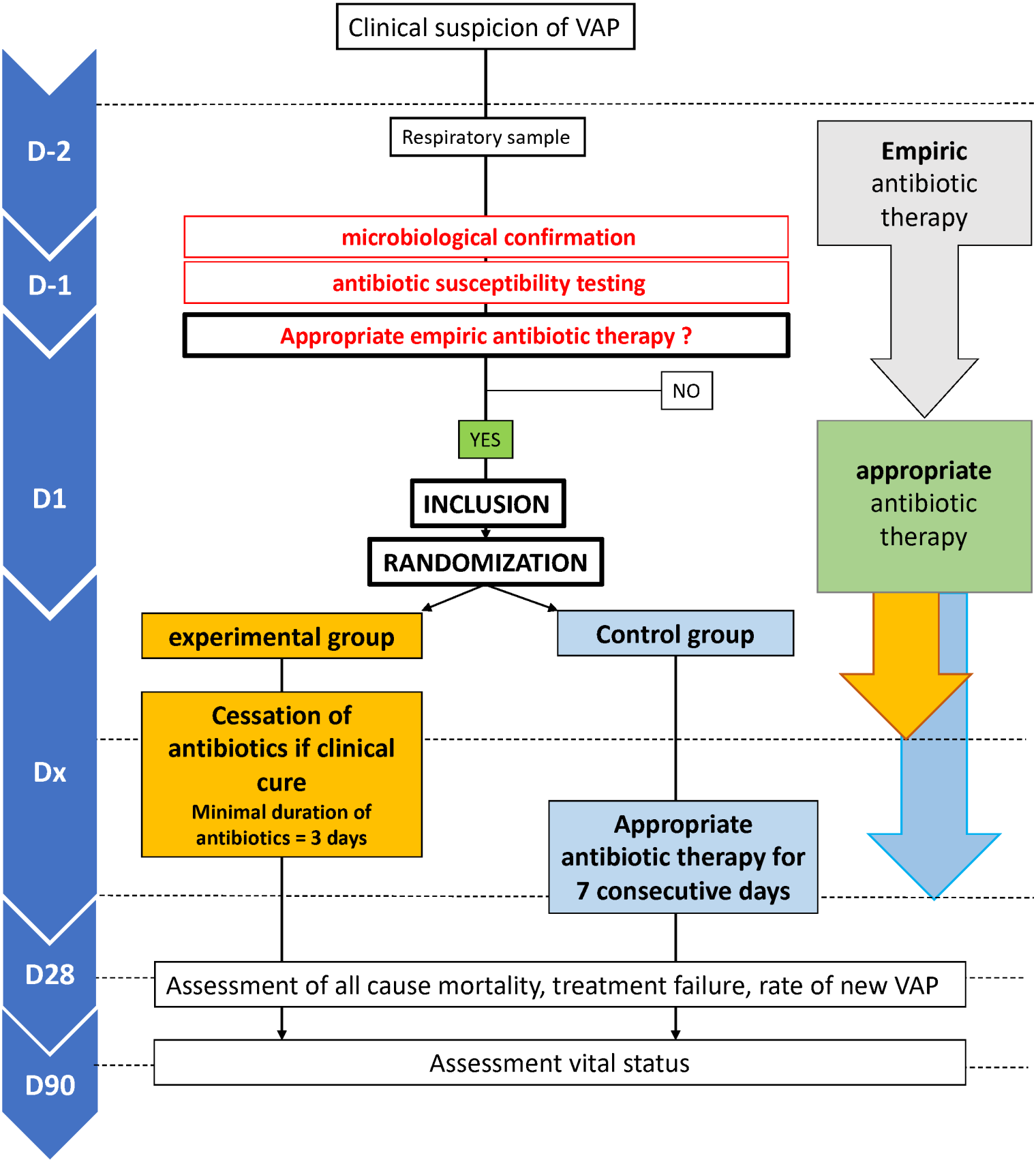
Figures and Table legends

Figure 1: General flowchart of the study

Figure 2: Criteria of clinical cure and criteria for discontinuation of antibiotic therapy in experimental arm

Figure 3: Description of microbiological categories of outcomes in relation to time of occurrence of new episode of VAP after inclusion adapted from(21)

Table 1: Chronology of the study and procedures


Clinical suspicion of VAP
D-2
Respiratory sample
Empiric antibiotic therapy
D-1
microbiological confirmation
antibiotic susceptibility testing
Appropriate empiric antibiotic therapy ?
NO
YES
D1
INCLUSION
RANDOMIZATION
appropriate antibiotic therapy
experimental group
Control group
Dx
Cessation of antibiotics if clinical cure
Minimal duration of antibiotics = 3 days
Appropriate antibiotic therapy for 7 consecutive days
D28
Assessment of all cause mortality, treatment failure, rate of new VAP
D90
Assessment vital status

Experimental group

- Antimicrobial stewardship based on daily clinical assessment of clinical cure of confirmed VAP are met. Intensivists will perform clinical assessment daily in order to decide on the pursuit or discontinuation of antibiotic therapy.
- Antibiotic therapy is stopped if signs of **clinical cure** of VAP are met (minimum 3 days)

CLINICAL CURE

STOP antibiotics if ≥ 3 criteria are met

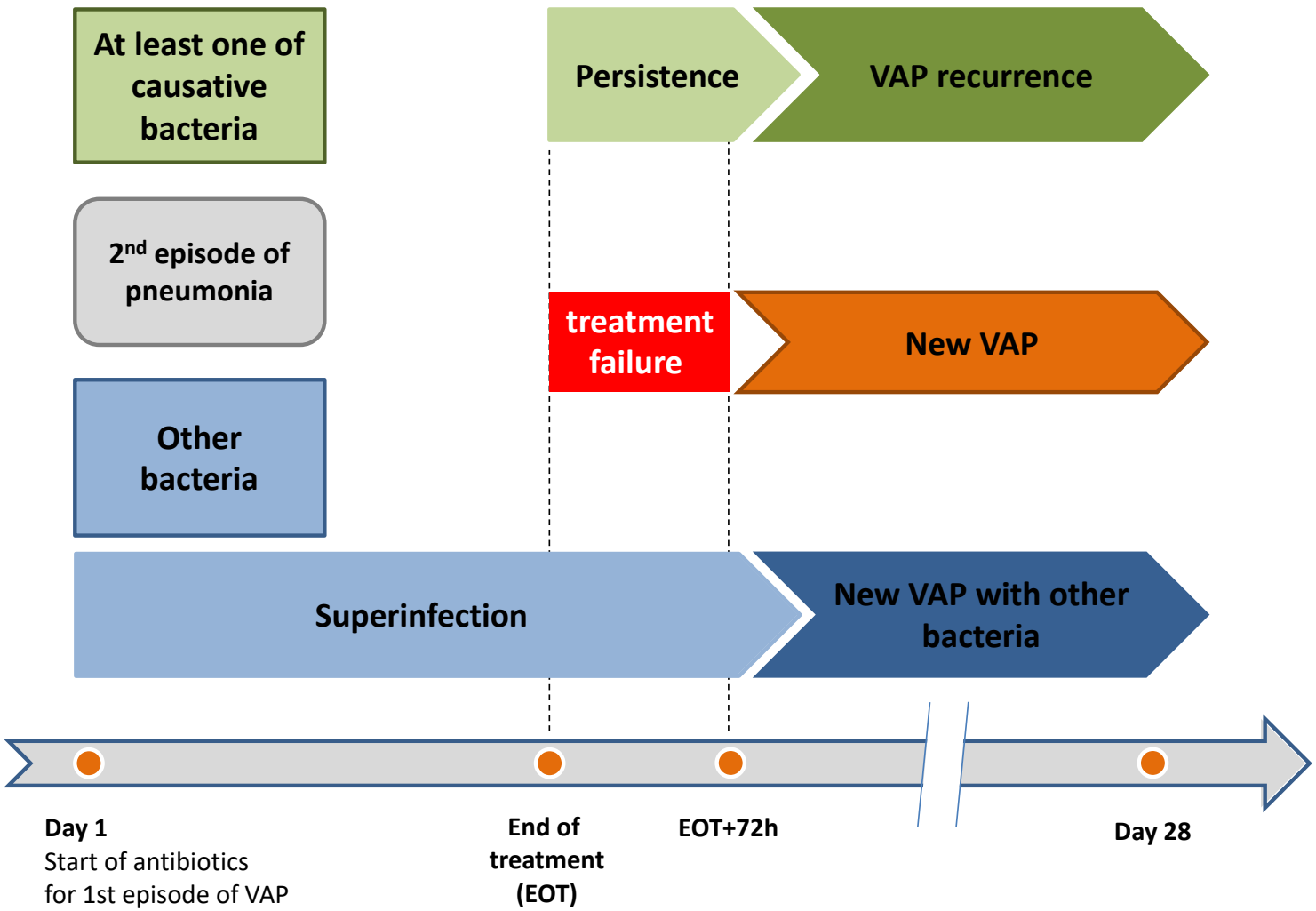
1. Regression* of purulent trachael **S**ecretions

2. Normo**T**hermia
36°C < T < 38.3°C

3. Improved*
Oxygenation, measured by an increase in the of the PaO2/FiO2 ratio

4. Absence of hy**P**otension

* compared to the day of initiation of antibiotic therapy


At least one of causative bacteria
2nd episode of pneumonia
Other bacteria
Persistence
VAP recurrence
treatment failure
New VAP
Superinfection
New VAP with other bacteria
Day 1
Start of antibiotics for 1st episode of VAP
End of treatment (EOT)
EOT+72h
Day 28

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	3
Funding	4	Sources and types of financial, material, and other support	25
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	25
	5b	Name and contact information for the trial sponsor	
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	18
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	14
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
	6b	Explanation for choice of comparators	
Objectives	7	Specific objectives or hypotheses	

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	10
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	10
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	12,13
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	14
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	14
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	14,15
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Fig 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	15
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	15
Methods: Assignment of interventions (for controlled trials)			
Allocation:			

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	11
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	11
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	11,12
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	12
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	17
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Table 1
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	17
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16,17
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	17,18

Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	21
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	21
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	22
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	18
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	18
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	19
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	19
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	NA
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18, 21
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	20,21
	31b	Authorship eligibility guidelines and any intended use of professional writers	22
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	yes
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Antimicrobial Stewardship for Ventilator Associated Pneumonia in Intensive Care (the ASPIC trial): study protocol for a randomized controlled trial

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Complete List of Authors:	FOUCRIER, Arnaud; Hospital Beaujon, Department of Anaesthesiology and Critical Care, Beaujon Hospital, DMU Parabol, AP-HP Nord, Université de Paris Roquilly, Antoine; CHU Nantes, Pôle anesthésie réanimations, CIC Immunologie et infectiologie, Service d'Anesthésie Réanimation chirurgicale, Hôtel Dieu, Nantes, F-44093 France Bachelet, Delphine; Hopital Bichat - Claude-Bernard, Département d'épidémiologie, Biostatistiques et Recherche Clinique, Hôpital Bichat, AP-HP Nord, Université de Paris, 75018, Paris, France Martin-Loeches, Ignacio; University of Dublin Trinity College, Multidisciplinary Intensive Care Research Organization (MICRO), Department of Intensive Care Medicine, St. James's University Hospital,; IDIBAPS, Hospital Clinic,Universidad de Barcelona, CIBERes, Barcelona, Spain Bougle, Adrien; APHP, Department of Anesthesiology and Critical Care Medicine, Cardiology Institute, Sorbonne University, GRC 29, Pitié-Salpêtrière Hospital, 47-83 Boulevard de l'Hôpital, 75013, Paris, France. Timsit, Jean-François; Hôpital Bichat - Claude-Bernard, Medical and Infectious Diseases ICU (MI2), F-75018 Paris, France; University of Paris, IAME, INSERM, F-75018 Paris, France Montravers, Philippe; CHU Bichat-Claude Bernard, Université Paris-Diderot, APHP, Département d'anesthésie-réanimation, université Paris VII Sorbonne Cité, CHU Bichat-Claude-Bernard Zahar, Jean-Ralph; Hopital Avicenne, Service de Microbiologie Clinique et Unité de Contrôle et de Prévention Du Risque Infectieux, Eloy, Philippine; Hôpital Bichat Claude-Bernard, Département d'épidémiologie, Biostatistiques et Recherche Clinique, Hôpital Bichat, AP-HP Nord, Université de Paris, 75018, Paris, France Weiss, Emmanuel; Hôpital Beaujon, Anesthesiology and Intensive Care
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Antimicrobial Stewardship for Ventilator Associated Pneumonia in Intensive Care (the ASPIC trial): study protocol for a randomized controlled trial

Arnaud FOUCRIER[1], Antoine ROQUILLY[2], Delphine BACHELET[3], Ignacio MARTIN-LOECHES[4,5], Adrien BOUGLE[6], Jean-François TIMSIT[7], Philippe MONTRAVERS[8], Jean-Ralph ZAHAR[9], Philippine ELOY[3], Emmanuel WEISS[1], ASPIC study group

[1] Department of Anaesthesiology and Critical Care, Beaujon Hospital, DMU Parabol, AP-HP Nord, Université de Paris, 100 Boulevard du Général Leclerc, 92110, Clichy, France

[2] Nantes Université, CHU Nantes, Pôle anesthésie réanimations, CIC Immunologie et infectiologie, Service d'Anesthésie Réanimation chirurgicale, Hôtel Dieu, Nantes, F-44093 France

[3] Département d'épidémiologie, Biostatistiques et Recherche Clinique, Hôpital Bichat, AP-HP Nord, Université de Paris, 75018, Paris, France

[4] Multidisciplinary Intensive Care Research Organization (MICRO), Department of Intensive Care Medicine, St. James's University Hospital, Trinity Centre for Health Sciences, Dublin, Ireland

[5] Hospital Clinic, IDIBAPS, Universidad de Barcelona, CIBERes, Barcelona, Spain

[6] Department of Anesthesiology and Critical Care Medicine, Cardiology Institute, Sorbonne University, GRC 29, AP-HP, Pitié-Salpêtrière Hospital, 47-83 Boulevard de l'Hôpital, 75013, Paris, France.

[7] AP-HP, Bichat Hospital, Medical and Infectious Diseases ICU (MI2), F-75018 Paris, France; University of Paris, IAME, INSERM, F-75018 Paris, France

[8] Département d'anesthésie-réanimation, université Paris VII Sorbonne Cité, CHU Bichat-Claude-Bernard, AP-HP, 46, rue Henri-Huchard, 75018 Paris, France

[9] Service de Microbiologie Clinique et Unité de Contrôle et de Prévention Du Risque Infectieux, Groupe Hospitalier Paris Seine Saint-Denis, AP-HP, 125 Rue de Stalingrad, 93000, Bobigny, France

Corresponding author

Arnaud FOUCRIER, Department of Anaesthesiology and Critical Care, Beaujon Hospital, DMU Parabol, AP-HP Nord, Université de Paris, 100 Boulevard du Général Leclerc, 92110, Clichy, France

email: arnaud.foucrier@aphp.fr

Abstract (218 words)

Introduction: Ventilator associated pneumonia (VAP) remains the leading cause of infections treated in the Intensive Care Units (ICU). In a personalized care approach, we hypothesize that the duration of treatment of VAP can be reduced in function of the response to treatment.

Methods and analysis: The ASPIC trial is a pragmatic national multicenter, phase III, non-inferiority, comparative randomized (1:1) single-blinded clinical trial. Five hundred ninety adult patients hospitalized in 24 French ICU with a microbiologically confirmed first episode of VAP that received appropriate empirical antibiotic therapy will be included. They will be randomly allocated to standard management with duration of appropriate antibiotic fixed for 7 days according to international guidelines or antimicrobial stewardship based on daily clinical assessment of clinical cure. The assessment of clinical cure will be repeated daily until at least 3 criteria of clinical cure are met, allowing the discontinuation of antibiotic therapy in experimental group. The primary endpoint is a composite endpoint combining of all-cause mortality measured at day 28, treatment failure or new episode of microbiologically confirmed VAP until day 28.

Discussion: Demonstrate that a strategy to reduce the duration of antibiotic therapy for VAP based on clinical assessment is safe could lead to changes in practice as part of a personalized therapeutic approach, by reducing exposure to antibiotics and their side effects.

Ethics and dissemination: The ASPIC trial has been approved by the French regulatory agency (Agence Nationale de Sécurité du Médicament et des Produits de Santé, ANSM; EUDRACT number 2021-002197-78, 19 August 2021) and an independent ethics committee the Comité de Protection des Personnes (CPP) Ile-de-France III (CNRIPH : 21.03.25.60729, 10 Ocotber 2021) for the study protocol (version ASPIC−1.3; 03 September 2021) for all study centers. Participant recruitment is scheduled to begin in 2022. Results will be published in international peer-reviewed medical journals.

Trial registration number: NCT05124977, first posted November 18, 2021

Protocol version identifier N°1-3, 03 September 2021

Strengths and limitations of this study

- High quality methodology using randomized controlled trial (RCT) design that will provide a high-level of evidence on antimicrobial stewardship for management of ventilator-associated pneumonia (VAP) antibiotic strategy

- First RCT conducting in Europe assessing the value of clinical cure criteria ('STOP criteria') supported by an international expert panel to develop an antimicrobial stewardship strategy

- Class of antibiotics prescription not imposed by the protocol, in a pragmatic approach and in order to maximize the external validity of the results

- Risk of poor adherence of investigator team to experimental strategy, which could lead to absence of antibiotic discontinuation even if 'STOP' criteria are met.

INTRODUCTION

Reduction of use of antibiotics is a major point to control antimicrobial resistance in ICU (1). VAP is the first cause of healthcare-associated infections in ICU and more than half of antibiotics prescriptions in ICU are due to respiratory tract infections (2,3). The association between increase in antibiotic consumption and resistance emergence has been well documented for all patients admitted to the ICU who received antibiotic treatment and for patients treated for VAP (4).

In the last few years, the concept of antimicrobial stewardship (ASP) has been developed. It refers to programs, education, interventions that aim to optimize antibiotic use (5). In a recent review by Dyar et al. reports different definitions of ASP used in the literature (6). Antimicrobial stewardship refers to the responsible use of antimicrobials by healthcare professionals, and more specifically, to selection of the most appropriate antibiotic, duration, dose and route of administration for a given patient with a demonstrated or suspected infection (7,8).

For VAP treatment, international guidelines (9–11) strongly recommend a 7-day course of antibiotic therapy rather than a longer duration but underline that "there are situations in which a shorter or longer duration of antibiotics may be indicated, depending upon the rate of improvement of clinical, radiologic, and laboratory parameters". In the absence of very specific situations (severe immunodepression, abscessed pneumonia, necrotizing pneumonia), it is recommended not to exceed the duration of antibiotic therapy by more than 7-8 days. These recommendations are based on the concordant results of two meta-analyses that compared two treatment durations: 7-8 days vs. longer durations (12,13).

Recently, Weiss et al. (14) poled a panel of international experts to develop consensus criteria to evaluate the clinical response to antibiotic treatment for hospital-acquired pneumonia (HAP)

and VAP. In this work, various innovative concepts are developed. First, the experts agree that the criteria usually used in the literature to characterize the suspicion of VAP are weighted differently. According to the experts, among 9 selected criteria, the first 4 criteria with the most significant impact were: 1. Worsening of gas exchange, 2. Hypotension / vasopressor requirement, 3. Temperature abnormalities (fever or hypothermia), 4. Purulent tracheal secretions (rated ex-aequo with temperature abnormalities). Logically, less specific signs (hyperleukocytosis, encephalopathy, auscultatory abnormalities) were ranked lower.

According to the experts, when these criteria regress or disappear, they are therefore considered associated with clinical cure of VAP. Considering the small differences in the relative weights of each criterion, it seems reasonable to consider that the association of at least 3 of these criteria is necessary to consider a clinical cure. To date, no prospective evaluation of the robustness of these criteria to guide antimicrobial treatment duration has been performed.

The ASPIC study aims at investigating whether an antimicrobial stewardship for microbiologically proven VAP based on daily assessment of clinical cure and antimicrobial discontinuation, if it is obtained, would be non-inferior to standard management in terms of all-cause mortality, treatment failure or occurrence of new episode of VAP before day 28.

METHODS AND ANALYSIS

Study design

This study is a pragmatic, national, multicenter, phase III, single-blinded, non-inferiority comparative randomized clinical trial (RCT) comparing two therapeutic strategies for microbiologically proven VAP on the basis of two parallel arms:

- Experimental group: Antimicrobial stewardship based on daily clinical assessment of clinical cure. Discontinuation of appropriate antibiotic therapy is made if clinical cure (daily assessment) criteria of VAP are met.
- Control group: Standard management: duration of 7 full days (7 times consecutive 24h) of appropriate antibiotic therapy according to VAP guidelines. In the control group, clinical cure assessment will be performed daily by the intensivist in charge of the patient but the antibiotic therapy will not be discontinued until 7 days whatever the clinical cure.

The trial overview is summarized in Figure 1. We report here the study protocol according to the SPIRIT (Standard Protocol Items: Recommendations for interventional Trials) statement (15).

Definitions

Appropriate empirical antibiotic therapy: the empirical antibiotic therapy is defined as appropriate if all the VAP causative pathogens are susceptible (*in vitro*) to at least one molecule of the empirical treatment. Empirical antibiotic therapy is defined as inappropriate if at least one causative bacteria is resistant (*in vitro*) to the empirical treatment.

Definitive diagnosis of VAP is defined, in accordance with international guidelines, by the association of:

- Mechanical ventilation requirement for more than 48 hours
- New pulmonary infiltrate of strongly suspected infectious origin
- Worsening oxygenation
- Purulent tracheal secretions and at least 1 of the following criteria within the 24 hours prior to the first dose of antibiotic therapy: (i) fever (body temperature >38,3°C) or hypothermia (body temperature <35°C) , (ii) white blood cell (WBC) count >10,000 cells/mm^3 or <4,000 cells/mm^3
- microbiological criteria (positive quantitative culture of a lower respiratory tract (LRT): bronchoalveolar lavage fluid (BAL) (positivity threshold $\geq 10^4$ colony-forming units/mL) or plugged telescopic catheter (PTC) (threshold $\geq 10^3$ colony-forming units/mL) or quantitative endotracheal aspirate (ETA) distal pulmonary secretion samples (significant threshold $\geq 10^5$ colony-forming units/mL)

Clinical cure

- complete resolution of at least 3 the 4 clinical signs and/of symptoms of VAP, according the STOP algorithm (items: purulent Secretions, body Temperature, Oxygenation, systolic blood Pressure – See Figure 2). AND

- No additional antibiotic therapy required for VAP treatment AND
- Patient is alive

Treatment failure defined by signs of VAP within 72 hours after the end antibiotic treatment at the test of cure visit

Superinfection: Isolation of a pathogen, other than the causative baseline pathogen, from a LRT specimen obtained in a subject with signs and symptoms of VAP developed during antibiotic treatment

Persistence: Continued presence of the original causative baseline pathogen(s) from a LRT culture obtained between EOT and 72 after EOT

New VAP: New episode of microbiologically documented VAP from 72h after the EOT to day 28

VAP-Recurrence: New VAP due to at least one of the original causative pathogen(s) found at baseline

Definitions of treatment failure, persistence, superinfection, persistence, VAP recurrence and new VAP are summarized in Figure 3.

Setting

This will be a French multicenter study involving 24 centers. Participants will be recruited in ICU wards during their hospital stay.

Study population

Participants in ICU wards will be eligible if they fulfilled following criteria:

Inclusion criteria:

- Aged 18 years or more
- Patient under mechanical ventilation (MV)
- Microbiologically confirmed diagnosis of first episode of VAP (see definition section)
- Initial appropriate (see definitions section) antibiotic therapy (whether empirical or not)
- Written informed consent from the patient or a legal representative if appropriate. If absence of a legal representative the patient can be included following an emergency procedure

Exclusion criteria:

- Patient under selective bowel decontamination
- Concomitant extra-respiratory infection requiring antibiotic therapy at inclusion
- Inclusion in another experimental study on antimicrobial stewardship
- Moribund at admission (IGS II>80)
- Thoracic trauma with Abbreviated Injury Scale (AIS) thorax ≥ 3
- Severely immunocompromised patients: congenital immunodeficiency, neutropenia (<0.5 G/l), leukopenia (<1 G/l), acute hematologic malignancy or stem cell transplant, HIV infection with CD4 count below 200/mm^3, immunosuppressive therapy or long term corticosteroid therapy > 0.5 mg/kg

- VAP due to: *Pseudomonas aeruginosa*, Carbapenem-resistant *Acinetobacter* spp, Carbapenem-resistant *Enterobacterales*
- Bacterial VAP occurring in the context of co-infection of COVID-19 or other viral VAP (confirmed by RT-PCR)
- Patients with empyema, necrotizing and abscessed pneumonia
- Pregnant women
- No health insurance coverage

Recruitment

The screening will aim at identifying patients hospitalized in ICU who underwent a LRT sample because a VAP was suspected. During this period, management of patients is similar to usual care with clinical, biological and radiological assessments. After microbiological diagnosis confirmation and reception of Antibiotic Susceptibility Testing (AST) proving that the initial empirical antibiotic therapy was appropriate, eligible patient will be offered participation in the trial. Written informed consent would be obtained by the investigator or by a physician representing the investigator, from all patients, their next of kin, as appropriate, accordingly to French regulatory agencies authorization (see section Methods for obtaining information and consent from research participants).

Treatment allocation and randomization

Participants will be randomized (Day 1) with a 1:1 ratio to either antimicrobial stewardship-guided antibiotic therapy strategy (experimental group) or standard management (control group) using a computer-generated randomization scheme of various-sized blocks, through an internet centralized randomization service running 24hrs/24hrs. Random block sizes proportional to the number of groups will be generated using a pre-specified maximum blindly

from the investigators. Permuted block technique will be used to assign treatment within the various-sized blocks. Randomization will be stratified by center. The randomization scheme will be generated by a statistician who is not involved in any other aspect of the study, and all researchers will be blinded to block size(s) and randomization list to avoid prediction of future patient's allocation. Allocation concealment will be ensured, as the service will not release the randomization code until the patient has been recruited into the trial.

Blinding

This study will be single-blinded. Participants will not be informed of their group allocation. Blinding will be ensured as most patients will be either sedated (within standard of care) or unable to have appropriate discussions with investigational team for the duration of the experimental at study. The statistician conducting the data analysis will also be blinded to group allocation. The medical staff cannot be blinded to the randomization arm due to the nature of experimental design and our choice to evaluate this strategy in real-life clinical practice conditions. If the patient is transferred to another clinical ward or leave the hospital during the 3-month follow-up, other healthcare professionals involved in their management will not be made aware of the randomization arm.

Study procedures

A pragmatic approach will be followed and usual patient management recommended by international guidelines (9–11) will be provided in participating ICUs. In particular the choice of antibiotic therapy will be left at investigator discretion (according current French guidelines(11). Table 1)

In the experimental group, the ICU physician will discontinue the antibiotic therapy as soon as clinical cure criteria of VAP are met. Minimal duration of appropriate antibiotic treatment will

be 3 days (including empirical antibiotic therapy). After 72 hours (usual delay to receive AST results) of appropriate antibiotic treatment, the assessment of clinical cure will be performed daily based on 4 criteria:

- Regression or the decreased abundance of purulent tracheal secretions
- Absence of fever or hypothermia
- Improvement of oxygenation (assessed by increase of PaO_2/FiO_2 ratio and PaO_2/FiO_2>150)
- Absence of arterial hypotension (hypotension is defined by mean arterial pressure < 70 mmHg(16,17)) or decreased need for epinephrine or norepinephrine by at least 0,1 µg/kg/mn compared to baseline (day of inclusion)

This assessment will be repeated daily until at least 3 of the 4 criteria are met, i.e. the patient is considered clinically cured, thereby allowing the discontinuation of antibiotic therapy.

A daily phone hotline, provided by coordinating investigator's team, will be accessible to investigators for multidisciplinary validation of antibiotic discontinuation in patients included in the experimental group.

For control group, duration of antibiotic therapy will be at least 7 full days (since the initiation of empirical antibiotic therapy), whatever clinical assessment.

For both groups, in case of non-clinical recovery after 7 full days (treatment failure) and/or in case of suspicion of new VAP during treatment (superinfection), a new lower respiratory tract sampling will be performed, and a new antibiotic therapy will be initiated. In case of new VAP, patients will be treated according to the usual practices of the center.

Following data will be collected daily from day 2 to day 28 or to ICU discharge in participants from both arms: vital status, ventilation status, PaO_2 and FiO_2 (if ventilated), temperature, tracheal secretions, blood pressure, use and dose of vasopressors, data on any infection throughout study period (infection site, bacteriological documentation, number of days of antibiotic therapy), antibiotic use (molecule; dosage; duration of treatment).

Additional data will be collected daily from Day 2 to Day 8: clinical assessment, focused pulmonary examination, laboratory assessment (usual tests, biochemical, hematological), radiological evaluation (Chest X-Ray/CT-scan), if performed as part of usual care.

Rectal swabbing for collection of data on colonization or acquisition of Multidrug Resistant (MDR) bacteria will be performed at ICU admission and weekly until ICU discharge as part as usual care.

All participants will be followed up to day 90 with vital status assessment.

Table 1. Choice of empirical antibiotic therapy according current French guidelines(11)

Situations	**Therapeutic agent**
Early VAP ≤ 5th day after admission and absence of: – septic shock – risk factor* of MDR	amoxillin+clavulanic acid OR 3rd cephalosporin
Early VAP ≤ 5th day after admission AND – septic shock – absence of risk factor* of MDR	amoxillicin+clavulanic acid OR 3rd cephalosporin AND aminosid
Delayed VAP > 5th day of admission Or other risk factor* non-fermenting GNB°	ceftazidim OR cefepim OR piperacillin+tazobactam (in absence of known carriage of MDR) OR imipenem or meropenem (if known carriage of MDR) AND amikacin or ciprofloxacin
Risk factor# of SAMR•	vancomycin OR linezolid

*Prior intravenous antibiotic use within 90 day, Septic shock at time of VAP, ARDS preceding pneumonia, five or more days of hospitalization prior to the occurrence of VAP, acute renal replacement therapy prior to VAP onset.
° GNB : Gram Negative Bacilli
• SAMR : *Staphyococcus aureus* methicillin-resistant
if local prevalence of SAMR is elevated, recent colonization to SAMR, chronic cutaneous lesion, chronic dialysis

Outcomes

The primary endpoint will be a composite of:

1. All-cause mortality (ACM) measured at day 28 after initiation of therapy OR

2. Treatment failure defined by signs of VAP within 72 hours after the end antibiotic treatment at the test of cure visit OR

3. New episode of microbiologically confirmed VAP from 72H after the end of antibiotic treatment to day 28 after initiation of VAP antibiotic treatment

To avoid interpretation bias for the primary outcome, clinical and microbiological records of all participants will be reviewed by adjudication committee composed with two experts in order to evaluate the presence of (i) clinical cure, (ii) treatment failure and (iii) new episode of VAP. This evaluation will be performed blindly from the randomization group and from the interpretation of the investigation team, according to predefined criteria (see Definition section). The adjudication committee will be composed of study investigators (including scientific committee of ASPIC). Each member will review the primary endpoints criteria of a subgroup of patients that were not enrolled in its center.

Secondary endpoints will be: day 28 all-cause mortality, proportion of treatment failure and of new episode of VAP; the number of antibiotic free days alive from initiation of VAP antibiotic therapy to day 28; the duration of invasive MV; the length of ICU stay, defined by the number of days between inclusion and ICU discharge or in-ICU death; the proportion of VAP recurrence assessed by the intensivist; the antibiotic related side effects; the proportion of acquisition of MDR bacteria (defined as the identification of a MDR bacteria carriage not present at admission); the proportion of protocol deviation i.e. lack of antibiotic therapy discontinuation despite a fulfillment of clinical cure definition in the experimental group ; the total cumulative costs of antibiotics and incremental cost effectiveness ratio; and the Desirability of Outcome Ranking (DOOR) and the Response Adjusted for Duration of Antibiotic Risk (RADAR) for each strategy (experimental and control groups)(18).

All trial participants will be ranked with respect to the desirability of their overall outcome and the distributions of DOORs will be compared between strategies Overall clinical outcomes at day 28 will be ranked from most to least desirable as followed:

1. Survival, clinical cure
2. Survival, new pulmonary infection
3. Death

In RADAR analyses, patients will be ranked overall clinical outcome, but in case of ex-aequo, the patient with a shorter duration of antibiotic use will receive a higher rank

Sample size justification

Assuming that 25% of the patients will encountered all-cause mortality, treatment failure or occurrence of new episode of VAP before day 28 in the control arm (19), 590 subjects (295 per arm) are needed to establish non-inferiority with the absolute difference of death, treatment failure or occurrence of new episode of VAP doesn't exceed 10% (non-inferiority margin) between experimental and control arms with a power of 80%, a type I error (alpha) of 2.5%.

A non-inferiority margin of 10% was chosen taking into account the methodological data applied to the randomized controlled trials dedicated to VAP. According European medicine Agency (20), the suggested non-inferiority margin should not exceed -12.5% for clinical outcome documented at a Test-of-Cure visit. In this recommendation, the margin of 12.5% do not include mortality.

In a published study (ASPECT)(21) designed to show non-inferiority for the primary endpoint in the intention-to-treat population, with a 10% non-inferiority margin to achieve 90% power at a one-sided significance level of 0,025 (based on regulatory agency guidance (22) and assuming a 28-day all-cause mortality rate of 20% in both groups.

Data analysis plan

The primary analysis will be performed on the intention-to-treat population (21). The 95% confidence interval of the difference in proportions of all-cause death, treatment failure or occurrence of new episode of VAP observed between the two groups will be estimated. This

confidence interval will be compared to the non-inferiority margin of 10%. If the lower limit of the confidence interval of the difference in proportions is less than or equal to -10%, then we cannot conclude that the antimicrobial stewardship-based strategy is non-inferior to the reference strategy. In the opposite case, if the lower limit of the confidence interval is strictly greater than -10%, then we will conclude that the antimicrobial stewardship-based strategy is non-inferior on all-cause mortality, treatment failure or occurrence of new episode of VAP at day 28 after inclusion. Sensitivity analysis on per-protocol population will be performed. All tests of superiority (secondary objectives) will be two-sided with type I error of 5% and tests of non-inferiority will be one-sided with type I error 2.5%. All statistical analyses will be performed using SAS software (SAS Institute Inc., Cary, NC) v. 9.4 or later, or R software (R Foundation for Statistical Computing, Vienna, Austria. http://www.r-project.org/) v. 4.0 or later.

The primary analysis will also been performed in the following subgroups of patients:

- Those whose baseline bacteriological samples were assessed by rapid microbiological technique (germ identification and AST)
- Patients admitted to ICU for trauma vs other reasons of admission
- Patients with early onset VAP (< 5 days after ICU admission) vs late onset VAP (≥5 days after ICU admission).

No strategy of imputation is forecasted in case of missing data for the primary assessment criterion. Information available at time of last follow-up will be taken into account.

Data collection and management

Data collection will be performed in electronic format. The statistical software used for data entry will be CleanWeb™; it will fulfill the regulatory requirements and security norms. Data will be handled according to the French law. All original records (including consent forms, reports of suspected unexpected serious adverse reactions and relevant correspondences) will be archived at trial sites for 15 years. The cleaned trial database file will be anonymized and maintained for 15 years. Data on primary and secondary endpoints, will be collected, as detailed in Study procedures section and Table 2. The data of this study will be available upon reasonable request from the corresponding author but it will not be publicly available due to privacy or ethical restrictions.

Table 2. Chronology of the study and procedures

Actions		D-2 to D1	D1	D2 to D8	D9 to D27 or discharge of hospital	D28	D90
Inclusion visit			X_R				
Verification of inclusion and non-inclusion criteria			X_R				
Information			X_R				
Written Informed consent			X_R				
Randomization			X_R				
Pregnancy test			X_R				
Medical history		X_C	X_C				
Physical examination		X_C	X_C	X_C	X_C	X_R	
Phone call							X_R
Chest X-Ray/CT-scan		X_C	X_C	X_C			
PaO_2/FiO_2 ratio		X_C	X_C	X_C	X_C		
Assessment of clinical symptoms of VAP		X_C	X_C				
Assessment of clinical recovery of VAP				Xc			
Start antibiotics			X_C				
Antibiotics			X_C	X_C	X_C		
Rectal swab				X_C	X_C		
Serum creatinin and calculated creatinin clearance			X^b_C				
White blood count		X_C	X_C	X_C	X_C		
SCORE	ISS	X_C					
	SOFA	X_C	X_R				
	IGS	X_C					
Assessment of rate of treatment failure and new episode of VAP						X_R	
Antibiotic free days						X_R	
Vital status						X_R	X_R
Adverse events			X_R	X_R	X_R	X_R	X_R
Hospital admissions				X_C	X_C	X_R	X_R

* length of antibiotic therapy depends on the clinical response. In the control group, predictable length is 7 days.

b creatinin clearance may be performed (Cl_{cr}= (urinary creatinin/serum creatinin)*urine $volume_{24h}$) as frequently as clinically indicated to guide appropriate antibiotic therapy in subjects with renal impair

X_C : made in usual care

X_R : acts added for research

TRIAL STATUS

Recruitment of participants started in October 2022 and the estimated completion date for inclusions is September 2025.

ETHICS AND DISSEMINATION

Legal obligations and approval

Sponsorship has been agreed by Assistance Publique—Hôpitaux de Paris (AP-HP, Clinical Research and Innovation Department) for this interventional research protocol involving human participants concerning a health product. AP-HP has obtained the approval of the French medicine regulatory agency (Agence Nationale de Sécurité du Médicament et des Produits de Santé, ANSM; EUDRACT number 2021-002197-78, 19 August 2021) and of the ethics comitee (Comité de Protection des Personnes (CPP) Ile-de-France III (CNRIPH: 21.03.25.60729, 10 October 2021)) for the study protocol (version ASPIC−1.3; 03 September 2021). The trial will be carried out in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines. Any substantial modification to the protocol will be sent to the sponsor, and then to the ANSM and the CPP for approval before the amendment can be implemented. The information sheet and the consent form can be revised if necessary, particularly if there is a substantial amendment to the study or if adverse reactions occur. AP-HP is the owner of the data. The data cannot be used or disclosed to a third party without its prior permission.

Methods for obtaining information and consent from research participants

In accordance with Article L.1122-1-1 of the French Public Health Code, no research will be carried out without patient free and informed consent, obtained in writing after the person has been given the information specified in Article L.1122-1 of said Code. Written informed consent will be obtained from all patients, their next of kin, as appropriate. If patients are unable to provide informed consent and if neither their next of kin nor other designated person is available, a procedure for inclusion in the study in emergency situations would be applied. A definitive post hoc consent form would be ultimately obtained from patients who survived but had been initially treated on the basis of the emergency consent. These procedures have been approved for the ASPIC trial by the french Commission nationale de l'informatique et des libertés (CNIL, ref MLD/MFI/AR2111748, 18 October 2021).

Patient and public involvement

The patient's (or next of kin's) free and informed written consent will be obtained after a reflection period of at least 15 minutes after information, by the investigator, or by a doctor representing the investigator, before enrollement in the trial, during the baseline visit.

The investigator will specify in the research participant's medical file the methods used for obtaining their consent as well as the methods used for providing information with a view to obtaining consent. The investigator will retain the original signed and dated consent form.

Subjects may exit the study at any time and for any reason.

Data deposition, quality control and curation

The persons responsible for the quality control of clinical matters will take all necessary precautions to ensure the confidentiality of information related to the study participants. These persons, as well as the investigators themselves, are bound by professional confidentiality. During or after the research, all data collected about the participants and sent to the sponsor by

the investigators (or any other specialized collaborators) will be anonymized. Under no circumstances should the names, addresses and other protector identifiers of the subjects involved be shown.

In any case of premature withdrawals and exits, the investigator must provide their reason(s) and try to collect primary endpoint, secondary endpoints and safety assessment, if the participant agrees. If a participant exits the study prematurely or withdraws consent, any data collected prior to the date of premature exit may still be used excepted if the participant refuses it in writing.

The research data will be collected and monitored using an eCRF through CleanWEB™ Electronic Observation Book and will be centralized on a server hosted by the AP-HP Operation Department.

Research staff of the Clinical Trial Unit will work with local investigators to obtain data that are as complete and accurate as possible. An independent Clinical Research Associate appointed by the sponsor will be responsible for the proper running of the study, for collecting, documenting, recording and reporting all handwritten data, in accordance with the Standard Operating Procedures applied within the Clinical Research and Innovation Department of AP-HP. The investigators agree to accept the quality assurance audits carried out by the sponsor as well as the inspections carried out by the competent authorities. All data, documents and reports may be subject to regulatory audits. These audits and inspections cannot be refused on the grounds of medical secrecy. An audit can be carried out at any time by independent individuals appointed by the sponsor, aiming at ensuring the quality of the study, the validity of the results and compliance with the legislation and regulations in force. The persons who manage and monitor the study agree to comply with the sponsor's audit requirements. The audit may encompass all stages of the study, from the development of the protocol to the publication of

the results and the storage of the data used or produced as part of the study. Sponsor is responsible for access to the study database.

The investigator will assess the seriousness of each adverse event, report all serious and non-serious adverse events in the case report form and assess the causal relationship of serious adverse events with the study procedures according to the WHO method.

A data monitoring committee is not needed for this trial as the expected risk for the participant is minimal.

Publication plan

Results will be published in international peer-reviewed medical journals. Scientific presentations and reports will be written under the responsibility of the coordinating investigator of the study with the agreement of the principal investigators and the methodologist. The co-authors of the reports and publications will be the investigators and clinicians involved, on a pro rata basis of their contribution in the study, as well as the biostatistician and associated researchers. Rules on publication will follow international recommendations (22).

Authors' contributions: AF and EW contributed to the conception and design of the research protocol, assisted by DB and PE. AR, IM-L, PM, J-FT, AB and J-RZ provided critical input pertaining to the design of the trial interventions and procedures. AF wrote the first draft of the protocol and this manuscript. DB and PE designed the statistical analysis plan. All authors critically revised and modified the protocol and the article. They all approved the final version to be published.

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Competing interests statement:

AF, DB, AB, PE: declare no competing interest

AR: grants from bioMerieux and Merck

IM-L: board on PFIZER, MSD, GILEAD

J-FT directly related to the protocol: none, participation to scientific advisory boards: Pfizer, Gilead, Merck, BD, Shionoghi; readings: Merck, Biomerieux, Pfizer, Shionogi; research grants to my research unit: thermofischer, Pfizer, Merck

J-RZ: consulting fees from MSD, Pfizer, speaker fees fom MSD, Pfizer, Shionogi, Correvio and Eumedica

EW: Speaker fees from MSD, Akcea therapeutics and LFB, support for attending meeting/travel: LFB and Akcea therapeutics

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1

Figures and Table legends

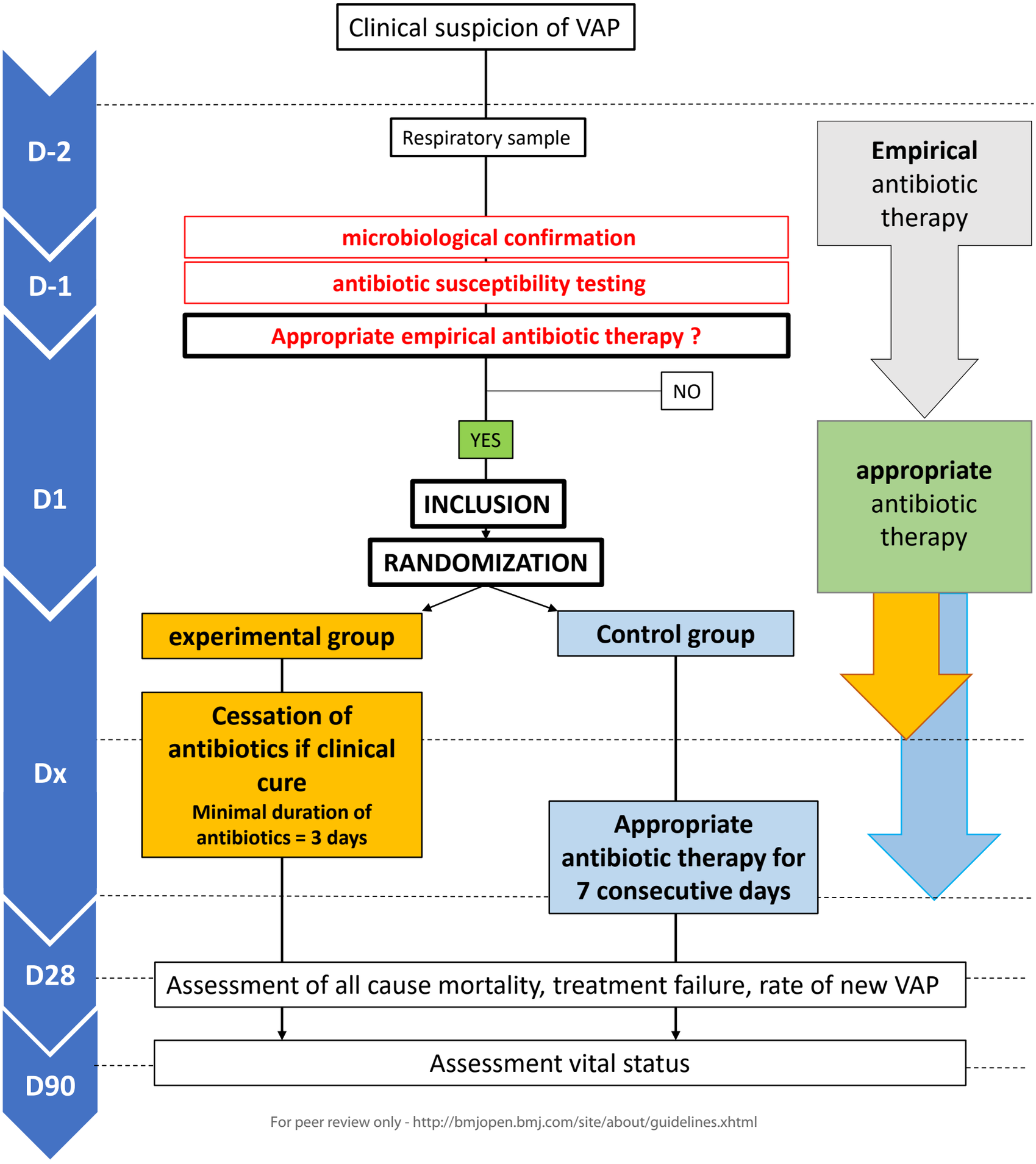
Figure 1: General flowchart of the study

Figure 2: Criteria of clinical cure and criteria for discontinuation of antibiotic therapy in experimental arm

Figure 3: Description of microbiological categories of outcomes in relation to time of occurrence of new episode of VAP after inclusion adapted from(21)

Table 1. Choice of empirical antibiotic therapy according current French guidelines

Table 2: Chronology of the study and procedures


Clinical suspicion of VAP
D-2
Respiratory sample
Empirical antibiotic therapy
D-1
microbiological confirmation
antibiotic susceptibility testing
Appropriate empirical antibiotic therapy ?
NO
YES
D1
INCLUSION
RANDOMIZATION
appropriate antibiotic therapy
experimental group
Control group
Dx
Cessation of antibiotics if clinical cure
Minimal duration of antibiotics = 3 days
Appropriate antibiotic therapy for 7 consecutive days
D28
Assessment of all cause mortality, treatment failure, rate of new VAP
D90
Assessment vital status

Experimental group

- Antimicrobial stewardship based on daily clinical assessment of clinical cure of confirmed VAP are met. Intensivists will perform clinical assessment daily in order to decide on the pursuit or discontinuation of antibiotic therapy.
- Antibiotic therapy is stopped if signs of **clinical cure** of VAP are met (minimum 3 days)

CLINICAL CURE

STOP antibiotics if ≥ 3 criteria are met

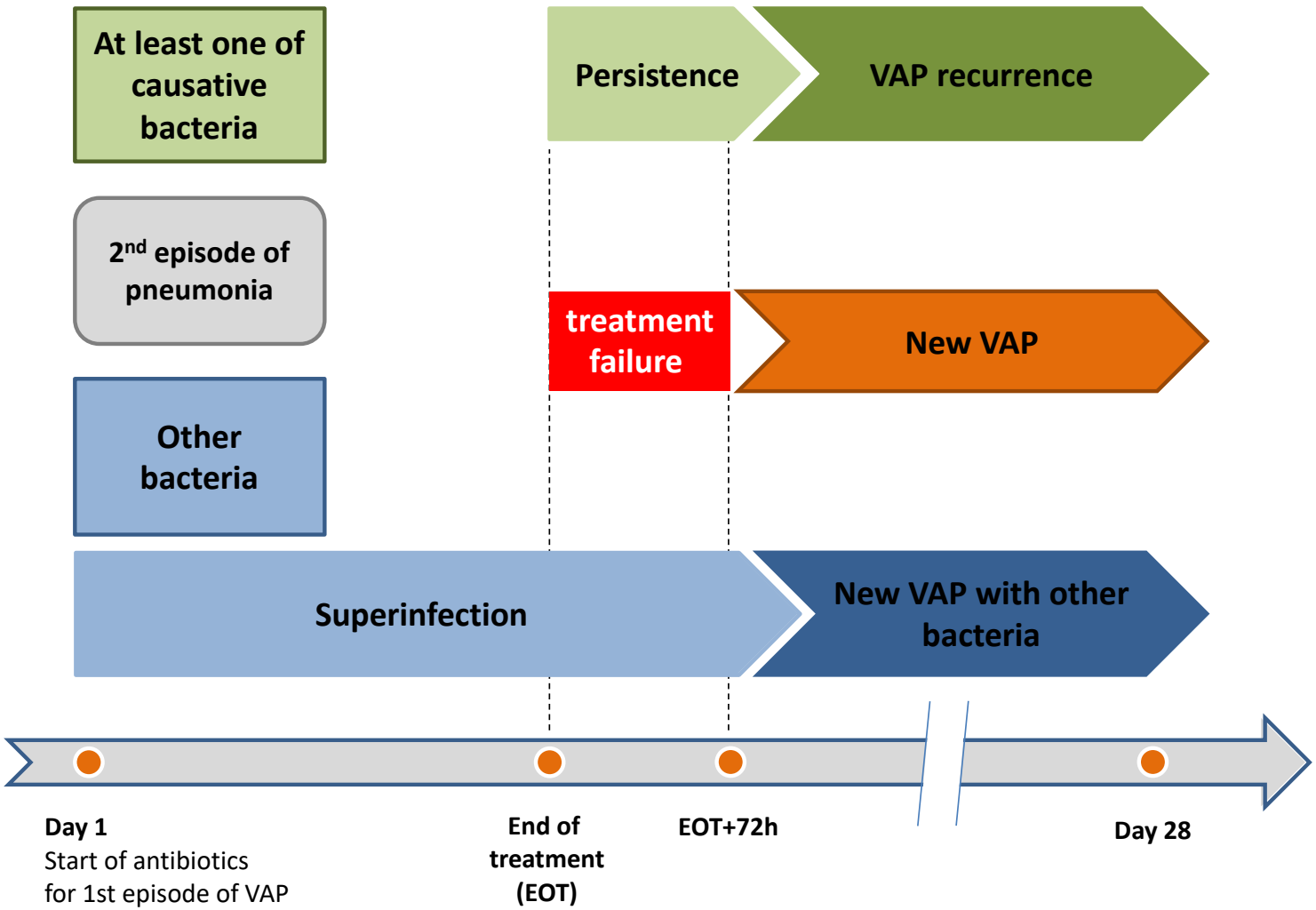
1. Regression* of purulent trachael **S**ecretions

2. Normo**T**hermia
36°C < T < 38.3°C

3. Improved*
Oxygenation, measured by an increase in the of the PaO2/FiO2 ratio

4. Absence of hy**P**otension

* compared to the day of initiation of antibiotic therapy


At least one of causative bacteria
2nd episode of pneumonia
Other bacteria
Persistence
VAP recurrence
treatment failure
New VAP
Superinfection
New VAP with other bacteria
Day 1
Start of antibiotics for 1st episode of VAP
End of treatment (EOT)
EOT+72h
Day 28

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	3
Funding	4	Sources and types of financial, material, and other support	25
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	25
	5b	Name and contact information for the trial sponsor	
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	18
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	14
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
	6b	Explanation for choice of comparators	
Objectives	7	Specific objectives or hypotheses	

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	10
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	10
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	12,13
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	14
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	14
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	14,15
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Fig 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	15
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	15
Methods: Assignment of interventions (for controlled trials)			
Allocation:			

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	11
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	11
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	11,12
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	12
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	17
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Table 1
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	17
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16,17
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	17,18

Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	21
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	21
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	22
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	18
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	18
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	19
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	19
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	NA
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18, 21
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	20,21
	31b	Authorship eligibility guidelines and any intended use of professional writers	22
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	yes
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.