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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-065293
Article Type:	Protocol
Date Submitted by the Author:	02-Jun-2022
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Keywords:	Adult intensive & critical care < ANAESTHETICS, Infection control < INFECTIOUS DISEASES, Respiratory infections < THORACIC MEDICINE

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3 **1 Antimicrobial Stewardship for Ventilator Associated Pneumonia in Intensive Care**  
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6 **2 (the ASPIC trial): study protocol for a randomized controlled trial**  
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3 29 **Abstract (233 words)**  
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6 30 **Introduction:** Ventilator associated pneumonia (VAP) remains the leading cause of infections  
7  
8 31 treated in the Intensive Care Units (ICU). Reducing antibiotic consumption in (ICU) is one  
9  
10 32 factor in reducing the emergence of resistance. In a personalized care approach, we hypothesize  
11  
12 33 that the duration of treatment of VAP can be reduced in function of the response to treatment.

13  
14 34 **Methods and analysis:** The ASPIC trial is a pragmatic prospective national multicenter, phase  
15  
16 35 III, non-inferiority, comparative randomized (1:1) single-blinded clinical trial. Five hundred  
17  
18 36 ninety adult patients hospitalized in 24 french ICU with a microbiologically confirmed first  
19  
20 37 episode of VAP that received appropriate empiric antibiotic therapy will be included. They will  
21  
22 38 be randomly allocated to standard management with duration of appropriate antibiotic fixed for  
23  
24 39 7 days according to international guidelines or antimicrobial stewardship based on daily clinical  
25  
26 40 assessment of clinical cure. The assessment of clinical cure will be repeated daily until at least  
27  
28 41 3 criteria of clinical cure are met, allowing the discontinuation of antibiotic therapy in  
29  
30 42 experimental group. The primary endpoint is a composite endpoint combining of all-cause  
31  
32 43 mortality measured at day 28, treatment failure or new episode of microbiologically confirmed  
33  
34 44 VAP until day 28.

35  
36 45 **Discussion:** Demonstrate that a strategy to reduce the duration of antibiotic therapy for VAP  
37  
38 46 based on clinical assessment is safe could lead to changes in practice as part of a personalized  
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40 47 therapeutic approach, by reducing exposure to antibiotics and their side effects.  
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3 48 **Ethics and dissemination:** The ASPIC trial has been approved by the French regulatory  
4 49 agency (Agence Nationale de Sécurité du Médicament et des Produits de Santé, ANSM;  
5 50 EUDRACT number 2021-002197-78, 19 August 2021) and an independent ethics committee  
6 51 the Comité de Protection des Personnes (CPP) Ile-de-France III (CNRIPH : 21.03.25.60729, 10  
7 52 October 2021) for the study protocol (version ASPIC-1.3; 03 September 2021) for all study  
8 53 centers. Participant recruitment is scheduled to begin in 2022. Results will be published in  
9 54 international peer-reviewed medical journals.

15  
16 55 **Trial registration number:** NCT05124977, first posted November 18, 2021

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18 56 **Protocol version identifier** N°1-3, 03 September 2021  
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3 **57 Strengths and limitations of this study**  
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6  
7 58 - High quality methodology using randomized controlled trial (RCT) design that will  
8  
9 59 provide a high-level of evidence on antimicrobial stewardship for management of ventilator-  
10  
11 60 associated pneumonia (VAP) antibiotic strategy  
12

13 61 - First RCT conducting in Europe assessing the value of clinical cure criteria ('STOP  
14  
15 62 criteria') supported by an international expert panel to develop an antimicrobial stewardship  
16  
17 63 strategy  
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19 64 - Class of antibiotics prescription not imposed by the protocol, in a pragmatic approach  
20  
21 65 and in order to maximize the external validity of the results  
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24 66 - Risk of poor adherence of investigator team to experimental strategy, which could lead  
25  
26 67 to absence of antibiotic discontinuation even if 'STOP' criteria are met.  
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## 68 INTRODUCTION

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

75 In the last few years, the concept of antimicrobial stewardship (ASP) has been developed. It  
76 refers to programs, education, interventions that aim to optimize antibiotic use (5). In a recent  
77 review by Dyar et al. reports different definitions of ASP used in the literature (6).  
78 Antimicrobial stewardship refers to the responsible use of antimicrobials by healthcare  
79 professionals, and more specifically, to selection of the most appropriate antibiotic, duration,  
80 dose and route of administration for a given patient with a demonstrated or suspected infection  
81 (7,8).

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

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



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3 92 and VAP. In this work, various innovative concepts are developed. First, the experts agree that  
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5 93 the criteria usually used in the literature to characterize the suspicion of VAP are weighted  
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8 94 differently. According to the experts, among 9 selected criteria, the first 4 criteria with the most  
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10 95 significant impact were: 1. Worsening of gas exchange, 2. Hypotension / vasopressor  
11  
12 96 requirement, 3. Temperature abnormalities (fever or hypothermia), 4. Purulent tracheal  
13  
14 97 secretions (rated ex-aequo with temperature abnormalities). Logically, less specific signs  
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16 98 (hyperleukocytosis, encephalopathy, auscultatory abnormalities) were ranked lower. More  
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18 99 surprisingly, the CPIS (Clinical Pulmonary Infection Score) was ranked 6th while it is no longer  
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21 100 considered a determinant for initiating antibiotic treatment.

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24 101 According to the experts, these criteria, when they regress or disappear, are therefore considered  
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26 102 associated with clinical cure of VAP. Considering the small differences in the relative weights  
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28 103 of each criterion, it seems reasonable to consider that the association of at least 3 of these criteria  
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30 104 is necessary to consider a clinical cure. To date, no prospective evaluation of the robustness of  
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32 105 these criteria to guide antimicrobial treatment duration has been performed.

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36 106 The ASPIC study aims at investigating whether an antimicrobial stewardship for  
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38 107 microbiologically proven VAP based on daily assessment of clinical cure and antimicrobial  
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40 108 discontinuation, if it is obtained, would be non-inferior to standard management in terms of all-  
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42 109 cause mortality, treatment failure or occurrence of new episode of VAP before day 28.

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3 110 **METHODS AND ANALYSIS**  
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6 111 **Study design**  
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9 112 This study is a pragmatic, national, multicenter, phase III, single-blinded, non-inferiority  
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11 113 comparative randomized clinical trial (RCT) comparing two therapeutic strategies for  
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13 114 microbiologically proven VAP on the basis of two parallel arms:

- 15  
16 115 - Experimental group: Antimicrobial stewardship based on daily clinical assessment of  
17  
18 116 clinical cure. Discontinuation of appropriate antibiotic therapy is made if clinical cure  
19  
20 117 (daily assessment) criteria of VAP are met.  
21  
22  
23 118 - Control group: Standard management: Fixed duration of 7 days of appropriate antibiotic  
24  
25 119 therapy according to VAP guidelines. In the control group, clinical cure assessment will  
26  
27 120 be performed daily by the intensivist in charge of the patient but the antibiotic therapy  
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29 121 will not be discontinued until 7 days whatever the clinical cure.  
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33 122 The trial overview is summarized in Figure 1. We report here the study protocol according to  
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35 123 the SPIRIT (Standard Protocol Items: Recommendations for interventional Trials) statement  
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37 124 (15).  
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## 125 **Definitions**

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

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

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

## 145 Clinical cure (Figure 2)

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

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3 149 - No additional antibiotic therapy required for VAP treatment AND  
4

5 150 - Patient is alive  
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7 151 Treatment failure defined by signs of VAP within 72 hours after the end antibiotic treatment  
8

9 152 at the test of cure visit  
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12 153 Superinfection: Isolation of a pathogen, other than the causative baseline pathogen, from a  
13

14 154 LRT specimen obtained in a subject with signs and symptoms of VAP developed during  
15

16 155 antibiotic treatment  
17  
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19 156 Persistence: Continued presence of the original causative baseline pathogen(s) from a LRT  
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21 157 culture obtained between EOT and 72 after EOT  
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24 158 New VAP: New episode of microbiologically documented VAP from 72h after the EOT to day  
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30 160 VAP-Recurrence: New VAP due to at least one of the original causative pathogen(s) found at  
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32 161 baseline  
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35 162 Definitions of treatment failure, persistence, superinfection, persistence, VAP recurrence and  
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37 163 new VAP are summarized in Figure 3.  
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3 164 **Setting**  
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6 165 This will be a French multicenter study involving 24 centers. Participants will be recruited in  
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8 166 ICU wards during their hospital stay.  
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14 168 **Study population**  
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17 169 Participants in ICU wards will be eligible if they fulfilled following criteria:  
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20 170 Inclusion criteria:  
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22 171 - Aged 18 years or more  
23

24 172 - Patient under mechanical ventilation (MV)  
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26 173 - Microbiologically confirmed diagnosis of first episode of VAP (see definition section)  
27

28 174 - Initial appropriate empiric antibiotic therapy (see definitions section)  
29

30 175 - Written informed consent from the patient or a legal representative if appropriate. If absence  
31  
32 176 of a legal representative the patient can be included following an emergency procedure  
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39 178 Exclusion criteria:  
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41 179 - Patient under selective bowel decontamination  
42

43 180 - Concomitant extra-respiratory infection requiring antibiotic therapy at inclusion  
44

45 181 - Inclusion in another experimental study on antimicrobial stewardship  
46

47 182 - Moribund at admission (IGS II>80)  
48

49 183 - Thoracic trauma with Abbreviated Injury Scale (AIS) thorax  $\geq 3$   
50

51 184 - Severely immunocompromised patients: congenital immunodeficiency, neutropenia (<0.5  
52  
53 185 G/l), leukopenia (<1 G/l), acute hematologic malignancy or stem cell transplant, HIV infection  
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55 186 with CD4 count below 200/mm<sup>3</sup>, immunosuppressive therapy or long term corticosteroid  
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57 187 therapy > 0.5 mg/kg  
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3 188 - VAP due to: *Pseudomonas aeruginosa*, Carbapenem-resistant *Acinetobacter* spp,  
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5 189 Carbapenem-resistant *Enterobacterales*  
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8 190 - Bacterial VAP occurring in the context of superinfection of COVID-19 or other viral VAP  
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10 191 (confirmed by RT-PCR)  
11  
12 192 - Patients with empyema, necrotizing and abscessed pneumonia  
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15 193 - Pregnant women  
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17 194 - No health insurance coverage  
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## 23 196 **Recruitment**

24 197 The screening will aim at identifying patients hospitalized in ICU who underwent a lower  
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26 198 respiratory tract sample because a VAP was suspected. During this period, management of  
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28 199 patients is similar to usual care with clinical, biological and radiological assessments. After  
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30 200 microbiological diagnosis confirmation and reception of Antibiotic Susceptibility Testing  
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32 201 (AST) proving that the initial empiric antibiotic therapy was appropriate, eligible patient will  
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34 202 be offered participation in the trial. Written informed consent would be obtained by the  
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36 203 investigator or by a physician representing the investigator, from all patients, their next of kin,  
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38 204 as appropriate, accordingly to French regulatory agencies authorization (see section Methods  
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40 205 for obtaining information and consent from research participants).  
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## 47 207 **Treatment allocation and randomization**

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49 208 Participants will be randomized (Day 1) with a 1:1 ratio to either antimicrobial stewardship-  
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51 209 guided antibiotic therapy strategy (experimental group) or standard management (control  
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53 210 group) using a computer-generated randomization scheme of various-sized blocks, through an  
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55 211 internet centralized randomization service running 24hrs/24hrs. Randomization will be  
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57 212 stratified by center. The randomization scheme will be generated by a statistician who is not  
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3 213 involved in any other aspect of the study, and all researchers will be  
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5 214 blinded to block size(s) and randomization list to avoid prediction of future patient's allocation.  
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8 215 Allocation concealment will be ensured, as the service will not release the randomization code  
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10 216 until the patient has been recruited into the trial.  
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### 14 218 **Blinding**

16  
17 219 This study will be single-blinded. Participants will not be informed of their group allocation.  
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19 220 Blinding will be ensured as most patients will be either sedated (within standard of care) or  
20  
21 221 unable to have appropriate discussions with investigational team for the duration of the  
22  
23 222 experimental at study. The statistician conducting the data analysis will also be blinded to  
24  
25 223 group allocation. The medical staff cannot be blinded to the randomization arm due to the nature  
26  
27 224 of experimental design and our choice to evaluate this strategy in real-life clinical practice  
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29 225 conditions. If the patient is transferred to another clinical ward or leave the hospital during the  
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31 226 3-month follow-up, other healthcare professionals involved in their management will not be  
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33 227 made aware of the randomization arm.  
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### 40 229 **Study procedures**

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43 230 The general flowchart of the study is shown in Figure 1. A pragmatic approach will be followed  
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45 231 and usual patient management recommended by international guidelines (9–11) will be  
46  
47 232 provided in participating ICUs. In particular the choice of antibiotic therapy will be left at  
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49 233 investigator discretion.  
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52 234 In the experimental group, the ICU physician will discontinue the antibiotic therapy as soon as  
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54 235 clinical cure criteria of VAP are met. Minimal duration of appropriate antibiotic treatment will  
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56 236 be 3 days (including empirical antibiotic therapy). After 72 hours (delay to receive AST results)  
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3 237 of appropriate antibiotic treatment, the assessment of clinical cure will be performed daily on  
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5 238 the basis of 4 criteria:

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7 239 - Regression or the decreased abundance of purulent tracheal secretions

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9 240 - Absence of fever or hypothermia

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11 241 - Improvement of oxygenation (assessed by increase of  $\text{PaO}_2/\text{FiO}_2$  ratio)

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13 242 - Absence of hypotension (hypotension is defined by mean arterial pressure  $< 70$  mmHg(16,17))

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15 243 or decreased need for epinephrine or norepinephrine by at least  $0,1 \mu\text{g}/\text{kg}/\text{mn}$  compared to  
16  
17 244 baseline (day of inclusion)

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19 245 This assessment will be repeated daily until at least 3 of the 4 criteria are met, i.e. the patient is  
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21 246 considered clinically cured, thereby allowing the discontinuation of antibiotic therapy (Figure  
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23 247 2).

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25 248 A daily phone hotline, provided by coordinating investigator's team, will be accessible to  
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27 249 investigators for multidisciplinary validation of antibiotic discontinuation in patients included  
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29 250 in the experimental group.

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31 251 For control group, fixed duration of antibiotic therapy will be at least 7 full days (since the  
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33 252 initiation of empirical antibiotic therapy), whatever clinical assessment.

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35 253 For both groups, in case of non-clinical recovery after 7 full days (treatment failure) and/or in  
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37 254 case of suspicion of new VAP during treatment (superinfection), a new lower respiratory tract  
38  
39 255 sampling will be performed, and a new antibiotic therapy will be initiated. In case of new VAP,  
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41 256 patients will be treated according to the usual practices of the center.

42  
43 257 Following data will be collected daily from day 2 to day 28 or to ICU discharge in participants  
44  
45 258 from both arms: vital status, ventilation status,  $\text{PaO}_2$  and  $\text{FiO}_2$  (if ventilated), temperature,  
46  
47 259 tracheal secretions, blood pressure, use and dose of vasopressors, data on any infection  
48  
49 260 throughout study period (infection site, bacteriological documentation, number of days of  
50  
51 261 antibiotic therapy), antibiotic use (molecule; dosage; duration of treatment).



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2  
3 262 Additional data will be collected daily from Day 2 to Day 8: clinical assessment, focused  
4  
5 263 pulmonary examination, laboratory assessment (usual tests, biochemical, hematological),  
6  
7 264 radiological evaluation (Chest X-Ray/CT-scan), if performed as part of usual care.

8  
9  
10 265 Rectal swabbing for collection of data on colonization or acquisition of Multidrug Resistant  
11  
12 266 (MDR) bacteria will be performed at ICU admission and weekly until ICU discharge as part as  
13  
14 267 usual care.

15  
16  
17 268 All participants will be followed up to day 90 with vital status assessment.

18  
19 269

20  
21  
22 270 **Outcomes**

23  
24  
25 271 The primary endpoint will be a composite of:

26  
27  
28 272 1. All-cause mortality (ACM) measured at day 28 after initiation of therapy OR

29  
30  
31 273 2. Treatment failure defined by signs of VAP within 72 hours after the end antibiotic treatment  
32  
33 274 at the test of cure visit OR

34  
35  
36 275 3. New episode of microbiologically confirmed VAP from 72H after the end of antibiotic  
37  
38 276 treatment to day 28 after initiation of VAP antibiotic treatment

39  
40  
41 277 To avoid interpretation bias for the primary outcome, clinical and microbiological records of  
42  
43 278 all participants will be reviewed by adjudication committee composed with two experts in order  
44  
45 279 to evaluate the presence of (i) clinical cure, (ii) treatment failure and (iii) new episode of VAP.

46  
47  
48 280 This evaluation will be performed blindly from the randomization group and from the  
49  
50 281 interpretation of the investigation team, according to predefined criteria (see Definition  
51  
52 282 section). The adjudication committee will be composed of study investigators (including  
53  
54 283 scientific committee of ASPIC). Each member will review the primary endpoints criteria of a  
55  
56 284 subgroup of patients that were not enrolled in its center.  
57  
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3 285 Secondary endpoints will be: day 28 all-cause mortality, proportion of treatment failure and of  
4  
5 286 new episode of VAP; the number of antibiotic free days alive from initiation of VAP antibiotic  
6  
7 287 therapy to day 28; the duration of invasive MV; the length of ICU stay, defined by the number  
8  
9  
10 288 of days between inclusion and ICU discharge or in-ICU death; the proportion of VAP  
11  
12 289 recurrence assessed by the intensivist; the antibiotic related side effects; the proportion of  
13  
14 290 acquisition of MDR bacteria (defined as the identification of a MDR bacteria carriage not  
15  
16  
17 291 present at admission); the proportion of protocol deviation i.e. lack of antibiotic therapy  
18  
19 292 discontinuation despite a fulfillment of clinical cure definition in the experimental group ; the  
20  
21 293 total cumulative costs of antibiotics and incremental cost effectiveness ratio; and the  
22  
23  
24 294 Desirability of Outcome Ranking (DOOR) and the Response Adjusted for Duration of  
25  
26 295 Antibiotic Risk (RADAR) for each strategy (experimental and control groups)(18).

27  
28 296 All trial participants will be ranked with respect to the desirability of their overall outcome and  
29  
30 297 the distributions of DOORs will be compared between strategies Overall clinical outcomes at  
31  
32  
33 298 day 28 will be ranked from most to least desirable as followed:

- 34  
35 299 1. Survival, clinical cure  
36  
37 300 2. Survival, new pulmonary infection  
38  
39  
40 301 3. Death

41  
42 302 In RADAR analyses, patients will be ranked overall clinical outcome, but in case of ex-aequo,  
43  
44 303 the patient with a shorter duration of antibiotic use will receive a higher rank

45  
46  
47 304

### 48 49 305 **Sample size justification**

50  
51  
52 306 Assuming that 25% of the patients will encountered all-cause mortality, treatment failure or  
53  
54 307 occurrence of new episode of VAP before day 28 in the control arm (19), 590 subjects (295 per  
55  
56  
57 308 arm) are needed to establish non-inferiority with the absolute difference of death, treatment  
58  
59 309 failure or occurrence of new episode of VAP doesn't exceed 10% (non-inferiority margin)

1  
2  
3 310 between experimental and control arms with a power of 80%, a type I error (alpha) of 2.5%.  
4  
5 311 Using data from Teixeira and al. (20), we derived an estimated absolute rate of 28-days survival  
6  
7 312 without treatment of 50% (absolute rate of treatment failure / new episode of VAP without  
8  
9 313 treatment cannot be estimated). The non-inferiority margin of 10% was chosen as the largest  
10  
11 314 difference that may be potentially clinically acceptable and so that antimicrobial stewardship  
12  
13 315 preserves at least half the effect of standard of care (21).  
14  
15  
16  
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19

### 20 317 **Data analysis plan**

21  
22  
23 318 The primary analysis will be performed on the intention-to-treat population (22). The 95%  
24  
25 319 confidence interval of the difference in proportions of all-cause death, treatment failure or  
26  
27 320 occurrence of new episode of VAP observed between the two groups will be estimated. This  
28  
29 321 confidence interval will be compared to the non-inferiority margin of 10%. If the lower limit of  
30  
31 322 the confidence interval of the difference in proportions is less than or equal to -10%, then we  
32  
33 323 cannot conclude that the antimicrobial stewardship-based strategy is non-inferior to the  
34  
35 324 reference strategy. In the opposite case, if the lower limit of the confidence interval is strictly  
36  
37 325 greater than -10%, then we will conclude that the antimicrobial stewardship-based strategy is  
38  
39 326 non-inferior on all-cause mortality, treatment failure or occurrence of new episode of VAP at  
40  
41 327 day 28 after inclusion. Sensitivity analysis on per-protocol population will be performed. All  
42  
43 328 tests of superiority (secondary objectives) will be two-sided with type I error of 5% and tests of  
44  
45 329 non-inferiority will be one-sided with type I error 2.5%. All statistical analyses will be  
46  
47 330 performed using SAS software (SAS Institute Inc., Cary, NC) v. 9.4 or later, or R software (R  
48  
49 331 Foundation for Statistical Computing, Vienna, Austria. <http://www.r-project.org/>) v. 4.0 or  
50  
51 332 later.  
52  
53 333 The primary analysis will also been performed in the following subgroups of patients:  
54  
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- 1  
2  
3 334 – Those whose baseline bacteriological samples were assessed by rapid microbiological  
4  
5 335 technique (germ identification and antibiogram) ;  
6  
7  
8 336 – Patients admitted to ICU for trauma vs other reasons of admission  
9  
10 337 – Patients with early onset PAVM (< 5 days after ICU admission) vs late onset PAVM ( $\geq 5$   
11  
12 338 days after ICU admission).

15  
16 339 No strategy of imputation is forecasted in case of missing data for the primary assessment  
17  
18 340 criterion. Information available at time of last follow-up will be taken into account.  
19  
20

### 21 341 **Data collection and management**

22  
23  
24  
25 342 Data collection will be performed in electronic format. The statistical software used for data  
26  
27 343 entry will be CleanWeb<sup>TM</sup>; it will fulfill the regulatory requirements and security norms. Data  
28  
29 344 will be handled according to the French law. All original records (including consent forms,  
30  
31 345 reports of suspected unexpected serious adverse reactions and relevant correspondences) will  
32  
33 346 be archived at trial sites for 15 years. The cleaned trial database file will be anonymized and  
34  
35 347 maintained for 15 years. Data on primary and secondary endpoints, will be collected, as detailed  
36  
37 348 in Study procedures section and Table 1. The data of this study will be available upon  
38  
39 349 reasonable request from the corresponding author but it will not be publicly available due to  
40  
41 350 privacy or ethical restrictions.  
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352 **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 <sub>R</sub>				
Verification of inclusion and non-inclusion criteria			X <sub>R</sub>				
Information			X <sub>R</sub>				
Written Informed consent			X <sub>R</sub>				
Randomization			X <sub>R</sub>				
Pregnancy test			X <sub>R</sub>				
Medical history		X <sub>C</sub>	X <sub>C</sub>				
Physical examination		X <sub>C</sub>	X <sub>C</sub>	X <sub>C</sub>	X <sub>C</sub>	X <sub>R</sub>	
Phone call							X <sub>R</sub>
Chest X-Ray/CT-scan		X <sub>C</sub>	X <sub>C</sub>	X <sub>C</sub>			
PaO <sub>2</sub> /FiO <sub>2</sub> ratio		X <sub>C</sub>	X <sub>C</sub>	X <sub>C</sub>	X <sub>C</sub>		
Assessment of clinical symptoms of VAP		X <sub>C</sub>	X <sub>C</sub>				
Assessment of clinical recovery of VAP				X <sub>C</sub>			
Start antibiotics			X <sub>C</sub>				
Antibiotics			X <sub>C</sub>	X <sub>C</sub>	X <sub>C</sub>		
Rectal swab				X <sub>C</sub>	X <sub>C</sub>		
Serum creatinin and calculated creatinin clearance			X <sup>b</sup> <sub>C</sub>				
White blood count		X <sub>C</sub>	X <sub>C</sub>	X <sub>C</sub>	X <sub>C</sub>		
SCORE	ISS	X <sub>C</sub>					
	SOFA	X <sub>C</sub>	X <sub>R</sub>				
	IGS	X <sub>C</sub>					
Assessment of rate of treatment failure and new episode of VAP						X <sub>R</sub>	
Antibiotic free days						X <sub>R</sub>	
Vital status						X <sub>R</sub>	X <sub>R</sub>
Adverse events			X <sub>R</sub>	X <sub>R</sub>	X <sub>R</sub>	X <sub>R</sub>	X <sub>R</sub>
Hospital admissions				X <sub>C</sub>	X <sub>C</sub>	X <sub>R</sub>	X <sub>R</sub>

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

355 <sup>b</sup> creatinin clearance may be performed ( $Cl_{cr} = (\text{urinary creatinin/serum creatinin}) \times \text{urine}$   
 356  $\text{volume}_{24h}$ ) as frequently as clinically indicated to guide appropriate antibiotic therapy in  
 357 subjects with renal impair

358 X<sub>C</sub> : made in usual care

359 X<sub>R</sub> : acts added for research

360

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3 361 **TRIAL STATUS**  
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6 362 Not yet recruiting. Participant recruitment is scheduled to begin in 2022 and the recruiting  
7  
8 363 period will last 36 months.  
9

10  
11 364 **ETHICS AND DISSEMINATION**  
12  
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14 365 **Legal obligations and approval**  
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16

17 366 Sponsorship has been agreed by Assistance Publique—Hôpitaux de Paris (AP-HP, Clinical  
18  
19 367 Research and Innovation Department) for this interventional research protocol involving human  
20  
21 368 participants concerning a health product. AP-HP has obtained the approval of the French  
22  
23 369 medicine regulatory agency (Agence Nationale de Sécurité du Médicament et des Produits de  
24  
25 370 Santé, ANSM; EUDRACT number 2021-002197-78, 19 August 2021) and of the ethics  
26  
27 371 comitee (Comité de Protection des Personnes (CPP) Ile-de-France III (CNRIPH :  
28  
29 372 21.03.25.60729, 10 October 2021)) for the study protocol (version ASPIC-1.3; 03 September  
30  
31 373 2021). The trial will be carried out in accordance with the Declaration of Helsinki and the Good  
32  
33 374 Clinical Practice guidelines. Any substantial modification to the protocol will be sent to the  
34  
35 375 sponsor, and then to the ANSM and the CPP for approval before the amendment can be  
36  
37 376 implemented. The information sheet and the consent form can be revised if necessary,  
38  
39 377 particularly if there is a substantial amendment to the study or if adverse reactions occur. AP-  
40  
41 378 HP is the owner of the data. The data cannot be used or disclosed to a third party without its  
42  
43  
44  
45  
46  
47 379 prior permission.  
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## 382 **Methods for obtaining information and consent from research participants**

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

### 393 **Patient and public involvement**

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

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

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

## 401 **Data deposition, quality control and curation**

402 The persons responsible for the quality control of clinical matters will take all necessary  
403 precautions to ensure the confidentiality of information related to the study participants. These  
404 persons, as well as the investigators themselves, are bound by professional confidentiality.

405 During or after the research, all data collected about the participants and sent to the sponsor by

1  
2  
3 406 the investigators (or any other specialized collaborators) will be anonymized. Under no  
4  
5 407 circumstances should the names, addresses and other protector identifiers of the subjects  
6  
7 408 involved be shown.  
8  
9

10 409 In any case of premature withdrawals and exits, the investigator must provide their reason(s)  
11  
12 410 and try to collect primary endpoint, secondary endpoints and safety assessment, if the  
13  
14 411 participant agrees. If a participant exits the study prematurely or withdraws consent, any data  
15  
16 412 collected prior to the date of premature exit may still be used excepted if the participant refuses  
17  
18 413 it in writing.  
19  
20  
21  
22

23 414 The research data will be collected and monitored using an eCRF through CleanWEB™  
24  
25 415 Electronic Observation Book and will be centralized on a server hosted by the AP-HP Operation  
26  
27 416 Department.  
28  
29

30 417 Research staff of the Clinical Trial Unit will work with local investigators to obtain data that  
31  
32 418 are as complete and accurate as possible. An independent Clinical Research Associate  
33  
34 419 appointed by the sponsor will be responsible for the proper running of the study, for collecting,  
35  
36 420 documenting, recording and reporting all handwritten data, in accordance with the Standard  
37  
38 421 Operating Procedures applied within the Clinical Research and Innovation Department of AP-  
39  
40 422 HP. The investigators agree to accept the quality assurance audits carried out by the sponsor as  
41  
42 423 well as the inspections carried out by the competent authorities. All data, documents and reports  
43  
44 424 may be subject to regulatory audits. These audits and inspections cannot be refused on the  
45  
46 425 grounds of medical secrecy. An audit can be carried out at any time by independent individuals  
47  
48 426 appointed by the sponsor, aiming at ensuring the quality of the study, the validity of the results  
49  
50 427 and compliance with the legislation and regulations in force. The persons who manage and  
51  
52 428 monitor the study agree to comply with the sponsor's audit requirements. The audit may  
53  
54 429 encompass all stages of the study, from the development of the protocol to the publication of  
55  
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1  
2  
3 430 the results and the storage of the data used or produced as part of the study. Sponsor is  
4  
5 431 responsible for access to the study database.  
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7

8 432 The investigator will assess the seriousness of each adverse event, report all serious and non-  
9  
10 433 serious adverse events in the case report form and assess the causal relationship of serious  
11  
12 434 adverse events with the study procedures according to the WHO method.  
13  
14

15  
16 435 A data monitoring committee is not needed for this trial as the expected risk for the participant  
17  
18 436 is minimal.  
19  
20

### 21 437 **Publication plan**

22  
23  
24 438 Results will be published in international peer-reviewed medical journals. Scientific  
25  
26 439 presentations and reports will be written under the responsibility of the coordinating  
27  
28 440 investigator of the study with the agreement of the principal investigators and the  
29  
30 441 methodologist. The co-authors of the reports and publications will be the investigators and  
31  
32 442 clinicians involved, on a pro rata basis of their contribution in the study, as well as the  
33  
34 443 biostatistician and associated researchers. Rules on publication will follow international  
35  
36 444 recommendations (23).  
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2  
3 446 **Authors' contributions:** AF and EW contributed to the conception and design of the research  
4  
5 447 protocol, assisted by DB and PE. AR, IM-L, PM, J-FT and J-RZ provided critical input  
6  
7 448 pertaining to the design of the trial interventions and procedures. AF wrote the first draft of the  
8  
9 449 protocol and this manuscript. DB and PE designed the statistical analysis plan. All authors  
10  
11 450 critically revised and modified the protocol and the article. They all approved the final version  
12  
13 451 to be published.  
14  
15  
16  
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18 452

19  
20 453 **Funding statement:** This work was supported by Programme Hospitalier de Recherche  
21  
22 454 Clinique - PHRC 2019 (French Ministry of Health) grant number 2020-A02837-32.  
23  
24  
25  
26 455

27  
28  
29 456 **Competing interests statement :**

30  
31 457 AF, DB, AB, PE: declare no competing interest

32  
33 458 AR: grants from bioMerieux and Merck

34  
35 459 IM-L: board on PFIZER, MSD, GILEAD

36  
37 460 J-FT directly related to the protocol: none, participation to scientific advisory boards: Pfizer,  
38 461 Gilead, Merck, BD, Shionogi; readings: Merck, Biomerieux, Pfizer, Shionogi; research grants  
39 462 to my research unit: thermofischer, Pfizer, Merck

40  
41 463 J-RZ: consulting fees from MSD, Pfizer, speaker fees fom MSD, Pfizer, Shionogi, Correvio  
42 464 and Eumedica

43  
44 465 EW: Speaker fees from MSD, Akcea therapeutics and LFB, support for attending  
45 466 meeting/travel: LFB and Akcea therapeutics  
46  
47 467

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9 554 Lancet Infect Dis. déc 2019;19(12):1299-311.  
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For peer review only

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3 **Figures and Table legends**  
4

5 **Figure 1:** General flowchart of the study  
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7 **Figure 2:** Criteria of clinical cure and criteria for discontinuation of antibiotic therapy in  
8 experimental arm  
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10

11 **Figure 3:** Description of microbiological categories of outcomes in relation to time of  
12 occurrence of new episode of VAP after inclusion adapted from(24)  
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16  
17 **Table 1:** Chronology of the study and procedures  
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Clinical suspicion of VAP

Respiratory sample

microbiological confirmation

antibiotic susceptibility testing

Appropriate empiric antibiotic therapy ?

NO

YES

INCLUSION

RANDOMIZATION

experimental group

Control group

Cessation of antibiotics if clinical cure

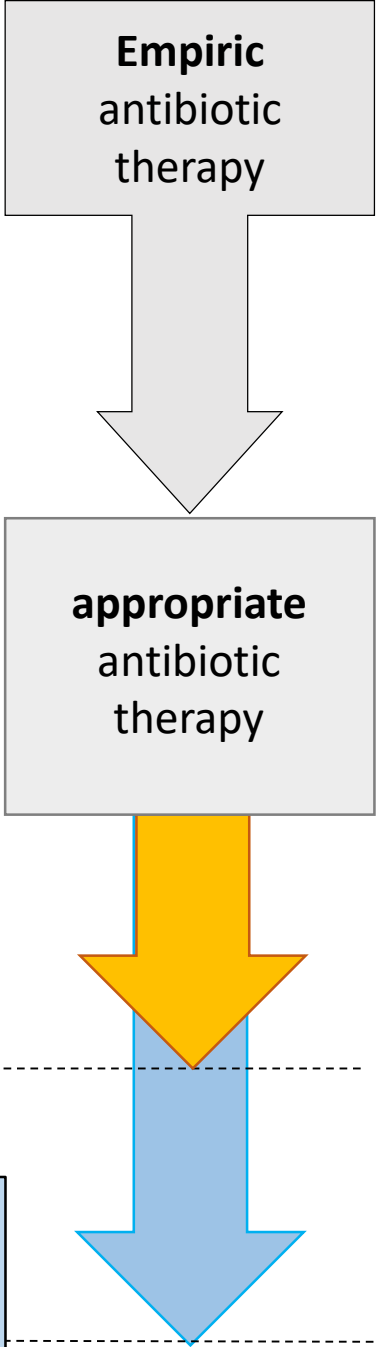
Appropriate antibiotic therapy for 7 consecutive days

Assessment of all cause mortality, treatment failure, rate of new VAP

Assessment vital status

Empiric antibiotic therapy

appropriate antibiotic therapy



# Experimental group

- Antimicrobial stewardship based on daily clinical assessment of clinical cure of confirmed pneumonia 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  $\geq 3$  criteria are met

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

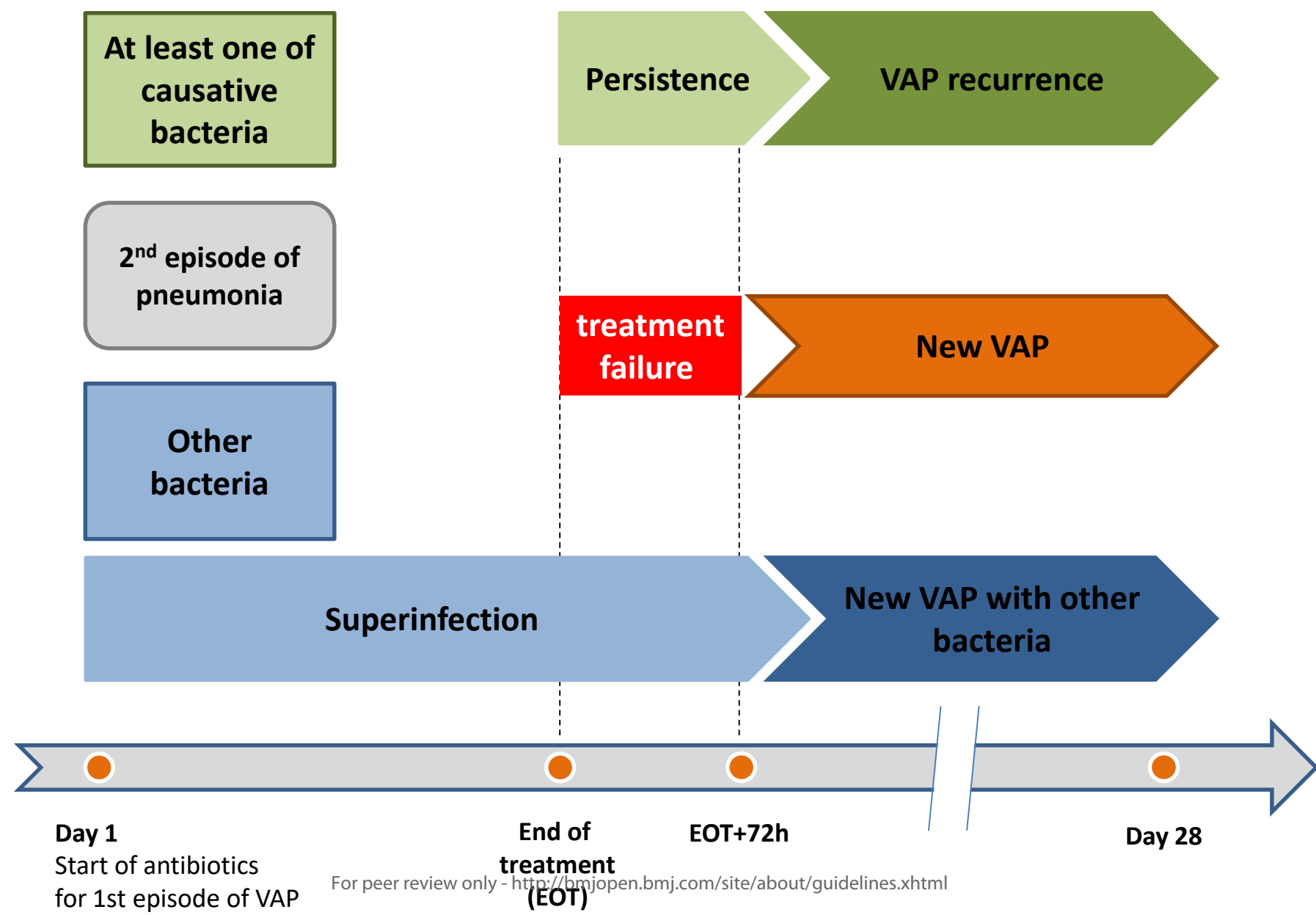
2. Normo**T**hermia  
 $36^{\circ}\text{C} < T < 38.3^{\circ}\text{C}$

3. Improved\*  
**O**xygenation, measured  
by an increase in the  
of the PaO<sub>2</sub>/FiO<sub>2</sub> ratio

4. Absence of  
**hyP**otension



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

Section/item	Item No	Description	Page
<b>Administrative information</b>			
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
<b>Introduction</b>			
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	

1				
2	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
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7				
8	<b>Methods: Participants, interventions, and outcomes</b>			
9				
10	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
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14	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
15				
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19	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	12,13
20				
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22		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
23				
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26		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	14
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31		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
32				
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34	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
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42	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
43				
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47	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
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51	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	15
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#### 54 **Methods: Assignment of interventions (for controlled trials)**

56 Allocation:

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2	Sequence	16a	Method of generating the allocation sequence (eg, computer-	11
3	generation		generated random numbers), and list of any factors for	
4			stratification. To reduce predictability of a random sequence,	
5			details of any planned restriction (eg, blocking) should be	
6			provided in a separate document that is unavailable to those who	
7			enrol participants or assign interventions	
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10	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central	11
11	concealment		telephone; sequentially numbered, opaque, sealed envelopes),	
12	mechanism		describing any steps to conceal the sequence until interventions	
13			are assigned	
14				
15	Implementation	16c	Who will generate the allocation sequence, who will enrol	11,12
16			participants, and who will assign participants to interventions	
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19	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial	12
20			participants, care providers, outcome assessors, data analysts),	
21			and how	
22				
23		17b	If blinded, circumstances under which unblinding is permissible,	NA
24			and procedure for revealing a participant's allocated intervention	
25			during the trial	
26				
27				
28	<b>Methods: Data collection, management, and analysis</b>			
29				
30	Data collection	18a	Plans for assessment and collection of outcome, baseline, and	17
31	methods		other trial data, including any related processes to promote data	
32			quality (eg, duplicate measurements, training of assessors) and a	
33			description of study instruments (eg, questionnaires, laboratory	
34			tests) along with their reliability and validity, if known. Reference	
35			to where data collection forms can be found, if not in the protocol	
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38		18b	Plans to promote participant retention and complete follow-up,	Table
39			including list of any outcome data to be collected for participants	1
40			who discontinue or deviate from intervention protocols	
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42	Data management	19	Plans for data entry, coding, security, and storage, including any	17
43			related processes to promote data quality (eg, double data entry;	
44			range checks for data values). Reference to where details of data	
45			management procedures can be found, if not in the protocol	
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48	Statistical methods	20a	Statistical methods for analysing primary and secondary	16
49			outcomes. Reference to where other details of the statistical	
50			analysis plan can be found, if not in the protocol	
51				
52		20b	Methods for any additional analyses (eg, subgroup and adjusted	16,17
53			analyses)	
54				
55		20c	Definition of analysis population relating to protocol non-	17,18
56			adherence (eg, as randomised analysis), and any statistical	
57			methods to handle missing data (eg, multiple imputation)	
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2	<b>Methods: Monitoring</b>			
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4	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
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12		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
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16	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
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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
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26	<b>Ethics and dissemination</b>			
27				
28	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	18
29				
30	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
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36	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	19
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40		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
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42				
43	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
44				
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47	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	NA
48				
49				
50	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
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55	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
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2	Dissemination	31a	Plans for investigators and sponsor to communicate trial results	20,21
3	policy		to participants, healthcare professionals, the public, and other	
4			relevant groups (eg, via publication, reporting in results	
5			databases, or other data sharing arrangements), including any	
6			publication restrictions	
7				
8		31b	Authorship eligibility guidelines and any intended use of	22
9			professional writers	
10				
11		31c	Plans, if any, for granting public access to the full protocol,	NA
12			participant-level dataset, and statistical code	
13				
14				
15	<b>Appendices</b>			
16				
17	Informed consent	32	Model consent form and other related documentation given to	yes
18	materials		participants and authorised surrogates	
19				
20	Biological	33	Plans for collection, laboratory evaluation, and storage of	NA
21	specimens		biological specimens for genetic or molecular analysis in the	
22			current trial and for future use in ancillary studies, if applicable	
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\*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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

# BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-065293.R1
Article Type:	Protocol
Date Submitted by the Author:	25-Nov-2022
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<b>Primary Subject Heading</b>:	Intensive care
Secondary Subject Heading:	Infectious diseases
Keywords:	Adult intensive & critical care < ANAESTHETICS, Infection control < INFECTIOUS DISEASES, Respiratory infections < THORACIC MEDICINE

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3 **1 Antimicrobial Stewardship for Ventilator Associated Pneumonia in Intensive Care**  
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6 **2 (the ASPIC trial): study protocol for a randomized controlled trial**  
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9 3 Arnaud FOUCRIER<sup>1</sup>, Antoine ROQUILLY<sup>2</sup>, Delphine BACHELET<sup>3</sup>, Ignacio MARTIN-LOECHES<sup>4,5</sup>,  
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1  
2  
3 **1 Abstract (218 words)**  
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5

6 **2 Introduction:** Ventilator associated pneumonia (VAP) remains the leading cause of infections  
7 treated in the Intensive Care Units (ICU). In a personalized care approach, we hypothesize that  
8 the duration of treatment of VAP can be reduced in function of the response to treatment.  
9  
10

11 **5 Methods and analysis:** The ASPIC trial is a pragmatic national multicenter, phase III, non-  
12 inferiority, comparative randomized (1:1) single-blinded clinical trial. Five hundred ninety  
13 adult patients hospitalized in 24 French ICU with a microbiologically confirmed first episode  
14 of VAP that received appropriate empiric antibiotic therapy will be included. They will be  
15 randomly allocated to standard management with duration of appropriate antibiotic fixed for 7  
16 days according to international guidelines or antimicrobial stewardship based on daily clinical  
17 assessment of clinical cure. The assessment of clinical cure will be repeated daily until at least  
18 3 criteria of clinical cure are met, allowing the discontinuation of antibiotic therapy in  
19 experimental group. The primary endpoint is a composite endpoint combining of all-cause  
20 mortality measured at day 28, treatment failure or new episode of microbiologically confirmed  
21 VAP until day 28.  
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31 **16 Discussion:** Demonstrate that a strategy to reduce the duration of antibiotic therapy for VAP  
32 based on clinical assessment is safe could lead to changes in practice as part of a personalized  
33 therapeutic approach, by reducing exposure to antibiotics and their side effects.  
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3 1 **Ethics and dissemination:** The ASPIC trial has been approved by the French regulatory  
4 agency (Agence Nationale de Sécurité du Médicament et des Produits de Santé, ANSM;  
5 2 EUDRACT number 2021-002197-78, 19 August 2021) and an independent ethics committee  
6 3 the Comité de Protection des Personnes (CPP) Ile-de-France III (CNRIPH : 21.03.25.60729, 10  
7 4 October 2021) for the study protocol (version ASPIC-1.3; 03 September 2021) for all study  
8 5 centers. Participant recruitment is scheduled to begin in 2022. Results will be published in  
9 6 international peer-reviewed medical journals.  
10 7

11 8 **Trial registration number:** NCT05124977, first posted November 18, 2021

12 9 **Protocol version identifier** N°1-3, 03 September 2021  
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3 **1 Strengths and limitations of this study**  
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- 6  
7 2 - High quality methodology using randomized controlled trial (RCT) design that will  
8  
9 3 provide a high-level of evidence on antimicrobial stewardship for management of ventilator-  
10  
11 4 associated pneumonia (VAP) antibiotic strategy  
12  
13 5 - First RCT conducting in Europe assessing the value of clinical cure criteria ('STOP  
14  
15 6 criteria') supported by an international expert panel to develop an antimicrobial stewardship  
16  
17 7 strategy  
18  
19 8 - Class of antibiotics prescription not imposed by the protocol, in a pragmatic approach  
20  
21 9 and in order to maximize the external validity of the results  
22  
23  
24 10 - Risk of poor adherence of investigator team to experimental strategy, which could lead  
25  
26 11 to absence of antibiotic discontinuation even if 'STOP' criteria are met.  
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## 1 INTRODUCTION

2 Reduction of use of antibiotics is a major point to control antimicrobial resistance in ICU (1).

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

8 In the last few years, the concept of antimicrobial stewardship (ASP) has been developed. It  
9 refers to programs, education, interventions that aim to optimize antibiotic use (5). In a recent  
10 review by Dyar et al. reports different definitions of ASP used in the literature (6).  
11 Antimicrobial stewardship refers to the responsible use of antimicrobials by healthcare  
12 professionals, and more specifically, to selection of the most appropriate antibiotic, duration,  
13 dose and route of administration for a given patient with a demonstrated or suspected infection  
14 (7,8).

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

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

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2  
3 1 and VAP. In this work, various innovative concepts are developed. First, the experts agree that  
4  
5 2 the criteria usually used in the literature to characterize the suspicion of VAP are weighted  
6  
7 3 differently. According to the experts, among 9 selected criteria, the first 4 criteria with the most  
8  
9 4 significant impact were: 1. Worsening of gas exchange, 2. Hypotension / vasopressor  
10  
11 5 requirement, 3. Temperature abnormalities (fever or hypothermia), 4. Purulent tracheal  
12  
13 6 secretions (rated ex-aequo with temperature abnormalities). Logically, less specific signs  
14  
15 7 (hyperleukocytosis, encephalopathy, auscultatory abnormalities) were ranked lower.  
16  
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19  
20 8 According to the experts, when these criteria regress or disappear, they are therefore considered  
21  
22 9 associated with clinical cure of VAP. Considering the small differences in the relative weights  
23  
24 10 of each criterion, it seems reasonable to consider that the association of at least 3 of these criteria  
25  
26 11 is necessary to consider a clinical cure. To date, no prospective evaluation of the robustness of  
27  
28 12 these criteria to guide antimicrobial treatment duration has been performed.  
29  
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31  
32 13 The ASPIC study aims at investigating whether an antimicrobial stewardship for  
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34 14 microbiologically proven VAP based on daily assessment of clinical cure and antimicrobial  
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36 15 discontinuation, if it is obtained, would be non-inferior to standard management in terms of all-  
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38 16 cause mortality, treatment failure or occurrence of new episode of VAP before day 28.  
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## 1 **METHODS AND ANALYSIS**

### 2 **Study design**

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

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

14 The trial overview is summarized in Figure 1. We report here the study protocol according to  
15 the SPIRIT (Standard Protocol Items: Recommendations for interventional Trials) statement  
16 (15).

## 1 **Definitions**

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

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

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

## 21 Clinical cure (Figure 2)

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



1 - No additional antibiotic therapy required for VAP treatment AND

2 - Patient is alive

3 Treatment failure defined by signs of VAP within 72 hours after the end antibiotic treatment

4 at the test of cure visit

5 Superinfection: Isolation of a pathogen, other than the causative baseline pathogen, from a

6 LRT specimen obtained in a subject with signs and symptoms of VAP developed during

7 antibiotic treatment

8 Persistence: Continued presence of the original causative baseline pathogen(s) from a LRT

9 culture obtained between EOT and 72 after EOT

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

11 28

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

13 baseline

14 Definitions of treatment failure, persistence, superinfection, persistence, VAP recurrence and

15 new VAP are summarized in Figure 3.

## 1 **Setting**

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

## 4 **Study population**

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

6 Inclusion criteria:

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

13 Exclusion criteria:

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

- 1  
2  
3 1 - VAP due to: *Pseudomonas aeruginosa*, Carbapenem-resistant *Acinetobacter* spp,  
4  
5 2 Carbapenem-resistant *Enterobacterales*  
6  
7 3 - Bacterial VAP occurring in the context of co-infection of COVID-19 or other viral VAP  
8  
9 4 (confirmed by RT-PCR)  
10  
11  
12 5 - Patients with empyema, necrotizing and abscessed pneumonia  
13  
14 6 - Pregnant women  
15  
16 7 - No health insurance coverage  
17  
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19 8

## 9 **Recruitment**

10 The screening will aim at identifying patients hospitalized in ICU who underwent a LRT sample  
11 because a VAP was suspected. During this period, management of patients is similar to usual  
12 care with clinical, biological and radiological assessments. After microbiological diagnosis  
13 confirmation and reception of Antibiotic Susceptibility Testing (AST) proving that the initial  
14 empiric antibiotic therapy was appropriate, eligible patient will be offered participation in the  
15 trial. Written informed consent would be obtained by the investigator or by a physician  
16 representing the investigator, from all patients, their next of kin, as appropriate, accordingly to  
17 French regulatory agencies authorization (see section Methods for obtaining information and  
18 consent from research participants).  
19

## 20 **Treatment allocation and randomization**

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

1  
2  
3 1 from the investigators. Permuted block technique will be used to assign treatment within the  
4  
5 2 various-sized blocks. Randomization will be stratified by center. The randomization scheme  
6  
7 3 will be generated by a statistician who is not involved in any other aspect of the study, and all  
8  
9 4 researchers will be blinded to block size(s) and randomization list to avoid prediction of future  
10  
11 5 patient's allocation. Allocation concealment will be ensured, as the service will not release the  
12  
13 6 randomization code until the patient has been recruited into the trial.  
14  
15  
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### 19 **Blinding**

20  
21 9 This study will be single-blinded. Participants will not be informed of their group allocation.  
22  
23 10 Blinding will be ensured as most patients will be either sedated (within standard of care) or  
24  
25 11 unable to have appropriate discussions with investigational team for the duration of the  
26  
27 12 experimental at study. The statistician conducting the data analysis will also be blinded to  
28  
29 13 group allocation. The medical staff cannot be blinded to the randomization arm due to the nature  
30  
31 14 of experimental design and our choice to evaluate this strategy in real-life clinical practice  
32  
33 15 conditions. If the patient is transferred to another clinical ward or leave the hospital during the  
34  
35 16 3-month follow-up, other healthcare professionals involved in their management will not be  
36  
37 17 made aware of the randomization arm.  
38  
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### 45 **Study procedures**

46  
47  
48 20 The general flowchart of the study is shown in Figure 1. A pragmatic approach will be followed  
49  
50 21 and usual patient management recommended by international guidelines (9–11) will be  
51  
52 22 provided in participating ICUs. In particular the choice of antibiotic therapy will be left at  
53  
54 23 investigator discretion.  
55  
56

57 24 In the experimental group, the ICU physician will discontinue the antibiotic therapy as soon as  
58  
59 25 clinical cure criteria of VAP are met. Minimal duration of appropriate antibiotic treatment will

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2  
3 1 be 3 days (including empirical antibiotic therapy). After 72 hours (usual delay to receive AST  
4  
5 2 results) of appropriate antibiotic treatment, the assessment of clinical cure will be performed  
6  
7 3 daily on the basis of 4 criteria:

- 8  
9  
10 4 - Regression or the decreased abundance of purulent tracheal secretions  
11  
12 5 - Absence of fever or hypothermia  
13  
14 6 - Improvement of oxygenation (assessed by increase of PaO<sub>2</sub>/FiO<sub>2</sub> ratio and PaO<sub>2</sub>/FiO<sub>2</sub>>150)  
15  
16 7 - Absence of arterial hypotension (hypotension is defined by mean arterial pressure < 70  
17  
18 8 mmHg(16,17)) or decreased need for epinephrine or norepinephrine by at least 0,1 µg/kg/mn  
19  
20 9 compared to baseline (day of inclusion)  
21  
22

23  
24 10 This assessment will be repeated daily until at least 3 of the 4 criteria are met, i.e. the patient is  
25  
26 11 considered clinically cured, thereby allowing the discontinuation of antibiotic therapy (Figure  
27  
28 12 2).

29  
30 13 A daily phone hotline, provided by coordinating investigator's team, will be accessible to  
31  
32 14 investigators for multidisciplinary validation of antibiotic discontinuation in patients included  
33  
34 15 in the experimental group.  
35  
36

37 16 For control group, ~~fixed~~ duration of antibiotic therapy will be at least 7 full days (since the  
38  
39 17 initiation of empirical antibiotic therapy), whatever clinical assessment.  
40  
41

42 18 For both groups, in case of non-clinical recovery after 7 full days (treatment failure) and/or in  
43  
44 19 case of suspicion of new VAP during treatment (superinfection), a new lower respiratory tract  
45  
46 20 sampling will be performed, and a new antibiotic therapy will be initiated. In case of new VAP,  
47  
48 21 patients will be treated according to the usual practices of the center.  
49  
50

51  
52 22 Following data will be collected daily from day 2 to day 28 or to ICU discharge in participants  
53  
54 23 from both arms: vital status, ventilation status, PaO<sub>2</sub> and FiO<sub>2</sub> (if ventilated), temperature,  
55  
56 24 tracheal secretions, blood pressure, use and dose of vasopressors, data on any infection  
57  
58  
59  
60

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

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

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

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

10

## 11 **Outcomes**

12 The primary endpoint will be a composite of:

- 13 1. All-cause mortality (ACM) measured at day 28 after initiation of therapy OR
- 14 2. Treatment failure defined by signs of VAP within 72 hours after the end antibiotic treatment  
15 at the test of cure visit OR
- 16 3. New episode of microbiologically confirmed VAP from 72H after the end of antibiotic  
17 treatment to day 28 after initiation of VAP antibiotic treatment

18 To avoid interpretation bias for the primary outcome, clinical and microbiological records of  
19 all participants will be reviewed by adjudication committee composed with two experts in order  
20 to evaluate the presence of (i) clinical cure, (ii) treatment failure and (iii) new episode of VAP.

21 This evaluation will be performed blindly from the randomization group and from the  
22 interpretation of the investigation team, according to predefined criteria (see Definition  
23 section). The adjudication committee will be composed of study investigators (including

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

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

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

- 17 1. Survival, clinical cure
- 18 2. Survival, new pulmonary infection
- 19 3. Death

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

### 22 23 **Sample size justification**

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

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

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

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

#### 14 **Data analysis plan**

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



1  
2  
3 1 tests of superiority (secondary objectives) will be two-sided with type I error of 5% and tests of  
4  
5 2 non-inferiority will be one-sided with type I error 2.5%. All statistical analyses will be  
6  
7 3 performed using SAS software (SAS Institute Inc., Cary, NC) v. 9.4 or later, or R software (R  
8  
9 4 Foundation for Statistical Computing, Vienna, Austria. <http://www.r-project.org/>) v. 4.0 or  
10  
11 5 later.  
12  
13

14 6 The primary analysis will also been performed in the following subgroups of patients:

- 15  
16  
17 7 – Those whose baseline bacteriological samples were assessed by rapid microbiological  
18  
19 8 technique (germ identification and AST)  
20  
21 9 – Patients admitted to ICU for trauma vs other reasons of admission  
22  
23  
24 10 – Patients with early onset VAP ( $\leq 5$  days after ICU admission) vs late onset VAP ( $\geq 5$  days  
25  
26 11 after ICU admission).  
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29  
30 12 No strategy of imputation is forecasted in case of missing data for the primary assessment  
31  
32 13 criterion. Information available at time of last follow-up will be taken into account.  
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## 1 **Data collection and management**

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

11

1 **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 <sub>R</sub>				
Verification of inclusion and non-inclusion criteria			X <sub>R</sub>				
Information			X <sub>R</sub>				
Written Informed consent			X <sub>R</sub>				
Randomization			X <sub>R</sub>				
Pregnancy test			X <sub>R</sub>				
Medical history		X <sub>C</sub>	X <sub>C</sub>				
Physical examination		X <sub>C</sub>	X <sub>C</sub>	X <sub>C</sub>	X <sub>C</sub>	X <sub>R</sub>	
Phone call							X <sub>R</sub>
Chest X-Ray/CT-scan		X <sub>C</sub>	X <sub>C</sub>	X <sub>C</sub>			
PaO <sub>2</sub> /FiO <sub>2</sub> ratio		X <sub>C</sub>	X <sub>C</sub>	X <sub>C</sub>	X <sub>C</sub>		
Assessment of clinical symptoms of VAP		X <sub>C</sub>	X <sub>C</sub>				
Assessment of clinical recovery of VAP				X <sub>C</sub>			
Start antibiotics			X <sub>C</sub>				
Antibiotics			X <sub>C</sub>	X <sub>C</sub>	X <sub>C</sub>		
Rectal swab				X <sub>C</sub>	X <sub>C</sub>		
Serum creatinin and calculated creatinin clearance			X <sup>b</sup> <sub>C</sub>				
White blood count		X <sub>C</sub>	X <sub>C</sub>	X <sub>C</sub>	X <sub>C</sub>		
SCORE	ISS	X <sub>C</sub>					
	SOFA	X <sub>C</sub>	X <sub>R</sub>				
	IGS	X <sub>C</sub>					
Assessment of rate of treatment failure and new episode of VAP						X <sub>R</sub>	
Antibiotic free days						X <sub>R</sub>	
Vital status						X <sub>R</sub>	X <sub>R</sub>
Adverse events			X <sub>R</sub>	X <sub>R</sub>	X <sub>R</sub>	X <sub>R</sub>	X <sub>R</sub>
Hospital admissions				X <sub>C</sub>	X <sub>C</sub>	X <sub>R</sub>	X <sub>R</sub>

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

4 <sup>b</sup> creatinin clearance may be performed ( $Cl_{cr} = (\text{urinary creatinin/serum creatinin}) \cdot \text{urine}$   
5  $\text{volume}_{24h}$ ) as frequently as clinically indicated to guide appropriate antibiotic therapy in  
6 subjects with renal impair

7 X<sub>C</sub> : made in usual care

8 X<sub>R</sub> : acts added for research

## 1 TRIAL STATUS

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

## 4 ETHICS AND DISSEMINATION

### 5 Legal obligations and approval

6 Sponsorship has been agreed by Assistance Publique—Hôpitaux de Paris (AP-HP, Clinical  
7 Research and Innovation Department) for this interventional research protocol involving human  
8 participants concerning a health product. AP-HP has obtained the approval of the French  
9 medicine regulatory agency (Agence Nationale de Sécurité du Médicament et des Produits de  
10 Santé, ANSM; EUDRACT number 2021-002197-78, 19 August 2021) and of the ethics  
11 comitee (Comité de Protection des Personnes (CPP) Ile-de-France III (CNRIPIH:  
12 21.03.25.60729, 10 October 2021)) for the study protocol (version ASPIC-1.3; 03 September  
13 2021). The trial will be carried out in accordance with the Declaration of Helsinki and the Good  
14 Clinical Practice guidelines. Any substantial modification to the protocol will be sent to the  
15 sponsor, and then to the ANSM and the CPP for approval before the amendment can be  
16 implemented. The information sheet and the consent form can be revised if necessary,  
17 particularly if there is a substantial amendment to the study or if adverse reactions occur. AP-  
18 HP is the owner of the data. The data cannot be used or disclosed to a third party without its  
19 prior permission.

## 1 **Methods for obtaining information and consent from research participants**

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

## 12 **Patient and public involvement**

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

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

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

## 20 **Data deposition, quality control and curation**

21 The persons responsible for the quality control of clinical matters will take all necessary  
22 precautions to ensure the confidentiality of information related to the study participants. These  
23 persons, as well as the investigators themselves, are bound by professional confidentiality.

24 During or after the research, all data collected about the participants and sent to the sponsor by

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

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

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

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

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

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

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

### 8 **Publication plan**

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

16

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

7  
8 **Funding statement:** This work was supported by Programme Hospitalier de Recherche  
9 Clinique - PHRC 2019 (Ministère de la Santé) grant number 2020-A02837-32.

10  
11 **Competing interests statement:**

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

13 AR: grants from bioMerieux and Merck

14 IM-L: board on PFIZER, MSD, GILEAD

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

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

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

22



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3 **Figures and Table legends**  
4

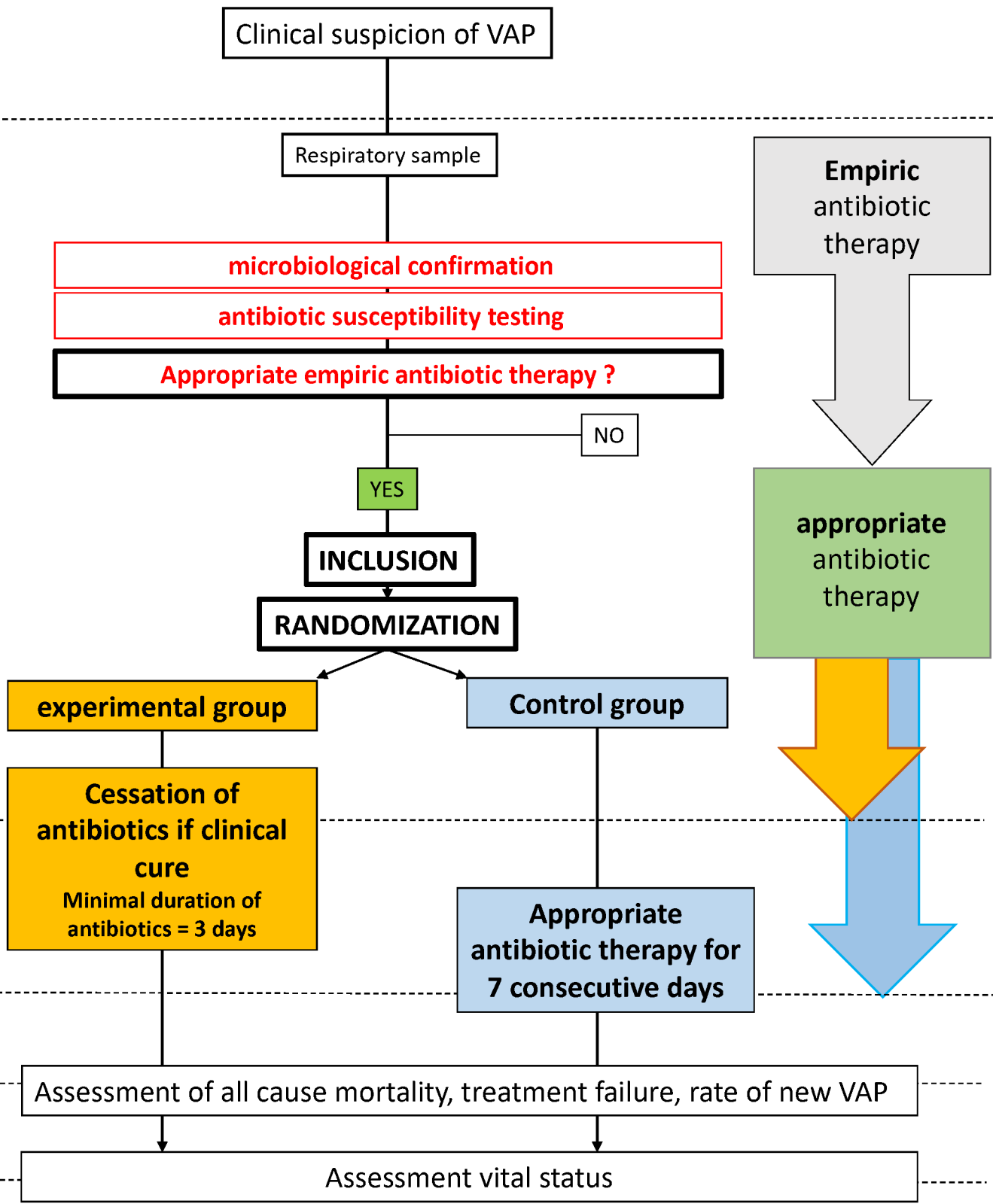
5 **Figure 1:** General flowchart of the study  
6

7 **Figure 2:** Criteria of clinical cure and criteria for discontinuation of antibiotic therapy in  
8 experimental arm  
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11 **Figure 3:** Description of microbiological categories of outcomes in relation to time of  
12 occurrence of new episode of VAP after inclusion adapted from(21)  
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18 **Table 1:** Chronology of the study and procedures  
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# 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  $\geq 3$  criteria are met

1. Regression\* of purulent tracheal Secretions

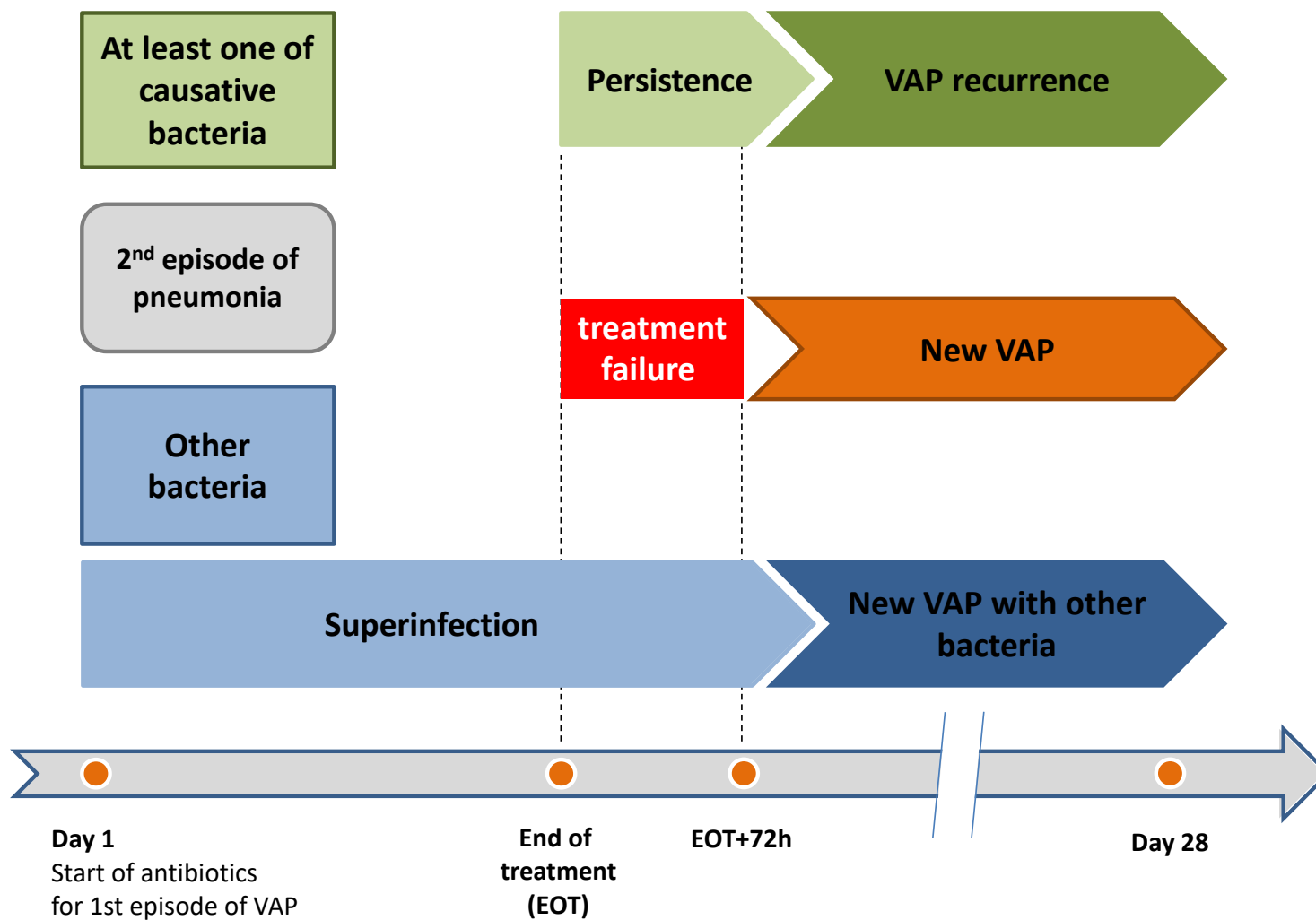
2. NormoThermia  
 $36^{\circ}\text{C} < T < 38.3^{\circ}\text{C}$

3. Improved\* Oxygenation, measured by an increase in the of the PaO<sub>2</sub>/FiO<sub>2</sub> ratio

4. Absence of hyPotension

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\* compared to the day of initiation of antibiotic therapy





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

Section/item	Item No	Description	Page
<b>Administrative information</b>			
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
<b>Introduction</b>			
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	



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2	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)
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8	<b>Methods: Participants, interventions, and outcomes</b>		
9			
10	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
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14	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)
15			
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19	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
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22		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)
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26		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
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31		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
32			
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34	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
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42	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)
43			
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47	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
48			
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51	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size
52			
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**Methods: Assignment of interventions (for controlled trials)**

Allocation:

1				
2	Sequence	16a	Method of generating the allocation sequence (eg, computer-	11
3	generation		generated random numbers), and list of any factors for	
4			stratification. To reduce predictability of a random sequence,	
5			details of any planned restriction (eg, blocking) should be	
6			provided in a separate document that is unavailable to those who	
7			enrol participants or assign interventions	
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10	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central	11
11	concealment		telephone; sequentially numbered, opaque, sealed envelopes),	
12	mechanism		describing any steps to conceal the sequence until interventions	
13			are assigned	
14				
15	Implementation	16c	Who will generate the allocation sequence, who will enrol	11,12
16			participants, and who will assign participants to interventions	
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18				
19	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial	12
20			participants, care providers, outcome assessors, data analysts),	
21			and how	
22				
23		17b	If blinded, circumstances under which unblinding is permissible,	NA
24			and procedure for revealing a participant's allocated intervention	
25			during the trial	
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28	<b>Methods: Data collection, management, and analysis</b>			
29				
30	Data collection	18a	Plans for assessment and collection of outcome, baseline, and	17
31	methods		other trial data, including any related processes to promote data	
32			quality (eg, duplicate measurements, training of assessors) and a	
33			description of study instruments (eg, questionnaires, laboratory	
34			tests) along with their reliability and validity, if known. Reference	
35			to where data collection forms can be found, if not in the protocol	
36				
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38		18b	Plans to promote participant retention and complete follow-up,	Table
39			including list of any outcome data to be collected for participants	1
40			who discontinue or deviate from intervention protocols	
41				
42	Data management	19	Plans for data entry, coding, security, and storage, including any	17
43			related processes to promote data quality (eg, double data entry;	
44			range checks for data values). Reference to where details of data	
45			management procedures can be found, if not in the protocol	
46				
47				
48	Statistical methods	20a	Statistical methods for analysing primary and secondary	16
49			outcomes. Reference to where other details of the statistical	
50			analysis plan can be found, if not in the protocol	
51				
52		20b	Methods for any additional analyses (eg, subgroup and adjusted	16,17
53			analyses)	
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55		20c	Definition of analysis population relating to protocol non-	17,18
56			adherence (eg, as randomised analysis), and any statistical	
57			methods to handle missing data (eg, multiple imputation)	
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2 **Methods: Monitoring**

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4	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
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12		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
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16	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
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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
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26	<b>Ethics and dissemination</b>			
27				
28	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	18
29				
30				
31	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
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36	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	19
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40		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
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42				
43	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
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47	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	NA
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51	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
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55	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
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2	Dissemination	31a	Plans for investigators and sponsor to communicate trial results	20,21
3	policy		to participants, healthcare professionals, the public, and other	
4			relevant groups (eg, via publication, reporting in results	
5			databases, or other data sharing arrangements), including any	
6			publication restrictions	
7				
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9		31b	Authorship eligibility guidelines and any intended use of	22
10			professional writers	
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12		31c	Plans, if any, for granting public access to the full protocol,	NA
13			participant-level dataset, and statistical code	
14				
15	<b>Appendices</b>			
16				
17	Informed consent	32	Model consent form and other related documentation given to	yes
18	materials		participants and authorised surrogates	
19				
20	Biological	33	Plans for collection, laboratory evaluation, and storage of	NA
21	specimens		biological specimens for genetic or molecular analysis in the	
22			current trial and for future use in ancillary studies, if applicable	
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\*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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

# BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-065293.R2
Article Type:	Protocol
Date Submitted by the Author:	21-Dec-2022
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<b>Primary Subject Heading</b>:	Intensive care
Secondary Subject Heading:	Infectious diseases
Keywords:	Adult intensive & critical care < ANAESTHETICS, Infection control < INFECTIOUS DISEASES, Respiratory infections < THORACIC MEDICINE

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3 **1 Antimicrobial Stewardship for Ventilator Associated Pneumonia in Intensive Care**  
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6 **2 (the ASPIC trial): study protocol for a randomized controlled trial**  
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3 **1 Abstract (218 words)**  
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6 **2 Introduction:** Ventilator associated pneumonia (VAP) remains the leading cause of infections  
7 treated in the Intensive Care Units (ICU). In a personalized care approach, we hypothesize that  
8  
9 3 the duration of treatment of VAP can be reduced in function of the response to treatment.  
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5 **5 Methods and analysis:** The ASPIC trial is a pragmatic national multicenter, phase III, non-  
6 inferiority, comparative randomized (1:1) single-blinded clinical trial. Five hundred ninety  
7 adult patients hospitalized in 24 French ICU with a microbiologically confirmed first episode  
8 of VAP that received appropriate empirical antibiotic therapy will be included. They will be  
9 randomly allocated to standard management with duration of appropriate antibiotic fixed for 7  
10 days according to international guidelines or antimicrobial stewardship based on daily clinical  
11 assessment of clinical cure. The assessment of clinical cure will be repeated daily until at least  
12 3 criteria of clinical cure are met, allowing the discontinuation of antibiotic therapy in  
13 experimental group. The primary endpoint is a composite endpoint combining of all-cause  
14 mortality measured at day 28, treatment failure or new episode of microbiologically confirmed  
15 VAP until day 28.

16 **16 Discussion:** Demonstrate that a strategy to reduce the duration of antibiotic therapy for VAP  
17 based on clinical assessment is safe could lead to changes in practice as part of a personalized  
18 therapeutic approach, by reducing exposure to antibiotics and their side effects.



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3 1 **Ethics and dissemination:** The ASPIC trial has been approved by the French regulatory  
4 agency (Agence Nationale de Sécurité du Médicament et des Produits de Santé, ANSM;  
5 2 EUDRACT number 2021-002197-78, 19 August 2021) and an independent ethics committee  
6 3 the Comité de Protection des Personnes (CPP) Ile-de-France III (CNRIPH : 21.03.25.60729, 10  
7 4 October 2021) for the study protocol (version ASPIC-1.3; 03 September 2021) for all study  
8 5 centers. Participant recruitment is scheduled to begin in 2022. Results will be published in  
9 6 international peer-reviewed medical journals.  
10 7

11 8 **Trial registration number:** NCT05124977, first posted November 18, 2021

12 9 **Protocol version identifier** N°1-3, 03 September 2021  
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3 **1 Strengths and limitations of this study**  
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7 2 - High quality methodology using randomized controlled trial (RCT) design that will  
8  
9 3 provide a high-level of evidence on antimicrobial stewardship for management of ventilator-  
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11 4 associated pneumonia (VAP) antibiotic strategy  
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13 5 - First RCT conducting in Europe assessing the value of clinical cure criteria ('STOP  
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15 6 criteria') supported by an international expert panel to develop an antimicrobial stewardship  
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17 7 strategy  
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19 8 - Class of antibiotics prescription not imposed by the protocol, in a pragmatic approach  
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21 9 and in order to maximize the external validity of the results  
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24 10 - Risk of poor adherence of investigator team to experimental strategy, which could lead  
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26 11 to absence of antibiotic discontinuation even if 'STOP' criteria are met.  
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## 1 INTRODUCTION

2 Reduction of use of antibiotics is a major point to control antimicrobial resistance in ICU (1).

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

8 In the last few years, the concept of antimicrobial stewardship (ASP) has been developed. It  
9 refers to programs, education, interventions that aim to optimize antibiotic use (5). In a recent  
10 review by Dyar et al. reports different definitions of ASP used in the literature (6).  
11 Antimicrobial stewardship refers to the responsible use of antimicrobials by healthcare  
12 professionals, and more specifically, to selection of the most appropriate antibiotic, duration,  
13 dose and route of administration for a given patient with a demonstrated or suspected infection  
14 (7,8).

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

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

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3 1 and VAP. In this work, various innovative concepts are developed. First, the experts agree that  
4  
5 2 the criteria usually used in the literature to characterize the suspicion of VAP are weighted  
6  
7 3 differently. According to the experts, among 9 selected criteria, the first 4 criteria with the most  
8  
9 4 significant impact were: 1. Worsening of gas exchange, 2. Hypotension / vasopressor  
10  
11 5 requirement, 3. Temperature abnormalities (fever or hypothermia), 4. Purulent tracheal  
12  
13 6 secretions (rated ex-aequo with temperature abnormalities). Logically, less specific signs  
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15 7 (hyperleukocytosis, encephalopathy, auscultatory abnormalities) were ranked lower.  
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20 8 According to the experts, when these criteria regress or disappear, they are therefore considered  
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22 9 associated with clinical cure of VAP. Considering the small differences in the relative weights  
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24 10 of each criterion, it seems reasonable to consider that the association of at least 3 of these criteria  
25  
26 11 is necessary to consider a clinical cure. To date, no prospective evaluation of the robustness of  
27  
28 12 these criteria to guide antimicrobial treatment duration has been performed.  
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32 13 The ASPIC study aims at investigating whether an antimicrobial stewardship for  
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34 14 microbiologically proven VAP based on daily assessment of clinical cure and antimicrobial  
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36 15 discontinuation, if it is obtained, would be non-inferior to standard management in terms of all-  
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38 16 cause mortality, treatment failure or occurrence of new episode of VAP before day 28.  
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## 1 **METHODS AND ANALYSIS**

### 2 **Study design**

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

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

14 The trial overview is summarized in Figure 1. We report here the study protocol according to  
15 the SPIRIT (Standard Protocol Items: Recommendations for interventional Trials) statement  
16 (15).

## 1 **Definitions**

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

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

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

## 21 Clinical cure

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

1 - No additional antibiotic therapy required for VAP treatment AND

2 - Patient is alive

3 Treatment failure defined by signs of VAP within 72 hours after the end antibiotic treatment

4 at the test of cure visit

5 Superinfection: Isolation of a pathogen, other than the causative baseline pathogen, from a

6 LRT specimen obtained in a subject with signs and symptoms of VAP developed during

7 antibiotic treatment

8 Persistence: Continued presence of the original causative baseline pathogen(s) from a LRT

9 culture obtained between EOT and 72 after EOT

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

11 28

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

13 baseline

14 Definitions of treatment failure, persistence, superinfection, persistence, VAP recurrence and

15 new VAP are summarized in Figure 3.

## 1 **Setting**

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

## 4 **Study population**

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

6 Inclusion criteria:

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

13 Exclusion criteria:

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



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3 1 - VAP due to: *Pseudomonas aeruginosa*, Carbapenem-resistant *Acinetobacter* spp,  
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5 2 Carbapenem-resistant *Enterobacterales*  
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7 3 - Bacterial VAP occurring in the context of co-infection of COVID-19 or other viral VAP  
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9 4 (confirmed by RT-PCR)  
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12 5 - Patients with empyema, necrotizing and abscessed pneumonia  
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14 6 - Pregnant women  
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16 7 - No health insurance coverage  
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## 9 **Recruitment**

10 The screening will aim at identifying patients hospitalized in ICU who underwent a LRT sample  
11 because a VAP was suspected. During this period, management of patients is similar to usual  
12 care with clinical, biological and radiological assessments. After microbiological diagnosis  
13 confirmation and reception of Antibiotic Susceptibility Testing (AST) proving that the initial  
14 empirical antibiotic therapy was appropriate, eligible patient will be offered participation in the  
15 trial. Written informed consent would be obtained by the investigator or by a physician  
16 representing the investigator, from all patients, their next of kin, as appropriate, accordingly to  
17 French regulatory agencies authorization (see section Methods for obtaining information and  
18 consent from research participants).  
19

## 20 **Treatment allocation and randomization**

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

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3 1 from the investigators. Permuted block technique will be used to assign treatment within the  
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5 2 various-sized blocks. Randomization will be stratified by center. The randomization scheme  
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7 3 will be generated by a statistician who is not involved in any other aspect of the study, and all  
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9 4 researchers will be blinded to block size(s) and randomization list to avoid prediction of future  
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11 5 patient's allocation. Allocation concealment will be ensured, as the service will not release the  
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13 6 randomization code until the patient has been recruited into the trial.  
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## 19 **Blinding**

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21 9 This study will be single-blinded. Participants will not be informed of their group allocation.  
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23 10 Blinding will be ensured as most patients will be either sedated (within standard of care) or  
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25 11 unable to have appropriate discussions with investigational team for the duration of the  
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27 12 experimental at study. The statistician conducting the data analysis will also be blinded to  
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29 13 group allocation. The medical staff cannot be blinded to the randomization arm due to the nature  
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31 14 of experimental design and our choice to evaluate this strategy in real-life clinical practice  
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33 15 conditions. If the patient is transferred to another clinical ward or leave the hospital during the  
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35 16 3-month follow-up, other healthcare professionals involved in their management will not be  
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37 17 made aware of the randomization arm.  
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## 45 **Study procedures**

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48 20 A pragmatic approach will be followed and usual patient management recommended by  
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50 21 international guidelines (9–11) will be provided in participating ICUs. In particular the choice  
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52 22 of antibiotic therapy will be left at investigator discretion (according current French  
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54 23 guidelines(11). Table 1)  
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57 24 In the experimental group, the ICU physician will discontinue the antibiotic therapy as soon as  
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59 25 clinical cure criteria of VAP are met. Minimal duration of appropriate antibiotic treatment will

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

- 4 - Regression or the decreased abundance of purulent tracheal secretions
- 5 - Absence of fever or hypothermia
- 6 - Improvement of oxygenation (assessed by increase of  $\text{PaO}_2/\text{FiO}_2$  ratio and  $\text{PaO}_2/\text{FiO}_2 > 150$ )
- 7 - Absence of arterial hypotension (hypotension is defined by mean arterial pressure  $< 70$   
8 mmHg(16,17)) or decreased need for epinephrine or norepinephrine by at least  $0,1 \mu\text{g}/\text{kg}/\text{mn}$   
9 compared to baseline (day of inclusion)

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

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

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

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

21 Following data will be collected daily from day 2 to day 28 or to ICU discharge in participants  
22 from both arms: vital status, ventilation status,  $\text{PaO}_2$  and  $\text{FiO}_2$  (if ventilated), temperature,  
23 tracheal secretions, blood pressure, use and dose of vasopressors, data on any infection  
24 throughout study period (infection site, bacteriological documentation, number of days of  
25 antibiotic therapy), antibiotic use (molecule; dosage; duration of treatment).

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3 1 Additional data will be collected daily from Day 2 to Day 8: clinical assessment, focused  
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5 2 pulmonary examination, laboratory assessment (usual tests, biochemical, hematological),  
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7 3 radiological evaluation (Chest X-Ray/CT-scan), if performed as part of usual care.  
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10 4 Rectal swabbing for collection of data on colonization or acquisition of Multidrug Resistant  
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12 5 (MDR) bacteria will be performed at ICU admission and weekly until ICU discharge as part as  
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14 6 usual care.  
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17 7 All participants will be followed up to day 90 with vital status assessment.  
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For peer review only

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

Situations	Therapeutic agent
<u>Early VAP</u> $\leq 5^{\text{th}}$ day after admission and absence of: <ul style="list-style-type: none"> <li>- septic shock</li> <li>- risk factor* of MDR</li> </ul>	amoxicillin+clavulanic acid  OR  3 <sup>rd</sup> cephalosporin
<u>Early VAP</u> $\leq 5^{\text{th}}$ day after admission AND <ul style="list-style-type: none"> <li>- septic shock</li> <li>- absence of risk factor* of MDR</li> </ul>	amoxicillin+clavulanic acid OR 3 <sup>rd</sup> cephalosporin  AND  aminosid
<u>Delayed VAP</u> $> 5^{\text{th}}$ day of admission Or other risk factor* non-fermenting GNB <sup>o</sup>	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 vancomycin OR linezolid
Risk factor <sup>#</sup> of SAMR*	

2 \*Prior intravenous antibiotic use within 90 day, Septic shock at time of VAP, ARDS preceding pneumonia, five or more days  
3 of hospitalization prior to the occurrence of VAP, acute renal replacement therapy prior to VAP onset.

4 <sup>o</sup> GNB : Gram Negative Bacilli

5 \* SAMR : *Staphyococcus aureus* methicillin-resistant

6 <sup>#</sup> if local prevalence of SAMR is elevated, recent colonization to SAMR, chronic cutaneous lesion, chronic dialysis

## 9 Outcomes

10 The primary endpoint will be a composite of:

- 11 1. All-cause mortality (ACM) measured at day 28 after initiation of therapy OR
- 12 2. Treatment failure defined by signs of VAP within 72 hours after the end antibiotic treatment
- 13 at the test of cure visit OR
- 14 3. New episode of microbiologically confirmed VAP from 72H after the end of antibiotic
- 15 treatment to day 28 after initiation of VAP antibiotic treatment

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2  
3 1 To avoid interpretation bias for the primary outcome, clinical and microbiological records of  
4  
5 2 all participants will be reviewed by adjudication committee composed with two experts in order  
6  
7 3 to evaluate the presence of (i) clinical cure, (ii) treatment failure and (iii) new episode of VAP.  
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10 4 This evaluation will be performed blindly from the randomization group and from the  
11  
12 5 interpretation of the investigation team, according to predefined criteria (see Definition  
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14 6 section). The adjudication committee will be composed of study investigators (including  
15  
16 7 scientific committee of ASPIC). Each member will review the primary endpoints criteria of a  
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18 8 subgroup of patients that were not enrolled in its center.  
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22 9 Secondary endpoints will be: day 28 all-cause mortality, proportion of treatment failure and of  
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24 10 new episode of VAP; the number of antibiotic free days alive from initiation of VAP antibiotic  
25  
26 11 therapy to day 28; the duration of invasive MV; the length of ICU stay, defined by the number  
27  
28 12 of days between inclusion and ICU discharge or in-ICU death; the proportion of VAP  
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30 13 recurrence assessed by the intensivist; the antibiotic related side effects; the proportion of  
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32 14 acquisition of MDR bacteria (defined as the identification of a MDR bacteria carriage not  
33  
34 15 present at admission); the proportion of protocol deviation i.e. lack of antibiotic therapy  
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36 16 discontinuation despite a fulfillment of clinical cure definition in the experimental group ; the  
37  
38 17 total cumulative costs of antibiotics and incremental cost effectiveness ratio; and the  
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40 18 Desirability of Outcome Ranking (DOOR) and the Response Adjusted for Duration of  
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42 19 Antibiotic Risk (RADAR) for each strategy (experimental and control groups)(18).  
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47 20 All trial participants will be ranked with respect to the desirability of their overall outcome and  
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49 21 the distributions of DOORs will be compared between strategies Overall clinical outcomes at  
50  
51 22 day 28 will be ranked from most to least desirable as followed:  
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53

- 54 23 1. Survival, clinical cure
- 55  
56 24 2. Survival, new pulmonary infection
- 57  
58 25 3. Death
- 59  
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3 1 In RADAR analyses, patients will be ranked overall clinical outcome, but in case of ex-aequo,  
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5 2 the patient with a shorter duration of antibiotic use will receive a higher rank  
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8 3

#### 10 4 **Sample size justification**

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12  
13 5 Assuming that 25% of the patients will encountered all-cause mortality, treatment failure or  
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15 6 occurrence of new episode of VAP before day 28 in the control arm (19), 590 subjects (295 per  
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17 7 arm) are needed to establish non-inferiority with the absolute difference of death, treatment  
18  
19 8 failure or occurrence of new episode of VAP doesn't exceed 10% (non-inferiority margin)  
20  
21 9 between experimental and control arms with a power of 80%, a type I error (alpha) of 2.5%.

22  
23  
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25  
26 10 A non-inferiority margin of 10% was chosen taking into account the methodological data  
27  
28 11 applied to the randomized controlled trials dedicated to VAP. According European medicine  
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30 12 Agency (20), the suggested non-inferiority margin should not exceed -12.5% for clinical  
31  
32 13 outcome documented at a Test-of-Cure visit. In this recommendation, the margin of 12.5% do  
33  
34 14 not include mortality.

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38 15 In a published study (ASPECT)(21) designed to show non-inferiority for the primary endpoint  
39  
40 16 in the intention-to-treat population, with a 10% non-inferiority margin to achieve 90% power  
41  
42 17 at a one-sided significance level of 0,025 (based on regulatory agency guidance (22) and  
43  
44 18 assuming a 28-day all-cause mortality rate of 20% in both groups.  
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#### 51 20 **Data analysis plan**

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54 21 The primary analysis will be performed on the intention-to-treat population (21). The 95%  
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56 22 confidence interval of the difference in proportions of all-cause death, treatment failure or  
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58 23 occurrence of new episode of VAP observed between the two groups will be estimated. This  
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3 1 confidence interval will be compared to the non-inferiority margin of 10%. If the lower limit of  
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5 2 the confidence interval of the difference in proportions is less than or equal to -10%, then we  
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7 3 cannot conclude that the antimicrobial stewardship-based strategy is non-inferior to the  
8  
9 4 reference strategy. In the opposite case, if the lower limit of the confidence interval is strictly  
10  
11 5 greater than -10%, then we will conclude that the antimicrobial stewardship-based strategy is  
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13 6 non-inferior on all-cause mortality, treatment failure or occurrence of new episode of VAP at  
14  
15 7 day 28 after inclusion. Sensitivity analysis on per-protocol population will be performed. All  
16  
17 8 tests of superiority (secondary objectives) will be two-sided with type I error of 5% and tests of  
18  
19 9 non-inferiority will be one-sided with type I error 2.5%. All statistical analyses will be  
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21 10 performed using SAS software (SAS Institute Inc., Cary, NC) v. 9.4 or later, or R software (R  
22  
23 11 Foundation for Statistical Computing, Vienna, Austria. <http://www.r-project.org/>) v. 4.0 or  
24  
25 12 later.

26  
27 13 The primary analysis will also been performed in the following subgroups of patients:

- 28  
29 14 – Those whose baseline bacteriological samples were assessed by rapid microbiological  
30  
31 15 technique (germ identification and AST)  
32  
33 16 – Patients admitted to ICU for trauma vs other reasons of admission  
34  
35 17 – Patients with early onset VAP (< 5 days after ICU admission) vs late onset VAP ( $\geq 5$  days  
36  
37 18 after ICU admission).

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39 19 No strategy of imputation is forecasted in case of missing data for the primary assessment  
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41 20 criterion. Information available at time of last follow-up will be taken into account.  
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## 1 **Data collection and management**

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

11

1 **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 <sub>R</sub>				
Verification of inclusion and non-inclusion criteria			X <sub>R</sub>				
Information			X <sub>R</sub>				
Written Informed consent			X <sub>R</sub>				
Randomization			X <sub>R</sub>				
Pregnancy test			X <sub>R</sub>				
Medical history		X <sub>C</sub>	X <sub>C</sub>				
Physical examination		X <sub>C</sub>	X <sub>C</sub>	X <sub>C</sub>	X <sub>C</sub>	X <sub>R</sub>	
Phone call							X <sub>R</sub>
Chest X-Ray/CT-scan		X <sub>C</sub>	X <sub>C</sub>	X <sub>C</sub>			
PaO <sub>2</sub> /FiO <sub>2</sub> ratio		X <sub>C</sub>	X <sub>C</sub>	X <sub>C</sub>	X <sub>C</sub>		
Assessment of clinical symptoms of VAP		X <sub>C</sub>	X <sub>C</sub>				
Assessment of clinical recovery of VAP				X <sub>C</sub>			
Start antibiotics			X <sub>C</sub>				
Antibiotics			X <sub>C</sub>	X <sub>C</sub>	X <sub>C</sub>		
Rectal swab				X <sub>C</sub>	X <sub>C</sub>		
Serum creatinin and calculated creatinin clearance			X <sup>b</sup> <sub>C</sub>				
White blood count		X <sub>C</sub>	X <sub>C</sub>	X <sub>C</sub>	X <sub>C</sub>		
SCORE	ISS	X <sub>C</sub>					
	SOFA	X <sub>C</sub>	X <sub>R</sub>				
	IGS	X <sub>C</sub>					
Assessment of rate of treatment failure and new episode of VAP						X <sub>R</sub>	
Antibiotic free days						X <sub>R</sub>	
Vital status						X <sub>R</sub>	X <sub>R</sub>
Adverse events			X <sub>R</sub>	X <sub>R</sub>	X <sub>R</sub>	X <sub>R</sub>	X <sub>R</sub>
Hospital admissions				X <sub>C</sub>	X <sub>C</sub>	X <sub>R</sub>	X <sub>R</sub>

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

4 <sup>b</sup> creatinin clearance may be performed ( $Cl_{cr} = (\text{urinary creatinin/serum creatinin}) \cdot \text{urine}$   
5  $\text{volume}_{24h}$ ) as frequently as clinically indicated to guide appropriate antibiotic therapy in  
6 subjects with renal impair

7 X<sub>C</sub> : made in usual care

8 X<sub>R</sub> : acts added for research

9

## 1 TRIAL STATUS

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

## 4 ETHICS AND DISSEMINATION

### 5 Legal obligations and approval

6 Sponsorship has been agreed by Assistance Publique—Hôpitaux de Paris (AP-HP, Clinical  
7 Research and Innovation Department) for this interventional research protocol involving human  
8 participants concerning a health product. AP-HP has obtained the approval of the French  
9 medicine regulatory agency (Agence Nationale de Sécurité du Médicament et des Produits de  
10 Santé, ANSM; EUDRACT number 2021-002197-78, 19 August 2021) and of the ethics  
11 comitee (Comité de Protection des Personnes (CPP) Ile-de-France III (CNRIPH:  
12 21.03.25.60729, 10 October 2021)) for the study protocol (version ASPIC–1.3; 03 September  
13 2021). The trial will be carried out in accordance with the Declaration of Helsinki and the Good  
14 Clinical Practice guidelines. Any substantial modification to the protocol will be sent to the  
15 sponsor, and then to the ANSM and the CPP for approval before the amendment can be  
16 implemented. The information sheet and the consent form can be revised if necessary,  
17 particularly if there is a substantial amendment to the study or if adverse reactions occur. AP-  
18 HP is the owner of the data. The data cannot be used or disclosed to a third party without its  
19 prior permission.

## 1 **Methods for obtaining information and consent from research participants**

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

## 12 **Patient and public involvement**

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

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

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

## 20 **Data deposition, quality control and curation**

21 The persons responsible for the quality control of clinical matters will take all necessary  
22 precautions to ensure the confidentiality of information related to the study participants. These  
23 persons, as well as the investigators themselves, are bound by professional confidentiality.

24 During or after the research, all data collected about the participants and sent to the sponsor by

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

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

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

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

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3 1 the results and the storage of the data used or produced as part of the study. Sponsor is  
4  
5 2 responsible for access to the study database.  
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8 3 The investigator will assess the seriousness of each adverse event, report all serious and non-  
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10 4 serious adverse events in the case report form and assess the causal relationship of serious  
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12 5 adverse events with the study procedures according to the WHO method.  
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16 6 A data monitoring committee is not needed for this trial as the expected risk for the participant  
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18 7 is minimal.  
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## 21 8 **Publication plan**

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24 9 Results will be published in international peer-reviewed medical journals. Scientific  
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26 10 presentations and reports will be written under the responsibility of the coordinating  
27  
28 11 investigator of the study with the agreement of the principal investigators and the  
29  
30 12 methodologist. The co-authors of the reports and publications will be the investigators and  
31  
32 13 clinicians involved, on a pro rata basis of their contribution in the study, as well as the  
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34 14 biostatistician and associated researchers. Rules on publication will follow international  
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36 15 recommendations (22).  
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1 **Authors' contributions:** AF and EW contributed to the conception and design of the research  
2 protocol, assisted by DB and PE. AR, IM-L, PM, J-FT, AB and J-RZ provided critical input  
3 pertaining to the design of the trial interventions and procedures. AF wrote the first draft of the  
4 protocol and this manuscript. DB and PE designed the statistical analysis plan. All authors  
5 critically revised and modified the protocol and the article. They all approved the final version  
6 to be published.

7  
8 **Funding statement:** This work was supported by Programme Hospitalier de Recherche  
9 Clinique - PHRC 2019 (Ministère de la Santé) grant number 2020-A02837-32.

10  
11 **Competing interests statement:**

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

13 AR: grants from bioMerieux and Merck

14 IM-L: board on PFIZER, MSD, GILEAD

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

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

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

22

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For peer review only

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3 **Figures and Table legends**  
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5 **Figure 1:** General flowchart of the study  
6

7 **Figure 2:** Criteria of clinical cure and criteria for discontinuation of antibiotic therapy in  
8 experimental arm  
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11 **Figure 3:** Description of microbiological categories of outcomes in relation to time of  
12 occurrence of new episode of VAP after inclusion adapted from(21)  
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18 **Table 1.** Choice of empirical antibiotic therapy according current French guidelines  
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20 **Table 2:** Chronology of the study and procedures  
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Clinical suspicion of VAP

Respiratory sample

microbiological confirmation

antibiotic susceptibility testing

Appropriate empirical antibiotic therapy ?

NO

YES

INCLUSION

RANDOMIZATION

experimental group

Control group

Cessation of antibiotics if clinical cure  
Minimal duration of antibiotics = 3 days

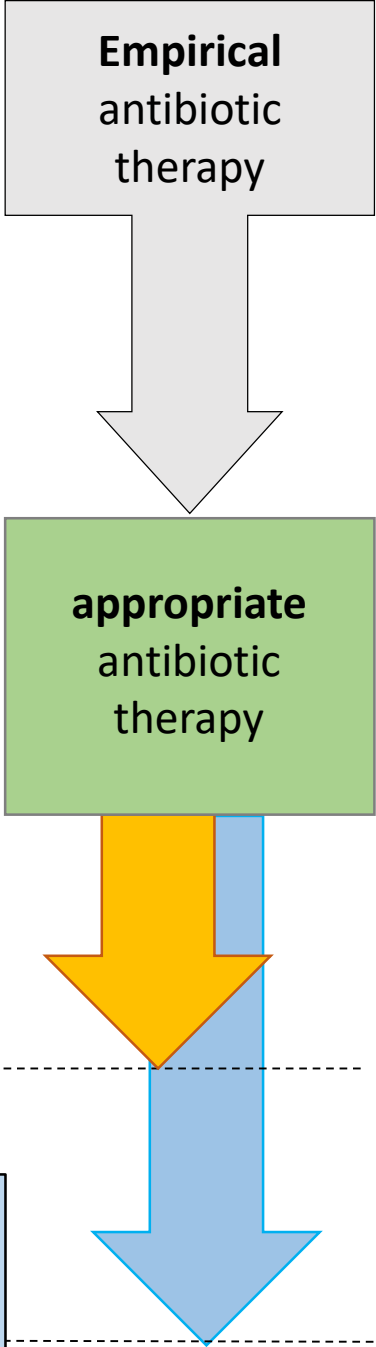
Appropriate antibiotic therapy for 7 consecutive days

Assessment of all cause mortality, treatment failure, rate of new VAP

Assessment vital status

Empirical antibiotic therapy

appropriate antibiotic therapy



# 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  $\geq 3$  criteria are met

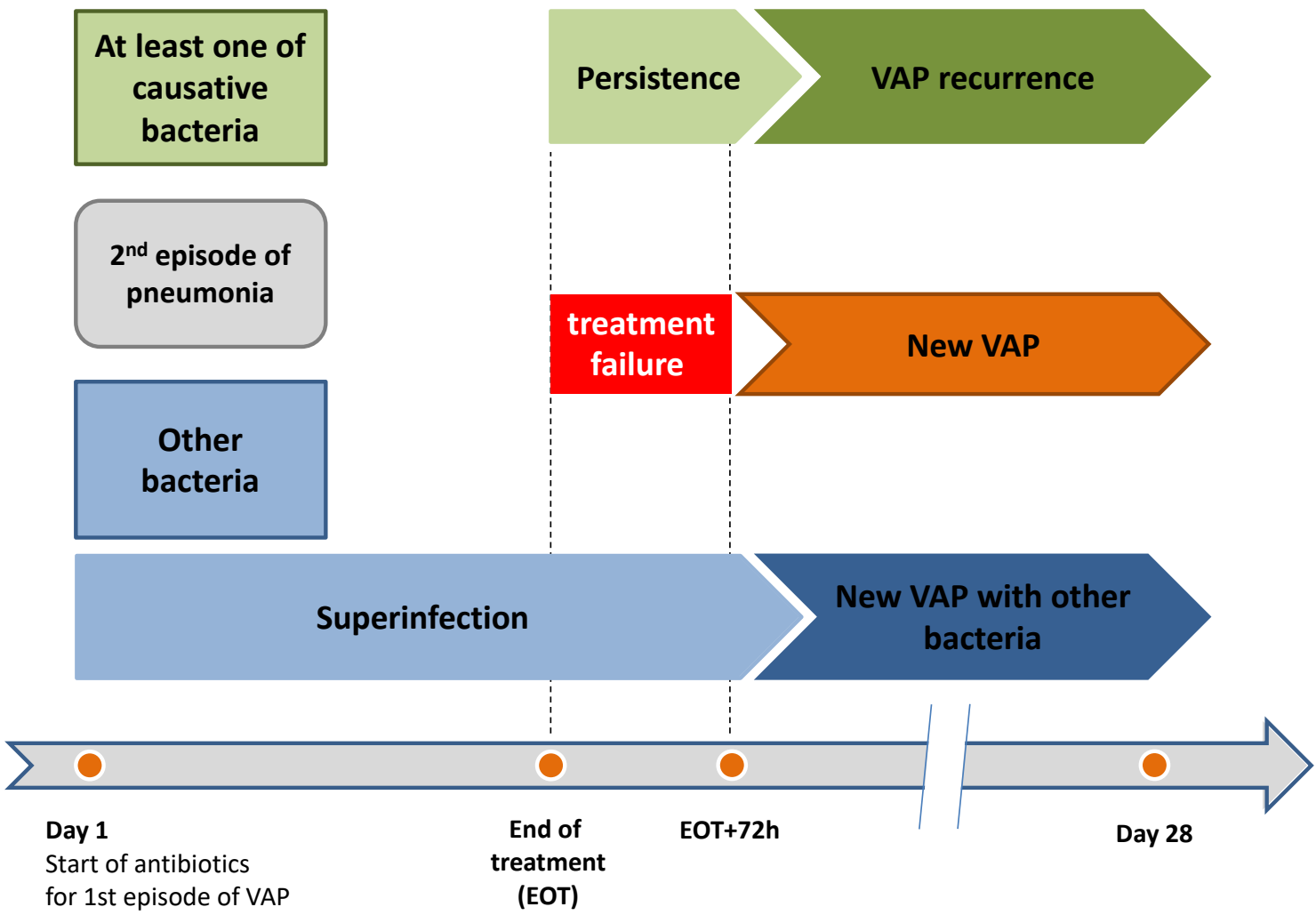
1. Regression\* of  
purulent tracheal  
**S**ecretions

2. Normo**T**hermia  
 $36^{\circ}\text{C} < T < 38.3^{\circ}\text{C}$

3. Improved\*  
**O**xygenation, measured  
by an increase in the  
of the PaO<sub>2</sub>/FiO<sub>2</sub> ratio

4. Absence of  
**hyP**otension

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

Section/item	Item No	Description	Page
<b>Administrative information</b>			
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
<b>Introduction</b>			
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	

1				
2	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
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8	<b>Methods: Participants, interventions, and outcomes</b>			
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10	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
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14	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
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19	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	12,13
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22		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
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26		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	14
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31		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
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34	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
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42	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
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47	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
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51	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	15
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#### Methods: Assignment of interventions (for controlled trials)

Allocation:

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2	Sequence	16a	Method of generating the allocation sequence (eg, computer-	11
3	generation		generated random numbers), and list of any factors for	
4			stratification. To reduce predictability of a random sequence,	
5			details of any planned restriction (eg, blocking) should be	
6			provided in a separate document that is unavailable to those who	
7			enrol participants or assign interventions	
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10	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central	11
11	concealment		telephone; sequentially numbered, opaque, sealed envelopes),	
12	mechanism		describing any steps to conceal the sequence until interventions	
13			are assigned	
14				
15	Implementation	16c	Who will generate the allocation sequence, who will enrol	11,12
16			participants, and who will assign participants to interventions	
17				
18				
19	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial	12
20			participants, care providers, outcome assessors, data analysts),	
21			and how	
22				
23		17b	If blinded, circumstances under which unblinding is permissible,	NA
24			and procedure for revealing a participant's allocated intervention	
25			during the trial	
26				
27				
28	<b>Methods: Data collection, management, and analysis</b>			
29				
30	Data collection	18a	Plans for assessment and collection of outcome, baseline, and	17
31	methods		other trial data, including any related processes to promote data	
32			quality (eg, duplicate measurements, training of assessors) and a	
33			description of study instruments (eg, questionnaires, laboratory	
34			tests) along with their reliability and validity, if known. Reference	
35			to where data collection forms can be found, if not in the protocol	
36				
37				
38		18b	Plans to promote participant retention and complete follow-up,	Table
39			including list of any outcome data to be collected for participants	1
40			who discontinue or deviate from intervention protocols	
41				
42	Data management	19	Plans for data entry, coding, security, and storage, including any	17
43			related processes to promote data quality (eg, double data entry;	
44			range checks for data values). Reference to where details of data	
45			management procedures can be found, if not in the protocol	
46				
47				
48	Statistical methods	20a	Statistical methods for analysing primary and secondary	16
49			outcomes. Reference to where other details of the statistical	
50			analysis plan can be found, if not in the protocol	
51				
52		20b	Methods for any additional analyses (eg, subgroup and adjusted	16,17
53			analyses)	
54				
55		20c	Definition of analysis population relating to protocol non-	17,18
56			adherence (eg, as randomised analysis), and any statistical	
57			methods to handle missing data (eg, multiple imputation)	
58				
59				
60				

1				
2	<b>Methods: Monitoring</b>			
3				
4	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
5				
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11				
12		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
13				
14				
15				
16	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
17				
18				
19				
20				
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
22				
23				
24				
25	<b>Ethics and dissemination</b>			
26				
27	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	18
28				
29				
30	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
31				
32				
33				
34				
35				
36	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	19
37				
38				
39				
40		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
41				
42				
43	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
44				
45				
46				
47	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	NA
48				
49				
50	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
51				
52				
53				
54				
55	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
56				
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59				
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1				
2	Dissemination	31a	Plans for investigators and sponsor to communicate trial results	20,21
3	policy		to participants, healthcare professionals, the public, and other	
4			relevant groups (eg, via publication, reporting in results	
5			databases, or other data sharing arrangements), including any	
6			publication restrictions	
7				
8		31b	Authorship eligibility guidelines and any intended use of	22
9			professional writers	
10				
11		31c	Plans, if any, for granting public access to the full protocol,	NA
12			participant-level dataset, and statistical code	
13				
14				
15	<b>Appendices</b>			
16				
17	Informed consent	32	Model consent form and other related documentation given to	yes
18	materials		participants and authorised surrogates	
19				
20	Biological	33	Plans for collection, laboratory evaluation, and storage of	NA
21	specimens		biological specimens for genetic or molecular analysis in the	
22			current trial and for future use in ancillary studies, if applicable	
23				
24				

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