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Targeted simplification versus antipseudomonal broad-spectrum beta-lactams in patients with bloodstream infections due to Enterobacteriaceae (SIMPLIFY): a study protocol for a multicenter, open-label, phase III randomized, controlled, non-inferiority clinical trial

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4 lactams in patients with bloodstream infections due to *Enterobacteriaceae*
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6 3 (SIMPLIFY): a study protocol for a multicenter, open-label, phase III
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8 4 randomized, controlled, non-inferiority clinical trial
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11 6

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3 284 29 **KEY WORDS:** De-escalation, *Enterobacteriaceae*, bloodstream infection,
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6 30 broad-spectrum antibiotics, antimicrobial stewardship.
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9 32 **ABSTRACT**10 33 **Introduction:** Within the context of antimicrobial stewardship programs, de-
11 34 escalation of antimicrobial therapy is one of the proposed strategies for
12 35 reducing the unnecessary use of broad-spectrum antibiotics (BSA). The
13 36 empirical treatment of nosocomial and some health-care associated
14 37 bloodstream infections (BSI) frequently includes a beta-lactam with
15 38 antipseudomonal activity as monotherapy or in combination with other drugs, so
16 39 there is a great opportunity to optimize the empirical therapy based on
17 40 microbiological data. De-escalation is assumed as standard-of-care for experts
18 41 in infectious diseases; However, it is less frequent than it would desirable.19 42 **Methods and analysis:** The SIMPLIFY trial is a multicenter, open-label, phase
20 43 III randomized controlled clinical trial, designed as a pragmatic 'real-practice'
21 44 trial. The aim of this trial is to demonstrate the non-inferiority of de-escalation
22 45 from an empirical beta-lactam with antipseudomonal activity to a targeted
23 46 narrow-spectrum antimicrobial in patients with BSI due to *Enterobacteriaceae*. It
24 47 will be conducted at 19 Spanish public and university hospitals.25 48 **Ethics and dissemination:** Each participating center has obtained the
26 49 approval of the Ethics Review Committee, the agreement of the Directors of the
27 50 Institutions, and authorization from the Spanish Regulatory Agency (AEMPS,
28 51 Agencia Española del Medicamento y Productos Sanitarios). Data will be
29 52 presented at international conferences and published in peer-reviewed journals.30 53 **Discussion:** Strategies to reduce the use of BSA should be a priority. Most of
31 54 the studies that support de-escalation are observational, retrospective, and
32 55 heterogeneous. A recent Cochrane review stated that well-designed clinical
33 56 trials should be conducted to assess the safety and efficacy of de-escalation.

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35 58 **STRENGTHS OF THIS STUDY**36 59 It will be the first trial on de-escalation specifically in patients with bacteremia
37 60 due to *Enterobacteriaceae*.

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3 61 It will include patients independently of the source of bacteraemia or severity of
4 62 clinical presentation.

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6 63 It has been designed with daily clinical practice in mind.
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10 65 **LIMITATIONS OF THIS STUDY**

11 66 The open-label design is theoretically more prone to bias but another design is
12 67 not possible using different options to de-escalate; however, we use a remote
13 68 automatic randomisation system, hard outcomes as secondary variables and
14 69 external evaluation by blinded investigators.

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18 70 Switching to oral therapy is allowed from the fourth day of randomization. This
19 71 could potentially reduce the number of days in which patients are assigned to
20 72 one or other arm, but we decided to include this possibility to avoid
21 73 unnecessary days of admission.
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3 75 **BACKGROUND**
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6 77 The worldwide spread of antimicrobial resistance is recognised as a current
7 78 global public health threat. The implementation of stewardship programs for
8 79 optimizing antibiotic use has been shown both to improve antibiotic use and
9 80 also to help combat antimicrobial resistance [1]. Streamlining or de-escalation of
10 81 antimicrobial therapy is a strategy proposed to reduce the unnecessary use of
11 82 broad-spectrum antimicrobials (BSA) [1,2]. This can be carried out by changing
12 83 from combination therapy to monotherapy or by replacing the empirical
13 84 antibiotic with one with a narrower spectrum of activity, irrespective of the
14 85 microbiology results [1].

15 86 Bloodstream infections (BSI) are known to be major causes of morbidity and
16 87 mortality. They represent suitable organisms for carrying out a de-escalation
17 88 strategy because they are very frequent, a high proportion of patients are
18 89 treated with BSA and the susceptibility of the causative organisms is known.
19 90 The *Enterobacteriaceae* as a group, is the most common cause of community-
20 91 and nosocomial BSI, with a crude associated mortality of around 15% [3]. The
21 92 empirical treatment for nosocomial and some healthcare-associated BSI
22 93 frequently includes a beta-lactam antibiotic with antipseudomonal activity in
23 94 monotherapy or in combination. This imposes strong selection pressure,
24 95 particularly on *Pseudomonas aeruginosa* isolates. De-escalation according to
25 96 microbiological results is assumed as standard-of-care by most infectologists;
26 97 however, the reality is that de-escalation is much less frequent than is desirable
27 98 [4,5]. Some of the possible reasons for this phenomenon [6-8] include the fact
28 99 that the safety and efficacy of this treatment strategy are based only on a few
29 100 observational studies [9,10] and expert recommendations [11,12]. This was
30 101 supported by a recent Cochrane review [13] conducted among adults with
31 102 sepsis, severe sepsis or septic shock, whose authors concluded that there is no
32 103 adequate direct evidence that de-escalation of antimicrobial agents is effective
33 104 and safe in this scenario. Randomized clinical trials of their safety and efficacy
34 105 are needed, in order to establish “proof of concept” and help make clinical
35 106 decisions.

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3 109 **METHODS/DESIGN**
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6 111 **Study hypothesis**
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8 112 The aim of the trial is to demonstrate that de-escalation from empirical therapy
9 113 with an antipseudomonal beta-lactam to a targeted therapy is as effective and
10 114 safe in patients with BSI due to *Enterobacteriaceae* as continuing with the
11 115 empirical regimen.
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16 117 **Design**
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18 118 The SIMPLIFY trial is a multicenter, open-label, phase III randomized controlled
19 119 clinical trial, powered to demonstrate the non-inferiority of de-escalation with
20 120 respect to continuing with the antipseudomonal agent and designed as a real-
21 121 world pragmatic trial. It was developed in accordance with an extension of the
22 122 CONSORT statement for reporting non-inferiority, superiority and equivalence
23 123 trials [14].
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29 125 **Participants and settings**
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31 126 The trial will be conducted at 19 public and academic hospitals with the support
32 127 of the Spanish Network for Research in Infectious Diseases (REIPI) and the
33 128 Spanish Clinical Research Network (SCReN). Patients will be evaluated for
34 129 eligibility once *Enterobacteriaceae* is isolated from blood cultures and
35 130 susceptibility data are available. Detection of eligible patients will be by daily
36 131 review of blood culture results by the bacteremia team at each center. To be
37 132 enrolled, participants will need to fulfill all inclusion and exclusion criteria (Table
38 133 1) plus give written informed consent (the patient or a legally authorized
39 134 representative).
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48 136 **Randomization**
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50 137 Stratified randomization in a 1:1 ratio will be achieved using a centralized, web-
51 138 based automated randomization system integrated with the eCRF (electronic
52 139 Case Report Form) to manage assignment to the treatment arms. A copy of the
53 140 randomization list will be kept in a safe place in case technical problems arise.
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55 141 The only criterion for stratification will be source of bloodstream infection
56 142 (urinary tract vs any other) in order to ensure that the percentage of patients
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3 143 with urinary tract infections is similar in the two groups being compared.
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6 145 **Intervention**

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8 146 A decision tree of enrolment to the study is included in Figure 1. As stated
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10 147 above, all included patients will already be receiving an antipseudomonal beta-
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12 148 lactam (meropenem, imipenem, piperacillin-tazobactam, cefepime, ceftazidime
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14 149 or aztreonam) before randomization occurs. Patients will be allocated to one of
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16 150 the following treatment arms:

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18 152 Experimental group:

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20 153 The patient will change to an intravenous therapy with an active narrow-
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22 154 spectrum antibiotic according to the susceptibility results (EUCAST or CLSI
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24 155 criteria); the antibiotic will be chosen in the following order (the first active drug
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26 156 will be used): (1) ampicillin, 2 g q6h; (2) trimethoprim/sulfamethoxazole,
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28 157 160/800 mg q8-12h; (3) cefuroxime, 750-1500 mg q8h; (4) cefotaxime 1-2g q8h
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30 158 or ceftriaxone, 1 g q12-24h; (5) amoxicillin/clavulanate, 1g/125 mg q8h; (6)
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32 159 ciprofloxacin, 400 mg q12h; and (7) ertapenem, 1g q24h.
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34 160 Trimethoprim/sulfamethoxazole will only be used in urinary tract infections in the
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36 161 absence of an undrained renal abscess. Ciprofloxacin is included because,
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38 162 apart from being active against *P. aeruginosa*, it is not a beta-lactam.

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40 164 Control group:

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42 165 Continuation of the antipseudomonal beta-lactam that was being administered
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44 166 on an empirical basis: meropenem, 1-2 g q8h; imipenem, 0.5-1g q6h;
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46 167 piperacillin-tazobactam, 4/0.5 g q6-8h; cefepime, 2 g q8-12h; ceftazidime, 1-2 g
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48 168 q8h; and aztreonam, 1-2 g q8h.

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50 170 Exceptions to the above rule:

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52 171 Third-generation cephalosporins should be avoided where there are inducible
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54 172 AmpC β -lactamase-producing *Enterobacteriaceae* (*Enterobacter* spp.,
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56 173 *Providencia* spp., *Morganella morganii*, *Serratia marcescens*, and *Citrobacter*
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58 174 *freundii*); hence, even if the isolates are strictly susceptible, for patients in the
59
60 175 control group, ceftazidime may be changed to any other antipseudomonal beta-
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177 176 lactam on the day of randomization. For patients allocated to the experimental

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3 177 arm, the options will be limited to trimethoprim/sulfamethoxazole, ciprofloxacin
4 178 or ertapenem.

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6 179 ESBL producers could be included in the study based on attending physician's
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8 180 criteria; in this cases, maximum doses of susceptible antibiotics are
9 181 recommended.

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12 13 183 Dose adjustment

14 184 Due to the nature of the study design as a real-world clinical practice trial,
15 185 antimicrobial dosage will be as deemed by the treating clinician, dependent on
16 186 pharmacokinetic and pharmacodynamic (PK/PD) characteristics (such as higher
17 187 doses for septic shock or high body mass). Dose adjustment will be made for all
18 188 drugs as necessary in the case of renal or hepatic dysfunction, following
19 189 Summary of Product Characteristics (SmPC) recommendations.
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26 191 Concomitant therapy

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28 192 Even if the BSI is monomicrobial, the attending physician may consider the
29 193 infection to be polymicrobial at source. If additional anaerobic or gram-positive
30 194 coverage is needed, concomitant use of oral metronidazole, clindamycin,
31 195 vancomycin, teicoplanin, daptomycin or linezolid is allowed in both arms.
32 196 Concomitant treatment with any other systemic antibiotic with intrinsic activity
33 197 against gram-negative bacilli is not allowed. The administration of any of these
34 198 drugs while the patient is receiving the study drug will be deemed a criterion for
35 199 withdrawal. There are no absolute contraindications for the use of any other
36 200 drug during the study. However, contraindications, warnings and precautions for
37 201 use and possible interactions with study drugs are to be taken into account.
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46 203 Duration of therapy

47 204 The appropriate duration of therapy is considered to be between 7 and 14 days,
48 205 according to the attending physician's criteria. Treatments lasting longer than
49 206 14 days will be allowed only when there is an undrained abscess present, in
50 207 which case, a 4-week treatment is permitted.
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56 209 Route of administration

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58 210 Switching to oral therapy is allowed from the sixth day of treatment if all the
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3 211 following conditions are fulfilled: clinical improvement has been achieved,
4 212 absence of fever (>38°C), hemodynamic stability, adequate control of the
5 213 source of BSI and absence of secondary foci, adequate oral intake, and no
6 214 gastrointestinal conditions that might compromise drug absorption.

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9 215 For patients in the experimental group, switching to oral therapy is allowed with
10 216 the same intravenous drugs as follows: trimethoprim/sulfamethoxazole 160/800
11 217 mg q8 -12h, cefuroxime axetil 500 mg q8-12h, amoxicillin/clavulanate 875/125
12 218 mg q8h, or ciprofloxacin 500 mg q12h. If the intravenous drug is ampicillin,
13 219 amoxicillin 1 g q8h will be used; if cefotaxime or ceftriaxone, then ceftibuten 400
14 220 mg q12-24h or cefixime 400 mg q12-24h will be used; if ertapenem, this drug
15 221 may be switched to the intramuscular route.

16 222 For patients in the control group, the preferred oral option is ciprofloxacin 500
17 223 mg q12h for all patients. The protocol allows treatment with cefuroxime-axetil
18 224 500 mg q8-12h or cefixime 400 mg q12-24h only in cases of resistance to
19 225 ciprofloxacin; finally, parenteral ertapenem 1g q24h may be used for
20 226 convenience if the isolate is resistant to all other oral options.

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22 228 Rescue medication

23 229 No rescue medication is planned on behalf of the study if a patient has to
24 230 withdraw from the trial for any reason; the attending physician will follow clinical
25 231 guidelines for routine clinical practice and GCP (Good clinical practice) rules.

26 232

27 233 Medication

28 234 As all the study drugs are officially approved for BSI caused by
29 235 *Enterobacteriaceae*, the sponsor will not provide the study drugs. Every site
30 236 participating in the study is authorised to use the drugs through the normal
31 237 provision of its hospital pharmacy.

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33 239 Schedule of visits

34 240 Patients included in the study will be followed for 60 days (\pm 5 days) after
35 241 diagnosis of the BSI (Figure 2). Follow-up will be organised in seven planned
36 242 visits at day 0 (baseline), day 1; day 3-5; day 7-14 (end of treatment); day 3-5
37 243 from end of treatment (test of cure, TOC); day 30 \pm 5; and day 60 \pm 5. Visits at
38 244 days 30 and 60 may be made by telephone.

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3 245 The visit schedule is planned so as to obtain data on clinical status, sample
4 246 collection, efficacy and safety variables, and adverse events. At the final
5 247 evaluation at 60 days, data on all outcome variables will be gathered.
6 248 Additionally, data will be collected at unplanned visits, with special
7 249 consideration given to the occurrence of any adverse event or recurrence.
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13 251 **Outcomes**

14 252 The primary outcome is clinical cure, which will be assessed at the TOC visit (3-
15 253 5 days after the end of antibiotic treatment). Secondary outcomes include early
16 254 (5 days after end of treatment) and late (60-day) clinical and microbiological
17 255 response, all-cause mortality (days 7, 14, and 30), length of hospital stay,
18 256 recurrence rates (relapse or reinfection) (day 60), safety of antibiotic treatment,
19 257 including *Clostridium difficile* infections and number of antibiotic treatments with
20 258 an antipseudomonal beta-lactam; in a subgroup of patients, the rate of intestinal
21 259 colonization by ESBL, AmpC- and carbapenemase-producing
22 260 *Enterobacteriaceae* will also be assessed by rectal swab. Some of these
23 261 secondary outcomes will be analyzed as composite variables, following the
24 262 DOOR/RADAR methodology. Outcome definitions, assessment, and time
25 263 frames for measurement are described in Table 2.
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37 265 **Data collection, management and monitoring**

38 266 The coordinating center for this study is the Hospital Universitario Virgen
39 267 Macarena, Seville, Spain, and the Clinical Trials Unit (CTU-Hospital
40 268 Universitario Virgen del Rocío) has delegated sponsor functions on behalf of
41 269 the Fundación Pública Andaluza para la Gestión de la Investigación en Salud
42 270 de Sevilla (FISEVI). Clinical research associates (CRAs) connected to the
43 271 Spanish Clinical Research Network (SCReN) in public hospitals will carry out
44 272 monitoring activities. Data collection will be conducted by trained staff at each
45 273 participating center and entered into a restricted access electronic case report
46 274 form (eCRF). Outstanding queries regarding the completion of the CRF will be
47 275 sent to all participating centers as necessary to ensure accuracy of data.
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276 In order to avoid any association with personal data, all study samples will be
277 anonymous and identifiable only by the patient's alphanumeric study code. The
278 objective and management of these samples are included in the patient's

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3 279 information sheet and informed consent form.
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5 280 The quality of all data collected will be carefully supervised by the CTU and
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7 281 specific visits for source data verification are organized according to the
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9 282 monitoring plan. Furthermore, in order to minimize bias, at the interim analysis
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11 283 (when 50% of the sample has been included), an independent committee (3
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13 284 independent investigators from the REIPI) blinded to treatment assignment will
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15 285 review all accumulated data. This committee will advise the sponsor on the
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17 286 appropriateness of continuing the clinical trial as designed.
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18 **Isolates**

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20 289 All isolates will be sent to the central laboratory in the Hospital Universitario
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22 290 Virgen Macarena in Seville for susceptibility testing using reference methods
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24 291 and PCR characterisation and sequencing if necessary.
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26 292 Eight selected hospitals will participate in the study of rectal carriage of ESBL-
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28 293 AmpC- and carbapenemase-producing *Enterobacteriaceae*, by taking rectal
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30 294 swabs from participants at different times (as set out in the schedule of visits). A
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32 295 written consent form for samples, approved by the ECs (Ethics Committees), is
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34 296 also provided for the study.
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35 **Definition of analysis population and outcome measures**

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37 299 The following populations will be considered: the intention-to-treat population
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39 300 (ITTP) includes all randomized patients; the modified ITTP (mITTP) includes
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41 301 randomized patients who have received at least one dose of intravenous
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43 302 antibiotics; the clinically evaluable population (CEP) includes patients who have
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45 303 completed 5 days of the intravenous study drug, or who die but have received
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47 304 at least one dose of intravenous antibiotics. The clinically and microbiologically
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49 305 evaluable population (CMEP) includes those in the CEP who have had
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51 306 microbiological tests (at least one blood culture 48 hours after randomization).
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53 307 The principal investigator will assess the primary outcome (clinical cure) in the
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55 308 clinically evaluable population (CEP) at TOC. Due to the intrinsic characteristics
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57 309 of the primary outcome (soft outcome) and the study methodology (non-
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59 310 blinded), the primary outcome will be reviewed on the basis of clinical data
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311 recovered on two occasions by the external blinded investigator: firstly, during
312 the interim analysis to monitor safety; secondly before the complete cleaning

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3 313 and closure of the eCRF. For secondary end points, the CMEP will be eligible
4 314 for early (day 5) and late (day 60) microbiological responses, the m-ITTP for all-
5 315 cause mortality and length of hospital stay, and the CEP for the evaluation of
6 316 recurrence rates and drug safety.
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11 318 **Sample size**

12 319 The sample size was calculated using Epidat 4.0. Some of the data used to
13 320 calculate it was derived from the study published by Retamar *et al* [15].
14 321 Assuming estimated clinical cure rates of 85% in both groups, a non-inferiority
15 322 margin of 10% difference between the 2 groups, and treatment assignment in a
16 323 1:1 ratio, 344 patients in total (172 per study arm) are needed to achieve 80%
17 324 power with a significance level of 5%. This allows for a 5% dropout rate.
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24 326 **Statistical analysis**

25 327 Absolute differences will be calculated with 95% confidence intervals for the
26 328 clinical cure rate between the two arms of the study at TOC. Multivariate
27 329 analysis using logistic regression for the main outcome will be performed in
28 330 order to ensure the independence of the treatment effect. Special consideration
29 331 will be given in the multivariate analysis to the center of origin of the study
30 332 sample. A Cox regression analysis of mortality at 5-7, 14, 30 and 60 days will
31 333 be performed on the mITTP. For the superiority analysis, logistic regression will
32 334 be used sequentially, using the methodology recently published by Evans *et al*
33 335 [16] for the composite variable (DOOR and RADAR analysis using survival at
34 336 day 14, number of days of antipseudomonal beta-lactam treatment avoided,
35 337 presence or absence of side effects, including *C. difficile* infections, secondary
36 338 MDRO infections, and all drug-related adverse events). Antimicrobial doses are
37 339 not fixed and sensitivity analyses will therefore be applied to control potential
38 340 bias.
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50 342 **Protocol violations**

51 343 All protocol violations occurring after randomization will be listed in the Clinical
52 344 Study Report, tabulated by subject and by recruitment center.
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347 ETHICAL ISSUES

348 Each of the participating centers has obtained the approval of an Ethics Review
349 Committee, the agreement of the Directors of the Institutions (who signed the
350 contract of agreement with the sponsor of the study) and authorisation from the
351 Spanish Regulatory Agency (AEMPS, Agencia Española del Medicamento y
352 Productos Sanitarios). Patients may withdraw from the study at any time without
353 prejudice, as is documented and explained at the time of providing consent.
354 The study will be carried out according to the principles of the Declaration of
355 Helsinki, and Directive 2001/20/EC of the European Parliament and of the
356 Council of 4 April 2001 on the harmonization of the laws, regulations and
357 administrative provisions of the Member States relating to the implementation of
358 Good Clinical Practice in the conduct of clinical trials on medicinal products for
359 human use until the new Clinical Trials Regulation (CTR) EU No 536/2014
360 becomes applicable, which will be no earlier than 28 May 2016. The
361 confidentiality of records that might identify subjects in this study will be
362 protected in accordance with EU Directive 2001/20/EC. All laws for the control
363 and protection of personal information will be carefully followed. The identities of
364 patients will not be disclosed in the e-CRF; names will be replaced by an
365 alphanumeric code and any material related to the trial, such as samples, will
366 be identified in the same way, so that no personal information will be revealed.

368 DISCUSSION

369 The extensive use of BSA and the dramatic increase in infections due to
370 multidrug-resistant organisms are forcing the scientific community to look for
371 strategies to combat this situation. In the real world, the application of de-
372 escalation to serious infections is less frequent than is desirable. The
373 arguments against de-escalation include: (1) the MIC of some narrow-spectrum
374 drugs are closer to susceptibility breakpoints than carbapenems, for example,
375 and some physicians may therefore feel safer using the latter; (2)
376 subpopulations resistant to narrow-spectrum drugs may be selected and appear
377 after some days of empirical treatment, leading to treatment failure in case of
378 de-escalation; (3) in the case of polymicrobial infections, it is not uncommon for
379 only one of the pathogens to be isolated in blood cultures, so that simplification
380 of treatment may be less safe and effective than a broad-spectrum treatment;

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3 381 (4) there is some doubt about the real effectiveness of certain drugs against
4 382 isolates producing specific mechanisms of resistance, such as ESBL.
5 383 Furthermore, although it is assumed that BSA has a greater impact on the
6 384 selection of multidrug-resistant strains, some studies suggest that it may
7 385 depend more on the duration of the treatment than the spectrum [16]. While
8 386 none of these arguments have been proven, it is also true that there is no
9 387 strong evidence for the safety of de-escalation strategies in these scenarios.

10 388 To the best of our knowledge, three randomized trials on de-escalation
11 389 strategies, none of them specifically focused on bacteremia, have been
12 390 published, which show significant differences from this study [17-19]. The one
13 391 published by Falguera *et al* [17] compared the efficacy of empirical versus
14 392 targeted treatment on the basis of urine antigen results in hospitalized patients
15 393 with community-acquired pneumonia. The article published by Kim *et al* [18]
16 394 evaluated the efficacy of early use of imipenem/cilastatin and vancomycin
17 395 followed by de-escalation versus conventional antimicrobials without de-
18 396 escalation for patients with hospital-acquired pneumonia in ICUs. The last one,
19 397 published recently by Leone *et al* [20], included a limited number (n=116) of
20 398 ICU-admitted patients with severe sepsis; Its primary outcome was duration of
21 399 ICU stay, and not effectiveness of both treatment strategies. In that study, de-
22 400 escalation followed the recommendations of guidelines, not a pre-specified
23 401 protocol based on the clinical impact of the antibiotics. There was no significant
24 402 difference in mortality, although unexpectedly, patients in the experimental arm
25 403 had a higher rate of superinfections (27% vs 11%, $P = 0.03$). These results
26 404 contrast with a recent systematic review and meta-analysis that included 25
27 405 studies with data on de-escalation based on culture results, which showed a
28 406 significant reduction in the relative risk of death (RR 0.44, 95% CI: 0.30–0.66;
29 407 $p < 0.0001$). It is important to note that many of the included studies in the meta-
30 408 analysis were observational, retrospective and had a high degree of
31 409 heterogeneity [21].

32 410 Several authors have warned about the considerable inconsistencies in
33 411 definitions of de-escalation. In 2015, Weiss *et al* [22] elaborated a consensual
34 412 definition of de-escalation that allowed beta-lactams to be ranked according to
35 413 both their spectra and their ecological impact. The authors underlined
36 414 the difficulty of reaching consensus on the relative ecological impact of each

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3 415 individual drug. In 2014, Madaras-Kelly *et al.* [23] used the Delphi approach to
4 416 develop an antibiotic spectrum score to measure de-escalation. We shall
5 417 therefore include both concepts in our analysis, using Outcome Ranking
6 418 (DOOR) and Response Adjusted for Duration of Antibiotic Risk (RADAR)
7 419 analyses [16].

8 420 Switching from intravenous to oral therapy as soon as the patient is clinically
9 421 stable can reduce the risk of adverse events related to intravenous therapy,
10 422 length of hospitalization, and cost. It can be applied regardless of the source of
11 423 infection and underlying conditions whenever a good option that achieves the
12 424 PK/PD targets is available [24]. In our study, switching to oral therapy is allowed
13 425 in both arms to avoid exposing patients in the control arm to unnecessary risks.

14 426 The SIMPLIFY trial has several strengths. In the first place, it will be the first trial
15 427 on de-escalation specifically in patients with bacteremia due to
16 428 *Enterobacteriaceae*. Second, it will include patients independently of the source
17 429 of bacteraemia or severity of clinical presentation. Third, it was designed with
18 430 daily clinical practice in mind. We hope that, if there is reasonable evidence to
19 431 reject the null hypothesis, it will encourage implementation of this type of
20 432 strategy in daily practice.

21 433

22 434 **TRIAL STATUS**

- 23 435
- 24 436 • Funding for the study was approved on 15/08/2015 and available for
25 437 study expenses in 01/01/2016.
 - 26 438 • EC approval for the 19 sites included was obtained on 15th March 2016.
 - 27 439 • Authorization from the Spanish Regulatory Authority was obtained on
28 440 18th March 2016.
 - 29 441 • The study has been approved for a recruitment period of 2 years.
 - 30 442 • Dissemination of results directed to patients will be channeled through
31 443 the Spanish Clinical Studies Registry (Agencia Española del
32 444 Medicamento y Productos Sanitarios), whose content is adapted to
33 445 patients.

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3 448 **REGISTRATION**

4 449 Trial registration number: EudraCT number: 2015-004219-19, start date: 18
5 March 2016. Protocol V.2.0, dated 16 May 2016.
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21 462 number 16.001.
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31 465 **COMPETING INTERESTS ESTATEMENT**

32 466 The authors have no competing interests to declare.
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36 468 **CONTRIBUTORSHIP STATEMENT**

37 469 JR-B and LEL-C were responsible for formulating the overall research questions
38 470 and for the methodological design of the study. CR-F, BA and LL-A collaborated
39 471 in the submission of the project for the Spanish funding, and collaborated in the
40 472 methodological aspects of the study. JR-B is the coordinating investigator and
41 473 leader of the Coordination Team. CR-F is responsible for the CTU. MN-N and is
42 474 the pharmacovigilance monitor, and JB-F, PR-G, and CL collaborated in the
43 475 organisation of the study. MD contributed in all the microbiological details of the
44 476 study. JR-B and LEL-C participated in its design and supervised the project. All
45 477 authors read and approved the final manuscript.
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52 479 **DATA SHARING STATEMENT**

53 480 No additional unpublished data from the study are available
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592 **Table 1. Inclusion and exclusion criteria**

<p>Inclusion criteria</p> <ol style="list-style-type: none">1. Written informed consent has been obtained from the patient or the legally authorised representative.2. Age \geq 18 years, not legally incapacitated.3. Hospitalised patients with monomicrobial bacteremia due to <i>Enterobacteriaceae</i> from any source.4. The patient has received active empiric antibiotic therapy with an antipseudomonal beta-lactam (imipenem, meropenem, piperacillin-tazobactam, cefepime, ceftazidime, aztreonam), alone or in combination with another antimicrobial agent, which started in the first 24 hours after the first positive blood culture was taken.5. The isolate is susceptible to at least one of antibiotics included in the experimental arm.6. Intravenous antimicrobial treatment is planned for at least 5 days once <i>Enterobacteriaceae</i> is isolated from the blood culture.
<p>Exclusion criteria</p> <ol style="list-style-type: none">1. Life expectancy $<$30 days.2. Pregnancy or nursing. For included women: failure to use a highly effective contraceptive method.3. Isolation of carbapenemase-producing <i>Enterobacteriaceae</i> (because most hospitals do not use monotherapy in these cases).4. Inclusion is delayed $>$48 h after susceptibility data of the isolate are available.5. Severe neutropenia ($<$500 cells/mm³) on the day of randomization.6. Planned duration of treatment $>$28 days (e.g. osteomyelitis, endocarditis).

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596 **Table 2. Outcome definitions and time frames**

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Primary End Point and Time Frame	Definition and Assessment
CLINICAL CURE Day 3-5 after treatment*	TOC, the situation where all the following conditions are met: survival at the time of the evaluation; complete resolution of all symptoms and signs of infection (or return to the situation prior to current infection); no need for prolonged antibiotic treatment beyond the recommended duration* and no need for treatment modification due to unfavorable clinical response.
*7-14 days according to IDSA, except in the presence of undrained or late-draining abscesses, when up to 4 weeks are allowed.	
Secondary End Point and Time Frame	Definition and Assessment
CLINICAL RESPONSE After 5 days of treatment (early response) Until Day 60 of follow-up (late response)	Same as clinical cure
MICROBIOLOGICAL CURE After 5 days of treatment (early response) Until Day 60 of follow-up (late response)	Negative blood cultures and where applicable, negative cultures from samples taken from initial infection focus. 'PRESUMPTIVE MICROBIOLOGIC CURE' is accepted in those cases where it is not possible to prove the negativization of isolates from initial focus.
ALL-CAUSE MORTALITY 7, 14 and 60-day of follow-up	Death for any reason
LENGTH OF HOSPITAL STAY	Time from randomisation to hospital discharge
CLINICAL RECURRENCE (RELAPSE OR REINFECTION) RATES 60-day of follow-up	Recurrence of at least one clinical and one analytical sepsis criterion, with presence or absence of bacteraemia
MICROBIOLOGICAL RECURRENCE (RELAPSE OR REINFECTION) RATES 60-day of follow-up	New BSI episode with the same isolate as initial cultures with previously clinical and microbiological cure
NUMBER OF DAYS OF APBL AVOIDED Until end of treatment	Number of days of antibiotic treatment with an antipseudomonal beta-lactam (APBL) avoided
ECOLOGICAL IMPACT 7-14, 12-21, 30 days	Intestinal colonization by multidrug-resistant Gram-negative bacilli
SAFETY OF DRUGS - adverse events Until Day 60 of follow-up	Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related.
COMPOSITE SECONDARY VARIABLES 7-14, 60-day follow up	Survival on day 14, number of days with an antipseudomonal beta-lactam avoided, presence or absence of side effects, including <i>C. difficile</i> infections, secondary MDRO infections and all drug-related adverse events

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3 601 Figure 1. SIMPLIFY – Decision tree of patient enrolment
4 602 Figure 2. Schedule of visits and assessments. Except where otherwise specified, these refer to
5 603 days from randomization.
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Figure 1.

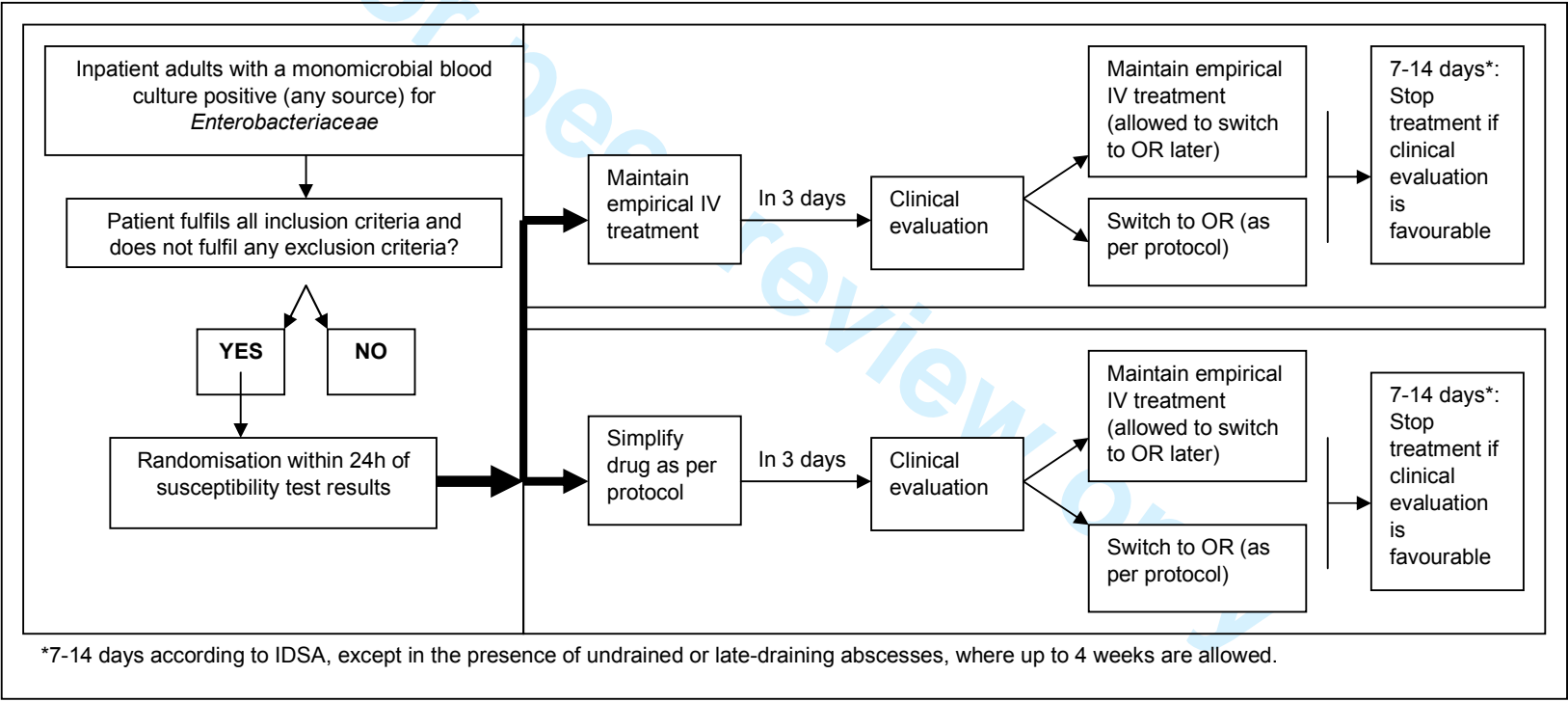


Figure 2.

Procedures	Selecti on visit (Day 0)	Visit 1 (Day 1)	Visit 2 (Day 3-5)	End of treatment (Day 7-14) ^{2,3}	Test of cure (Day 12-21) ¹	Follow-up visit (Day 30±5) ²	End of study (Day 60) ²
Randomization	X						
Informed consent	X						
Check in/exclusion criteria	X						
Pregnancy test	X						
Demographic data/ medical history	X	X	X	X	X	X	X
Physical examination	X	X	X	X ²	X	X ²	X ²
Laboratory data		X	X	X ²	X		
Blood culture	X		X	X ³			
Rectal swab ⁴	X			X	X	X	
Ancillary drugs	X	X	X	X		X	X
Drug dispensing control	X	X	X	X			
Adverse events		X	X	X	X	X	X

(1) In the presence of an undrained abscess, TOC will be performed on day 28 or if drainage occurs after day 7 of treatment, TOC is to be done 7 days after that day; (2) This visit may be made by telephone if the patient has been discharged. In this scenario, no physical examination or lab tests are requested; (3) Only if previous blood cultures or symptoms remain positive; (4) Only in selected hospitals and face-to-face scheduled visits



CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4
	2b	Specific objectives or hypotheses	4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	5
Participants	4a	Eligibility criteria for participants	5
	4b	Settings and locations where the data were collected	5-8, 9
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	9
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	9-10
	6b	Any changes to trial outcomes after the trial commenced, with reasons	11
Sample size	7a	How sample size was determined	11
	7b	When applicable, explanation of any interim analyses and stopping guidelines	9-10
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	5
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	5
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	5
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	5
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	---

1			
2		assessing outcomes) and how	
3			
4		11b If relevant, description of the similarity of interventions	----
5	Statistical methods	12a Statistical methods used to compare groups for primary and secondary outcomes	11
6		12b Methods for additional analyses, such as subgroup analyses and adjusted analyses	11
7			
8	Results		
9	Participant flow (a	13a For each group, the numbers of participants who were randomly assigned, received intended treatment, and	10-11
10	diagram is strongly	were analysed for the primary outcome	
11	recommended)	13b For each group, losses and exclusions after randomisation, together with reasons	
12	Recruitment	14a Dates defining the periods of recruitment and follow-up	
13		14b Why the trial ended or was stopped	
14			
15	Baseline data	15 A table showing baseline demographic and clinical characteristics for each group	
16	Numbers analysed	16 For each group, number of participants (denominator) included in each analysis and whether the analysis was	
17		by original assigned groups	
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19	Outcomes and	17a For each primary and secondary outcome, results for each group, and the estimated effect size and its	
20	estimation	precision (such as 95% confidence interval)	
21		17b For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
22	Ancillary analyses	18 Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing	
23		pre-specified from exploratory	
24			
25	Harms	19 All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
26			
27	Discussion		
28	Limitations	20 Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	12-14
29	Generalisability	21 Generalisability (external validity, applicability) of the trial findings	12-14
30	Interpretation	22 Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	12-14
31			
32	Other information		
33	Registration	23 Registration number and name of trial registry	15
34	Protocol	24 Where the full trial protocol can be accessed, if available	15
35	Funding	25 Sources of funding and other support (such as supply of drugs), role of funders	15
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38 *We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also

39 recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials.

40 Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

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BMJ Open

Targeted simplification versus antipseudomonal broad-spectrum beta-lactams in patients with bloodstream infections due to Enterobacteriaceae (SIMPLIFY): a study protocol for a multicenter, open-label, phase III randomized, controlled, non-inferiority clinical trial

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2016-015439.R1
Article Type:	Protocol
Date Submitted by the Author:	28-Feb-2017
Complete List of Authors:	<p>López-Cortés, Luis Eduardo; Hospital Universitario Virgen Macarena, Enfermedades Infecciosas y Microbiología Clínica Rosso-Fernández, Clara; Hospital Universitario Virgen del Rocío, Unidad de Ensayos clínicos; Hospital Universitario Virgen del Rocío, Farmacología Clínica Núñez-Núñez, María; Instituto de Biomedicina de Sevilla (IBiS)/Hospital Universitario Virgen Macarena /CSIC/Universidad de Sevilla. Sevilla, Spain., Unidad Clínica de Enfermedades Infecciosas, Microbiología y Medicina Preventiva; Hospital Universitario Virgen Macarena, Unidad Clínica de Farmacia Lavín-Alconero, Lucía; Hospital Universitario Virgen del Rocío, Unidad de ensayos clínicos Bravo-Ferrer, José; Hospitales Universitarios Virgen Macarena y Virgen del Rocío, Unidad de Gestión Clínica de Enfermedades Infecciosas, Microbiología y Medicina Preventiva Barriga, Ángel; Hospital Universitario Virgen del Rocío, Unidad de ensayos clínicos Delgado, Mercedes; Hospital Universitario Virgen Macarena, Microbiología Clínica Lupión, Carmen; Hospital Universitario Virgen Macarena, Enfermedades Infecciosas y Microbiología Clínica Retamar, Pilar; Hospital Universitario Virgen Macarena, Enfermedades Infecciosas y Microbiología Clínica Rodríguez-Baño, Jesús; Hospital Universitario Virgen Macarena,</p>
Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Medical management
Keywords:	De-escalation, Enterobacteriaceae, bloodstream infection, broad-spectrum antibiotics, antimicrobial stewardship

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Manuscripts

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3 1 Title: Targeted simplification versus antipseudomonal broad-spectrum beta-
4
5 2 lactams in patients with bloodstream infections due to *Enterobacteriaceae*
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7 3 (SIMPLIFY): a study protocol for a multicenter, open-label, phase III
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9 4 randomized, controlled, non-inferiority clinical trial
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16 32 **ABSTRACT**

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18 33 **Introduction:** Within the context of antimicrobial stewardship programs, de-
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20 34 escalation of antimicrobial therapy is one of the proposed strategies for
21
22 35 reducing the unnecessary use of broad-spectrum antibiotics (BSA). The
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24 36 empirical treatment of nosocomial and some health-care associated
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26 37 bloodstream infections (BSI) frequently includes a beta-lactam with
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28 38 antipseudomonal activity as monotherapy or in combination with other drugs, so
29
30 39 there is a great opportunity to optimize the empirical therapy based on
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32 40 microbiological data. De-escalation is assumed as standard-of-care for experts
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34 41 in infectious diseases; However, it is less frequent than it would be desirable.
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38 42 **Methods and analysis:** The SIMPLIFY trial is a multicenter, open-label, non-
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40 43 inferiority phase III randomized controlled clinical trial, designed as a pragmatic
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42 44 'real-practice' trial. The aim of this trial is to demonstrate the non-inferiority of
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44 45 de-escalation from an empirical beta-lactam with antipseudomonal activity to a
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46 46 targeted narrow-spectrum antimicrobial in patients with BSI due to
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48 47 *Enterobacteriaceae*. The primary outcome is clinical cure, which will be
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50 48 assessed at the test of cure visit. It will be conducted at 19 Spanish public and
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52 49 university hospitals.
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3 50 **Ethics and dissemination:** Each participating center has obtained the
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5 51 approval of the Ethics Review Committee, the agreement of the Directors of the
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7 52 Institutions, and authorization from the Spanish Regulatory Agency (AEMPS,
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9 53 Agencia Española del Medicamento y Productos Sanitarios). Data will be
10
11 54 presented at international conferences and published in peer-reviewed journals.

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14 55 **Discussion:** Strategies to reduce the use of BSA should be a priority. Most of
15
16 56 the studies that support de-escalation are observational, retrospective, and
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18 57 heterogeneous. A recent Cochrane review stated that well-designed clinical
19
20 58 trials should be conducted to assess the safety and efficacy of de-escalation.

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24 25 60 **REGISTRATION**

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27 61 Trial registration number: EudraCT number: 2015-004219-19, start date: 18
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29 62 March 2016. Protocol V.2.0, dated 16 May 2016.

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33 34 64 **STRENGTHS OF THIS STUDY**

- 35
36 65 • It will be the first trial on de-escalation specifically in patients with
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38 66 bacteremia due to *Enterobacteriaceae*.
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40 67 • It will include patients independently of the source of bacteraemia or
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42 68 severity of clinical presentation.
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44 69 • A remote automatic randomisation system and external evaluation by
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46 70 blinded investigators were used to avoid bias.
- 47
48 71 • It has been designed with daily clinical practice in mind.

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52 53 73 **LIMITATIONS OF THIS STUDY**

- 54
55 74 • The open-label design is theoretically more prone to bias.

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3 75 • Switching to oral therapy could potentially reduce the number of days in
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5 76 which patients are assigned to one or other arm.
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10 78 **KEYWORDS:**

11 79 De-escalation, *Enterobacteriaceae*, bloodstream infection, broad-spectrum
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13 80 antibiotics, antimicrobial stewardship.
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For peer review only

82 BACKGROUND

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84 The worldwide spread of antimicrobial resistance is recognised as a current
85 global public health threat. The implementation of stewardship programs for
86 optimizing antibiotic use has been shown both to improve antibiotic use and
87 also to help combat antimicrobial resistance [1]. Streamlining or de-escalation of
88 antimicrobial therapy is a strategy proposed to reduce the unnecessary use of
89 broad-spectrum antimicrobials (BSA) [1,2]. This can be carried out by changing
90 from combination therapy to monotherapy or by replacing the empirical
91 antibiotic with one with a narrower spectrum of activity, irrespective of the
92 microbiology results [1].

93 Bloodstream infections (BSI) are known to be major causes of morbidity and
94 mortality. They represent suitable organisms for carrying out a de-escalation
95 strategy because they are very frequent, a high proportion of patients are
96 treated with BSA and the susceptibility of the causative organisms is known.

97 The *Enterobacteriaceae* as a group, is the most common cause of community-
98 and nosocomial BSI, with a crude associated mortality of around 15% [3]. The
99 empirical treatment for nosocomial and some healthcare-associated BSI
100 frequently includes a beta-lactam antibiotic with antipseudomonal activity in
101 monotherapy or in combination. This imposes strong selection pressure,
102 particularly on *Pseudomonas aeruginosa* isolates, and maybe selecting
103 multidrug resistant *Enterobacteriaceae* isolates. De-escalation according to
104 microbiological results is assumed as standard-of-care by most infectologists;
105 however, the reality is that de-escalation is much less frequent than is desirable
106 [4,5]. Some of the possible reasons for this phenomenon [6-8] include the fact

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3 107 that the safety and efficacy of this treatment strategy are based only on a few
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5 108 observational studies [9,10] and expert recommendations [11,12]. This was
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7 109 supported by a recent Cochrane review [13] conducted among adults with
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9 110 sepsis, severe sepsis or septic shock, whose authors concluded that there is no
10
11 111 adequate direct evidence that de-escalation of antimicrobial agents is effective
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13 112 and safe in this scenario. Randomized clinical trials of their safety and efficacy
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15 113 are needed, in order to establish “proof of concept” and help make clinical
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17 114 decisions.
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24 25 117 **METHODS/DESIGN**

26 27 118 28 29 119 **Study hypothesis**

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31 120 The aim of the trial is to demonstrate that de-escalation from empirical therapy
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33 121 with an antipseudomonal beta-lactam to a targeted therapy is as effective and
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35 122 safe in patients with BSI due to *Enterobacteriaceae* as continuing with the
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37 123 empirical regimen.
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42 43 124 44 125 **Design**

45 126 The SIMPLIFY trial is a multicenter, open-label, phase III randomized controlled
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47 127 clinical trial, powered to demonstrate the non-inferiority of de-escalation with
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49 128 respect to continuing with the antipseudomonal agent and designed as a real-
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51 129 world pragmatic trial. It was developed in accordance with an extension of the
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53 130 SPIRIT statement for reporting non-inferiority, superiority and equivalence trials
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55 131 [14,15].
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5 133 **Participants and settings**

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7 134 The trial will be conducted at 19 public and tertiary hospitals with the support of
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9 135 the Spanish Network for Research in Infectious Diseases (REIPI) and the
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11 136 Spanish Clinical Research Network (SCReN). Thirteen of them are University
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13 137 hospitals. Patients will be evaluated for eligibility once *Enterobacteriaceae* is
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15 138 isolated from blood cultures and susceptibility data are available. Detection of
16
17 139 eligible patients will be by daily review of blood culture results by the bacteremia
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19 140 team at each center. To be enrolled, participants will need to fulfill all inclusion
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21 141 and exclusion criteria (Table 1) plus give written informed consent (the patient
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23 142 or a legally authorized representative).
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29 144 **Table 1. Inclusion and exclusion criteria**

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32 **Inclusion criteria**

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34 1. Written informed consent has been obtained from the patient or the
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39 2. Age \geq 18 years, not legally incapacitated.
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41 3. Hospitalised patients with monomicrobial bacteremia due to
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- Written informed consent has been obtained from the patient or the legally authorised representative.
 - Age \geq 18 years, not legally incapacitated.
 - Hospitalised patients with monomicrobial bacteremia due to *Enterobacteriaceae* from any source.
 - The patient has received active empiric antibiotic therapy with an antipseudomonal beta-lactam (imipenem, meropenem, piperacillin-tazobactam, cefepime, ceftazidime, aztreonam), alone or in combination with another antimicrobial agent, which started in the first 24 hours after the first positive blood culture was taken.
 - The isolate is susceptible to at least one of antibiotics included in the

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experimental arm.

6. Intravenous antimicrobial treatment is planned for at least 5 days once *Enterobacteriaceae* is isolated from the blood culture.

Exclusion criteria

1. Life expectancy <30 days.
2. Pregnancy or nursing. For included women: failure to use a highly effective contraceptive method.
3. Isolation of carbapenemase-producing *Enterobacteriaceae* (because most hospitals do not use monotherapy in these cases).
4. Inclusion is delayed >48 h after susceptibility data of the isolate are available.
5. Severe neutropenia (<500 cells/mm³) on the day of randomization.
6. Planned duration of treatment >28 days (e.g. osteomyelitis, endocarditis).

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147 Randomization

148 Stratified randomization in a 1:1 ratio will be achieved using a centralized, web-
149 based automated randomization system integrated with the eCRF (electronic
150 Case Report Form) to manage assignment to the treatment arms. A copy of the
151 randomization list will be kept in a safe place in case technical problems arise.
152 The only criterion for stratification will be source of bloodstream infection
153 (urinary tract vs any other) in order to ensure that the percentage of patients
154 with urinary tract infections is similar in the two groups being compared. To
155 guarantee an appropriate allocation concealment in an open trial, randomization

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3 156 will not be stratified by site.
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7 158 **Intervention**

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9 159 A decision tree of enrolment to the study is included in Figure 1. As stated
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11 160 above, all included patients will already be receiving an antipseudomonal beta-
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13 161 lactam (meropenem, imipenem, piperacillin-tazobactam, cefepime, ceftazidime
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15 162 or aztreonam) before randomization occurs. Patients will be allocated to one of
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17 163 the following treatment arms:
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21 165 Experimental group:

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23 166 The patient will change to an intravenous therapy with an active narrow-
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25 167 spectrum antibiotic according to the susceptibility results (EUCAST or CLSI
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27 168 criteria); the antibiotic will be chosen in the following order (the first active drug
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29 169 will be used): (1) ampicillin, 2 g q6h; (2) trimethoprim/sulfamethoxazole,
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31 170 160/800 mg q8-12h; (3) cefuroxime, 750-1500 mg q8h; (4) cefotaxime 1-2g q8h
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33 171 or ceftriaxone, 1 g q12-24h; (5) amoxicillin/clavulanate, 1g/125 mg q8h; (6)
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35 172 ciprofloxacin, 400 mg q12h; and (7) ertapenem, 1g q24h.
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37 173 Trimethoprim/sulfamethoxazole will only be used in urinary tract infections in the
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39 174 absence of an undrained renal abscess. Ciprofloxacin is included because,
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41 175 apart from being active against *P. aeruginosa*, it is not a beta-lactam.
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49 177 Control group:

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51 178 Continuation of the antipseudomonal beta-lactam that was being administered
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53 179 on an empirical basis: meropenem, 1-2 g q8h; imipenem, 0.5-1g q6h;
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55 180 piperacillin-tazobactam, 4/0.5 g q6-8h; cefepime, 2 g q8-12h; ceftazidime, 1-2 g
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3 181 q8h; and aztreonam, 1-2 g q8h.

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7 183 Exceptions to the above rule:

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9 184 Third-generation cephalosporins should be avoided where there are inducible

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11 185 AmpC β -lactamase-producing *Enterobacteriaceae* (*Enterobacter* spp.,

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13 186 *Providencia* spp., *Morganella morganii*, *Serratia marcescens*, and *Citrobacter*

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15 187 *freundii*); hence, even if the isolates are strictly susceptible, for patients in the

16
17 188 control group, ceftazidime may be changed to any other antipseudomonal beta-

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19 189 lactam on the day of randomization. For patients allocated to the experimental

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21 190 arm, the options will be limited to trimethoprim/sulfamethoxazole, ciprofloxacin

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23 191 or ertapenem.

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25 192 ESBL producers could be included in the study based on attending physician's

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27 193 criteria; in this cases, maximum doses of susceptible antibiotics are

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29 194 recommended.

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33 196 Dose adjustment

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35 197 Due to the nature of the study design as a real-world clinical practice trial,

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37 198 antimicrobial dosage will be as deemed by the treating clinician, dependent on

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39 199 pharmacokinetic and pharmacodynamic (PK/PD) characteristics (such as higher

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41 200 doses for septic shock or high body mass). Dose adjustment will be made for all

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43 201 drugs as necessary in the case of renal or hepatic dysfunction, following

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45 202 Summary of Product Characteristics (SmPC) recommendations.

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49 204 Concomitant therapy

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51 205 Even if the BSI is monomicrobial, the attending physician may consider the

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3 206 infection to be polymicrobial at source. If additional anaerobic or gram-positive
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5 207 coverage is needed, concomitant use of oral metronidazole, clindamycin,
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7 208 vancomycin, teicoplanin, daptomycin or linezolid is allowed in both arms.
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9 209 Concomitant treatment with any other systemic antibiotic with intrinsic activity
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11 210 against gram-negative bacilli is not allowed. The administration of any of these
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13 211 drugs while the patient is receiving the study drug will be deemed a criterion for
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15 212 withdrawal. There are no absolute contraindications for the use of any other
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17 213 drug during the study. However, contraindications, warnings and precautions for
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19 214 use and possible interactions with study drugs are to be taken into account.
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25 216 Duration of therapy

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27 217 The appropriate duration of therapy is considered to be between 7 and 14 days,
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29 218 according to the attending physician's criteria. Treatments lasting longer than
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31 219 14 days will be allowed only when there is an undrained abscess present, in
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33 220 which case, a 4-week treatment is permitted.
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38 222 Route of administration

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40 223 Switching to oral therapy is allowed after the third day of therapy after
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42 224 randomisation if all the following conditions are fulfilled: clinical improvement
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44 225 has been achieved, absence of fever ($>38^{\circ}\text{C}$), hemodynamic stability, adequate
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46 226 control of the source of BSI and absence of secondary foci, adequate oral
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48 227 intake, and no gastrointestinal conditions that might compromise drug
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50 228 absorption.
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53 229 For patients in the experimental group, switching to oral therapy is allowed with
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55 230 the same intravenous drugs as follows: trimethoprim/sulfamethoxazole 160/800
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3 231 mg q8 -12h, cefuroxime axetil 500 mg q8-12h, amoxicillin/clavulanate 875/125
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5 232 mg q8h, or ciprofloxacin 500 mg q12h. If the intravenous drug is ampicillin,
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7 233 amoxicillin 1 g q8h will be used; if cefotaxime or ceftriaxone, then ceftibuten 400
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9 234 mg q12-24h or cefixime 400 mg q12-24h will be used; if ertapenem, this drug
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11 235 may be switched to the intramuscular route.

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14 236 For patients in the control group, the preferred oral option is ciprofloxacin 500
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16 237 mg q12h for all patients. The protocol allows treatment with cefuroxime-axetil
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18 238 500 mg q8-12h or cefixime 400 mg q12-24h only in cases of resistance to
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20 239 ciprofloxacin; finally, parenteral ertapenem 1g q24h may be used for
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22 240 convenience if the isolate is resistant to all other oral options.

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27 242 Rescue medication

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29 243 No rescue medication is planned on behalf of the study if a patient has to
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31 244 withdraw from the trial for any reason; the attending physician will follow clinical
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33 245 guidelines for routine clinical practice and GCP (Good clinical practice) rules.

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38 247 Medication

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40 248 As all the study drugs are recommended for BSI caused by *Enterobacteriaceae*,
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42 249 the sponsor will not provide the study drugs [16]. Every site participating in the
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44 250 study is authorised to use the drugs through the normal provision of its hospital
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46 251 pharmacy.

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51 253 Schedule of visits

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53 254 Patients included in the study will be followed for 60 days (\pm 5 days) after
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55 255 diagnosis of the BSI (Figure 2). Follow-up will be organised in seven planned

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3 256 visits at day 0 (baseline), day 1; day 3-5; day 7-14 (end of treatment); day 3-5
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5 257 from end of treatment (test of cure, TOC); day 30 ± 5; and day 60 ± 5. Visits at
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7 258 days 30 and 60 may be made by telephone.
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10 259 The visit schedule is planned so as to obtain data on clinical status, sample
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12 260 collection, efficacy and safety variables, and adverse events. At the final
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14 261 evaluation at 60 days, data on all outcome variables will be gathered.
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16 262 Additionally, data will be collected at unplanned visits, with special
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18 263 consideration given to the occurrence of any adverse event or recurrence.
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22 23 265 **Outcomes**

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25 266 The primary outcome is clinical cure, which will be assessed at the TOC visit (3-
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27 267 5 days after the end of antibiotic treatment). Death during treatment, change of
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29 268 antibiotic therapy due to clinical failure, or need to prolong the treatment will be
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31 269 considered as failures. Secondary outcomes include early (5 days after end of
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33 270 treatment) and late (60-day) clinical and microbiological response, all-cause
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35 271 mortality (days 7, 14, and 30), length of hospital stay, recurrence rates (relapse
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37 272 or reinfection) (day 60), safety of antibiotic treatment, including *Clostridium*
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39 273 *difficile* infections and number of antibiotic treatments with an antipseudomonal
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41 274 beta-lactam; in a subgroup of patients, the rate of intestinal colonization by *P.*
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43 275 *aeruginosa* resistant to carbapenemase or piperacillin / tazobactam,
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45 276 *Stenotrophomonas* spp., multiresistant *A. baumannii* and enterobacteria
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47 277 producing ESBL, carbapenemase and chromosomal AmpC (hyperproduction)
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49 278 or plasmid will be sought. Some of these secondary outcomes will be analyzed
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51 279 as composite variables, following the DOOR/RADAR methodology. Outcome
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53 280 definitions, assessment, and time frames for measurement are described in
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3 281 Table 2.

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5 282 **Table 2. Outcome definitions and time frames**
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Primary End Point and Time Frame	Definition and Assessment
CLINICAL CURE Day 3-5 after treatment*	TOC, the situation where all the following conditions are met: survival at the time of the evaluation; complete resolution of all symptoms and signs of infection (or return to the situation prior to current infection); no need for prolonged antibiotic treatment beyond the recommended duration* and no need for treatment modification due to unfavorable clinical response.
*7-14 days according to IDSA, except in the presence of undrained or late-draining abscesses, when up to 4 weeks are allowed.	
Secondary End Point and Time Frame	Definition and Assessment
CLINICAL RESPONSE After 5 days of treatment (early response) Until Day 60 of follow-up (late response)	Same as clinical cure
MICROBIOLOGICAL CURE After 5 days of treatment (early response)	Negative blood cultures and where applicable, negative

<p>Until Day 60 of follow-up (late response)</p>	<p>cultures from samples taken from initial infection focus.</p> <p>'PRESUMPTIVE MICROBIOLOGIC CURE' is accepted in those cases where it is not possible to prove the negativization of isolates from initial focus.</p>
<p>ALL-CAUSE MORTALITY</p> <p>7, 14 and 60-day of follow-up</p>	<p>Death for any reason</p>
<p>LENGTH OF HOSPITAL STAY</p>	<p>Time from randomisation to hospital discharge</p>
<p>CLINICAL RECURRENCE (RELAPSE OR REINFECTION) RATES</p> <p>60-day of follow-up</p>	<p>Recurrence of at least one clinical and one analytical sepsis criterion, with presence or absence of bacteraemia</p>
<p>MICROBIOLOGICAL RECURRENCE (RELAPSE OR REINFECTION) RATES</p> <p>60-day of follow-up</p>	<p>New BSI episode with the same isolate as initial cultures with previously clinical and microbiological cure</p>
<p>NUMBER OF DAYS OF APBL AVOIDED</p> <p>Until end of treatment</p>	<p>Number of days of antibiotic treatment with an antipseudomonal beta-lactam (APBL) avoided</p>

<p>ECOLOGICAL IMPACT</p> <p>7-14, 12-21, 30 days</p>	<p>Intestinal colonization by multidrug-resistant Gram-negative bacilli</p>
<p>SAFETY OF DRUGS - adverse events</p> <p>Until Day 60 of follow-up</p>	<p>Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related.</p>
<p>COMPOSITE SECONDARY VARIABLES</p> <p>7-14, 60-day follow up</p>	<p>Survival on day 14, number of days with an antipseudomonal beta-lactam avoided, presence or absence of side effects, including <i>C. difficile</i> infections, secondary MDRO infections and all drug-related adverse events</p>

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285 **Data collection, management and monitoring**

286 The coordinating center for this study is the Hospital Universitario Virgen
 287 Macarena, Seville, Spain, and the Clinical Trials Unit (CTU-Hospital
 288 Universitario Virgen del Rocío) has delegated sponsor functions on behalf of
 289 the Fundación Pública Andaluza para la Gestión de la Investigación en Salud
 290 de Sevilla (FISEVI - <http://www.fisevi.com>). Clinical research associates (CRAs)
 291 connected to the Spanish Clinical Research Network (SCReN) in public
 292 hospitals will carry out monitoring activities. Data collection will be conducted by
 293 trained staff at each participating center and entered into a restricted access

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3 294 electronic case report form (eCRF). Outstanding queries regarding the
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5 295 completion of the CRF will be sent to all participating centers as necessary to
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7 296 ensure accuracy of data.
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10 297 In order to avoid any association with personal data, all study samples will be
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12 298 anonymous and identifiable only by the patient's alphanumeric study code. The
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14 299 objective and management of these samples are included in the patient's
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16 300 information sheet and informed consent form.
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19 301 The quality of all data collected will be carefully supervised by the CTU and
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21 302 specific visits for source data verification are organized according to the
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23 303 monitoring plan. Furthermore, in order to minimize bias, at the interim analysis
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25 304 (when 50% of the sample has been included), an independent committee (3
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27 305 independent investigators from the REIPI) blinded to treatment assignment will
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29 306 review all accumulated data. This committee will advise the sponsor on the
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31 307 appropriateness of continuing the clinical trial as designed.
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35 36 309 **Isolates**

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38 310 All isolates will be sent to the central laboratory in the Hospital Universitario
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40 311 Virgen Macarena in Seville for susceptibility testing using reference methods
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42 312 and PCR characterisation and sequencing if necessary.
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45 313 Eight selected hospitals will participate in the study of rectal carriage of ESBL-
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47 314 AmpC- and carbapenemase-producing *Enterobacteriaceae*, by taking rectal
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49 315 swabs from participants at different times (as set out in the schedule of visits).

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51 316 To do this, samples will be taken by rectal swab from the patients of both
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53 317 treatment arms on the day of randomization, the day when treatment finish, the
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55 318 day of test of cure, and visit of day 30. The presence of *P. aeruginosa* resistant
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3 319 to carbapenemase or piperacillin / tazobactam, *Stenotrophomonas* spp.,
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5 320 multiresistant *A. baumannii* and enterobacteria producing ESBL,
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7 321 carbapenemase and chromosomal AmpC (hyperproduction) or plasmid will be
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9 322 sought. A written consent form for samples, approved by the ECs (Ethics
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11 323 Committees), is also provided for the study.

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15 325 **Definition of analysis population and outcome measures**

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17 326 The following populations will be considered: the intention-to-treat population
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19 327 (ITTP) includes all randomized patients; the modified ITTP (mITTP) includes
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21 328 randomized patients who have received at least one dose of intravenous
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23 329 antibiotics; the clinically evaluable population (CEP) includes patients who have
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25 330 completed 5 days of the intravenous study drug, or who die but have received
26
27 331 at least one dose of intravenous antibiotics. The clinically and microbiologically
28
29 332 evaluable population (CMEP) includes those in the CEP who have had
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31 333 microbiological tests (at least one blood culture 48 hours after randomization).

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33
34 334 The local principal investigator in the centre where the patient was included will
35
36 335 assess the primary outcome (clinical cure) in the clinically evaluable population
37
38 336 (CEP) at TOC. Due to the intrinsic characteristics of the primary outcome (soft
39
40 337 outcome) and the study methodology (non-blinded), this evaluation done will be
41
42 338 reviewed later on the basis of clinical data recovered on two occasions by an
43
44 339 external blinded investigator: firstly, during the interim analysis to monitor
45
46 340 safety; secondly before the complete cleaning and closure of the eCRF. For
47
48 341 secondary end points, the CMEP will be eligible for early (day 5) and late (day
49
50 342 60) microbiological responses, the m-ITTP for all-cause mortality and length of
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52 343 hospital stay, and the CEP for the evaluation of recurrence rates and drug
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3 344 safety.
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7 346 **Sample size**
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10 347 The sample size was calculated using Epidat 4.0. Some of the data used to
11
12 348 calculate it was derived from the study published by Retamar *et al* [17].
13
14 349 Assuming estimated clinical cure rates of 85% in both groups, a non-inferiority
15
16 350 margin of 10% difference between the 2 groups, and treatment assignment in a
17
18 351 1:1 ratio, 344 patients in total (172 per study arm) are needed to achieve 80%
19
20 352 power with a significance level of 5%. This allows for a 5% dropout rate. The
21
22 353 10% non-inferiority margin was chosen as in recent trials of complicated urinary
23
24 354 tract and intraabdominal infections [18,19].
25
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29 356 **Statistical analysis**
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32 357 Absolute differences will be calculated with 95% confidence intervals for the
33
34 358 clinical cure rate between the two arms of the study at TOC. Multivariate
35
36 359 analysis using logistic regression for the main outcome will be performed in
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38 360 order to ensure the independence of the treatment effect. Special consideration
39
40 361 will be given in the multivariate analysis to the center of origin of the study
41
42 362 sample. A Cox regression analysis of mortality until 60 days will be performed
43
44 363 on the mITTP. For the superiority analysis, logistic regression will be used
45
46 364 sequentially, using the methodology recently published by Evans et al [20] for
47
48 365 the composite variable (DOOR and RADAR analysis using survival at day 14,
49
50 366 number of days of antipseudomonal beta-lactam treatment avoided, presence
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52 367 or absence of side effects, including *C. difficile* infections, secondary MDRO
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3 368 infections, and all drug-related adverse events). Antimicrobial doses are not
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5 369 fixed and sensitivity analyses will therefore be applied to control potential bias.
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10 371 **Protocol violations**

11 372 All protocol violations occurring after randomization will be listed in the Clinical
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13 373 Study Report, tabulated by subject and by recruitment center.
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20 376 **ETHICAL ISSUES**

21
22 377 Each of the participating centers has obtained the approval of an Ethics Review
23
24 378 Committee, the agreement of the Directors of the Institutions (who signed the
25
26 379 contract of agreement with the sponsor of the study) and authorisation from the
27
28 380 Spanish Regulatory Agency (AEMPS, Agencia Española del Medicamento y
29
30 381 Productos Sanitarios). Patients may withdraw from the study at any time without
31
32 382 prejudice, as is documented and explained at the time of providing consent.
33

34
35 383 The study will be carried out according to the principles of the Declaration of
36
37 384 Helsinki, and Directive 2001/20/EC of the European Parliament and of the
38
39 385 Council of 4 April 2001 on the harmonization of the laws, regulations and
40
41 386 administrative provisions of the Member States relating to the implementation of
42
43 387 Good Clinical Practice in the conduct of clinical trials on medicinal products for
44
45 388 human use until the new Clinical Trials Regulation (CTR) EU No 536/2014
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47 389 becomes applicable, which will be no earlier than 28 May 2016. The
48
49 390 confidentiality of records that might identify subjects in this study will be
50
51 391 protected in accordance with EU Directive 2001/20/EC. All laws for the control
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53 392 and protection of personal information will be carefully followed. The identities of
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3 393 patients will not be disclosed in the e-CRF; names will be replaced by an
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5 394 alphanumeric code and any material related to the trial, such as samples, will
6
7 395 be identified in the same way, so that no personal information will be revealed.
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11 397 **DISCUSSION**

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14 398 The extensive use of BSA and the dramatic increase in infections due to
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16 399 multidrug-resistant organisms are forcing the scientific community to look for
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18 400 strategies to combat this situation. In the real world, the application of de-
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20 401 escalation to serious infections is less frequent than is desirable. The
21
22 402 arguments against de-escalation include: (1) the MIC of some narrow-spectrum
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24 403 drugs are closer to susceptibility breakpoints than carbapenems, for example,
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26 404 and some physicians may therefore feel safer using the latter; (2)
27
28 405 subpopulations resistant to narrow-spectrum drugs may be selected and appear
29
30 406 after some days of empirical treatment, leading to treatment failure in case of
31
32 407 de-escalation; (3) in the case of polymicrobial infections, it is not uncommon for
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34 408 only one of the pathogens to be isolated in blood cultures, so that simplification
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36 409 of treatment may be less safe and effective than a broad-spectrum treatment;
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38 410 (4) there is some doubt about the real effectiveness of certain drugs against
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40 411 isolates producing specific mechanisms of resistance. Furthermore, although it
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42 412 is assumed that BSA has a greater impact on the selection of multidrug-
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44 413 resistant strains, some studies suggest that it may depend more on the duration
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46 414 of the treatment than the spectrum [16]. While none of these arguments have
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48 415 been proven, it is also true that there is no strong evidence for the safety of de-
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50 416 escalation strategies in these scenarios.
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3 417 To the best of our knowledge, three randomized trials on de-escalation
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5 418 strategies, none of them specifically focused on bacteremia, have been
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7 419 published, which show significant differences from this study [21-23]. The one
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9 420 published by Falguera *et al* [22] compared the efficacy of empirical versus
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11 421 targeted treatment on the basis of urine antigen results in hospitalized patients
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13 422 with community-acquired pneumonia. The article published by Kim *et al* [23]
14
15 423 evaluated the efficacy of early use of imipenem/cilastatin and vancomycin
16
17 424 followed by de-escalation versus conventional antimicrobials without de-
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19 425 escalation for patients with hospital-acquired pneumonia in ICUs. The last one,
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21 426 published recently by Leone *et al* [24], included a limited number (n=116) of
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23 427 ICU-admitted patients with severe sepsis; Its primary outcome was duration of
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25 428 ICU stay, and not effectiveness of both treatment strategies. In that study, de-
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27 429 escalation followed the recommendations of guidelines, not a pre-specified
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29 430 protocol based on the clinical impact of the antibiotics. There was no significant
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31 431 difference in mortality, although unexpectedly, patients in the experimental arm
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33 432 had a higher rate of superinfections (27% vs 11%, $P = 0.03$). These results
34
35 433 contrast with a recent systematic review and meta-analysis that included 25
36
37 434 studies with data on de-escalation based on culture results, which showed a
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39 435 significant reduction in the relative risk of death (RR 0.44, 95% CI: 0.30–0.66;
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41 436 $p < 0.0001$). It is important to note that many of the included studies in the meta-
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43 437 analysis were observational, retrospective and had a high degree of
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45 438 heterogeneity [25].

46
47 439 Several authors have warned about the considerable inconsistencies in
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49 440 definitions of de-escalation. In 2015, Weiss *et al* [26] elaborated a consensual
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51 441 definition of de-escalation that allowed beta-lactams to be ranked according to
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3 442 both their spectra and their ecological impact. The authors underlined
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5 443 the difficulty of reaching consensus on the relative ecological impact of each
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7 444 individual drug. In 2014, Madaras-Kelly *et al.* [27] used the Delphi approach to
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9 445 develop an antibiotic spectrum score to measure de-escalation. We shall
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11 446 therefore include both concepts in our analysis, using Outcome Ranking
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13 447 (DOOR) and Response Adjusted for Duration of Antibiotic Risk (RADAR)
14
15 448 analyses [20].

16
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18 449 Switching from intravenous to oral therapy as soon as the patient is clinically
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20 450 stable can reduce the risk of adverse events related to intravenous therapy,
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22 451 length of hospitalization, and cost. It can be applied regardless of the source of
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24 452 infection and underlying conditions whenever a good option that achieves the
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26 453 PK/PD targets is available [28]. In our study, switching to oral therapy is allowed
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28 454 in both arms to avoid exposing patients in the control arm to unnecessary risks.
29
30 455 The SIMPLIFY trial has several strengths. In the first place, it will be the first trial
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32 456 on de-escalation specifically in patients with bacteremia due to
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34 457 *Enterobacteriaceae*. Second, it will include patients independently of the source
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36 458 of bacteraemia or severity of clinical presentation. Third, it was designed with
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38 459 daily clinical practice in mind. We hope that, if there is reasonable evidence to
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40 460 reject the null hypothesis, it will encourage implementation of this type of
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42 461 strategy in daily practice.
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50 TRIAL STATUS

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52 464 • Funding for the study was approved on 15/08/2015 and available for
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54 465 study expenses in 01/01/2016.
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56 466 • EC approval for the 19 sites included was obtained on 15th March 2016.
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3 467 • Authorization from the Spanish Regulatory Authority was obtained on
4
5 468 18th March 2016.

6
7 469 • The study has been approved for a recruitment period of 2 years.

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9 470 • Dissemination of results directed to patients will be channeled through
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11 471 the Spanish Clinical Studies Registry (Agencia Española del
12
13 472 Medicamento y Productos Sanitarios), whose content is adapted to
14
15 473 patients.
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23
24
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26
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28
29 479 document number: PI15/00439. The ISCIII is the main public research entity in
30
31 480 Spain and reports directly to the Ministry of Economy and Competitiveness and
32
33 481 in operational terms to both this Ministry and to the Ministry of Health, Social
34
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36
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38
39 484 Instituto de Salud Carlos III, integrated in the national I+D+i 2013-2016 and co-
40
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42
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44
45 487 number 16.001.

46 488 **Role of the funding source**

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48
49 489 The funders of the study had no role in the study design or in manuscript
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51 490 development.
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3 492 **COMPETING INTERESTS ESTATEMENT**

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5 493 The authors have no competing interests to declare.
6
7 494

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9 495 **CONTRIBUTORSHIP STATEMENT**

10
11 496 JR-B and LEL-C were responsible for formulating the overall research questions
12
13 497 and for the methodological design of the study. CR-F, BA and LL-A collaborated
14
15 498 in the submission of the project for the Spanish funding, and collaborated in the
16
17 499 methodological aspects of the study. JR-B is the coordinating investigator and
18
19 500 leader of the Coordination Team. CR-F is responsible for the CTU. MN-N
20
21 501 collaborated with writing of the manuscript and with the pharmacovigilance
22
23 502 design, and JB-F, PR-G, and CL collaborated in the organisation of the study.
24
25 503 MD contributed in all the microbiological details of the study. JR-B and LEL-C
26
27 504 participated in its design and supervised the project. All authors read and
28
29 505 approved the final manuscript.
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36 507 **DATA SHARING STATEMENT**

37
38 508 No additional unpublished data from the study are available
39
40 509

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3 635 Figure 1. SIMPLIFY – Decision tree of patient enrolment
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5 636 Figure 2. Schedule of visits and assessments. Except where otherwise
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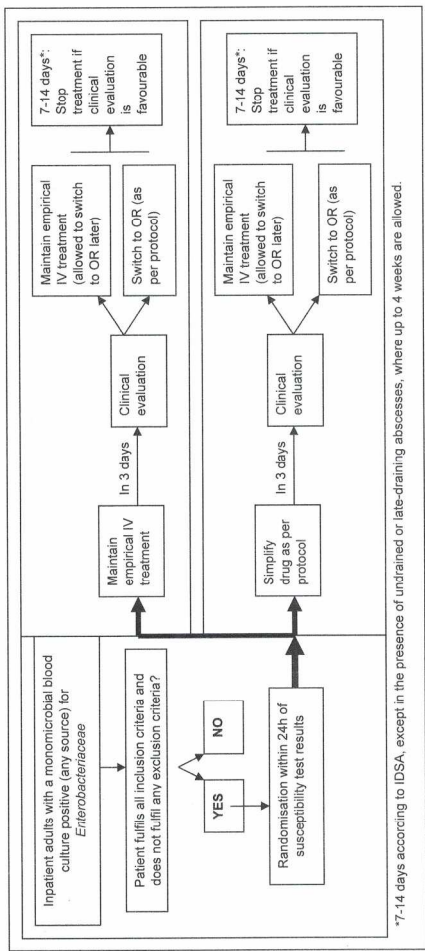
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For peer review only

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Figure 1.



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Figure 2.

Procedures	Selecti on visit (Day 0)	Visit 1 (Day 1)	Visit 2 (Day 3-5)	End of treatment (Day 7-14) ^{2,3}	Test of cure (Day 12-21) ¹	Follow-up visit (Day 30±5) ²	End of study (Day 60) ²
Randomization	X						
Informed consent	X						
Check in/exclusion criteria	X						
Pregnancy test	X						
Demographic data/ medical history	X	X	X	X	X	X	X
Physical examination	X	X	X	X ²	X	X ²	X ²
Laboratory data		X	X	X ²	X		
Blood culture	X		X	X ³			
Rectal swab ⁴	X			X	X	X	
Ancillary drugs	X	X	X	X		X	X
Drug dispensing control	X	X	X	X			
Adverse events		X	X	X	X	X	X

(1) In the presence of an undrained abscess, TOC will be performed on day 28 or if drainage occurs after day 7 of treatment, TOC is to be done 7 days after that day; (2) This visit may be made by telephone if the patient has been discharged. In this scenario, no physical examination or lab tests are requested; (3) Only if previous blood cultures or symptoms remain positive; (4) Only in selected hospitals and face-to-face scheduled visits

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	__Page 1__
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	__Page 3__
	2b	All items from the World Health Organization Trial Registration Data Set	__Page 3__
Protocol version	3	Date and version identifier	__Page 3__
Funding	4	Sources and types of financial, material, and other support	__Page 24__
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	__Page 1/25__
	5b	Name and contact information for the trial sponsor	__Page 16__
	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	__Page 24__
	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)	__Page 25__

1
2
3 **Introduction**
4

5 Background and	6a	Description of research question and justification for undertaking the trial, including summary of relevant	__Page 5 __
6 rationale		studies (published and unpublished) examining benefits and harms for each intervention	
7			
8	6b	Explanation for choice of comparators	__Page 5 __
9			
10 Objectives	7	Specific objectives or hypotheses	__Page 6 __
11			
12 Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group),	__Page 6 __
13		allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	
14			
15			
16 Methods: Participants, interventions, and outcomes			
17			
18 Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will	__Page 7 __
19		be collected. Reference to where list of study sites can be obtained	
20			
21 Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and	__Page 7 __
22		individuals who will perform the interventions (eg, surgeons, psychotherapists)	
23			
24 Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be	__Page 9 __
25		administered	
26			
27	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose	__Page 12 __
28		change in response to harms, participant request, or improving/worsening disease)	
29			
30	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence	__Page 9 __
31		(eg, drug tablet return, laboratory tests)	
32			
33	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	__Page 10 __
34			
35 Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood	__Page 13 __
36		pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg,	
37		median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen	
38		efficacy and harm outcomes is strongly recommended	
39			
40			
41 Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for	__Page 14 __
42		participants. A schematic diagram is highly recommended (see Figure)	
43			
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3 Sample size 14 Estimated number of participants needed to achieve study objectives and how it was determined, including __Page 19 __
4 clinical and statistical assumptions supporting any sample size calculations

5
6 Recruitment 15 Strategies for achieving adequate participant enrolment to reach target sample size __ N/A __
7

8 **Methods: Assignment of interventions (for controlled trials)**
9

10 Allocation: __Page 8 __
11

12 Sequence generation 16a Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any __Page 8 __
13 factors for stratification. To reduce predictability of a random sequence, details of any planned restriction
14 (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants
15 or assign interventions
16

17 Allocation concealment mechanism 16b Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, __Page 8 __
18 opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
19
20

21 Implementation 16c Who will generate the allocation sequence, who will enrol participants, and who will assign participants to __Page 8 __
22 interventions
23

24 Blinding (masking) 17a Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome __Page 8 __
25 assessors, data analysts), and how
26

27
28 17b If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's __Page 8 __
29 allocated intervention during the trial
30
31

32 **Methods: Data collection, management, and analysis**
33

34 Data collection methods 18a Plans for assessment and collection of outcome, baseline, and other trial data, including any related __Page 16 __
35 processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of
36 study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known.
37 Reference to where data collection forms can be found, if not in the protocol
38

39 18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be __Page 16 __
40 collected for participants who discontinue or deviate from intervention protocols
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3	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	__Page 16 __
4				
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6				
7	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	__Page 14/19 __
8				
9				
10		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	__Page 14/19 __
11				
12		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	__Page 14/19 __
13				
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16 **Methods: Monitoring**

17				
18	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	__Page 16 __
19				
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23		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	__Page 17 __
24				
25				
26	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	__Page 19 __
27				
28				
29	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	__Page 17 __
30				
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33 **Ethics and dissemination**

34				
35	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	__Page 20 __
36				
37				
38	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)	__Page 16 __
39				
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3	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	__Page 20__
4				
5				
6		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	__Page 20__
7				
8				
9	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	__Page 20__
10				
11				
12	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	__Page 25__
13				
14				
15	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	__Page 25__
16				
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18	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	__Page 19__
19				
20				
21	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	__Page 3__
22				
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26		31b	Authorship eligibility guidelines and any intended use of professional writers	__N/A__
27				
28		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	__Page 20__
29				
30	Appendices			
31				
32	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	__N/A__
33				
34				
35	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	__N/A__
36				
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38 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.
 39 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons
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BMJ Open

Targeted simplification versus antipseudomonal broad-spectrum beta-lactams in patients with bloodstream infections due to Enterobacteriaceae (SIMPLIFY): a study protocol for a multicenter, open-label, phase III randomized, controlled, non-inferiority clinical trial

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2016-015439.R2
Article Type:	Protocol
Date Submitted by the Author:	04-Apr-2017
Complete List of Authors:	López-Cortés, Luis Eduardo; Hospital Universitario Virgen Macarena, Enfermedades Infecciosas y Microbiología Clínica Rosso-Fernández, Clara; Hospital Universitario Virgen del Rocío, Unidad de Ensayos clínicos; Hospital Universitario Virgen del Rocío, Farmacología Clínica Núñez-Núñez, María; Instituto de Biomedicina de Sevilla (IBiS)/Hospital Universitario Virgen Macarena /CSIC/Universidad de Sevilla. Sevilla, Spain., Unidad Clínica de Enfermedades Infecciosas, Microbiología y Medicina Preventiva; Hospital Universitario Virgen Macarena, Unidad Clínica de Farmacia Lavín-Alconero, Lucía; Hospital Universitario Virgen del Rocío, Unidad de ensayos clínicos Bravo-Ferrer, José; Hospitales Universitarios Virgen Macarena y Virgen del Rocío, Unidad de Gestión Clínica de Enfermedades Infecciosas, Microbiología y Medicina Preventiva Barriga, Ángel; Hospital Universitario Virgen del Rocío, Unidad de ensayos clínicos Delgado, Mercedes; Hospital Universitario Virgen Macarena, Microbiología Clínica Lupián, Carmen; Hospital Universitario Virgen Macarena, Enfermedades Infecciosas y Microbiología Clínica Retamar, Pilar; Hospital Universitario Virgen Macarena, Enfermedades Infecciosas y Microbiología Clínica Rodríguez-Baño, Jesús; Hospital Universitario Virgen Macarena,
Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Medical management
Keywords:	De-escalation, Enterobacteriaceae, bloodstream infection, broad-spectrum antibiotics, antimicrobial stewardship

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Manuscripts

For peer review only

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3 1 Title: Targeted simplification versus antipseudomonal broad-spectrum beta-
4 lactams in patients with bloodstream infections due to *Enterobacteriaceae*
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6 2 lactams in patients with bloodstream infections due to *Enterobacteriaceae*
7
8 3 (SIMPLIFY): a study protocol for a multicenter, open-label, phase III
9
10 4 randomized, controlled, non-inferiority clinical trial
11
12 5

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25

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11 30 **ABSTRACT**

12 31 **Introduction:** Within the context of antimicrobial stewardship programs, de-
13
14 32 escalation of antimicrobial therapy is one of the proposed strategies for
15
16 33 reducing the unnecessary use of broad-spectrum antibiotics (BSA). The
17
18 34 empirical treatment of nosocomial and some health-care associated
19
20 35 bloodstream infections (BSI) frequently includes a beta-lactam with
21
22 36 antipseudomonal activity as monotherapy or in combination with other drugs, so
23
24 37 there is a great opportunity to optimize the empirical therapy based on
25
26 38 microbiological data. De-escalation is assumed as standard-of-care for experts
27
28 39 in infectious diseases; However, it is less frequent than it would be desirable.
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32 40 **Methods and analysis:** The SIMPLIFY trial is a multicenter, open-label, non-
33
34 41 inferiority phase III randomized controlled clinical trial, designed as a pragmatic
35
36 42 'real-practice' trial. The aim of this trial is to demonstrate the non-inferiority of
37
38 43 de-escalation from an empirical beta-lactam with antipseudomonal activity to a
39
40 44 targeted narrow-spectrum antimicrobial in patients with BSI due to
41
42 45 *Enterobacteriaceae*. The primary outcome is clinical cure, which will be
43
44 46 assessed at the test of cure visit. It will be conducted at 19 Spanish public and
45
46 47 university hospitals.
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49 48 **Ethics and dissemination:** Each participating center has obtained the
50
51 49 approval of the Ethics Review Committee, the agreement of the Directors of the
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53 50 Institutions, and authorization from the Spanish Regulatory Agency (AEMPS,
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3 51 Agencia Española del Medicamento y Productos Sanitarios). Data will be
4
5 52 presented at international conferences and published in peer-reviewed journals.
6

7 53 **Discussion:** Strategies to reduce the use of BSA should be a priority. Most of
8
9 54 the studies that support de-escalation are observational, retrospective, and
10
11 55 heterogeneous. A recent Cochrane review stated that well-designed clinical
12
13 56 trials should be conducted to assess the safety and efficacy of de-escalation.
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18 58 **REGISTRATION**

19
20 59 The European Union Clinical Trials Register: EudraCT number 2015-004219-
21
22 60 19.

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24 61 Clinical Trials.gov: NCT02795949

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26 62 Protocol version: V.2.0, dated 16 May 2016.
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31 63

32 64 All items from the World Health Organization Trial Registration Data Set are
33
34 65 included in the registry.
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38 67 **STRENGTHS OF THIS STUDY**

39
40 68 • It will be the first trial on de-escalation specifically in patients with
41
42 69 bacteremia due to *Enterobacteriaceae*.

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44 70 • It will include patients independently of the source of bacteraemia or
45
46 71 severity of clinical presentation.
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49 72 • A remote automatic randomisation system and external evaluation by
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51 73 blinded investigators were used to avoid bias.
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54 74 • It has been designed with daily clinical practice in mind.
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3 76 **LIMITATIONS OF THIS STUDY**
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- 5 77 • The open-label design is theoretically more prone to bias.
6
7 78 • Switching to oral therapy could potentially reduce the number of days in
8
9
10 79 which patients are assigned to one or other arm.
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12 80

13
14 81 **KEYWORDS:**

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16 82 De-escalation, *Enterobacteriaceae*, bloodstream infection, broad-spectrum
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18 83 antibiotics, antimicrobial stewardship.
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3 85 **BACKGROUND**
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7 87 The worldwide spread of antimicrobial resistance is recognised as a current
8
9 88 global public health threat. The implementation of stewardship programs for
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11 89 optimizing antibiotic use has been shown both to improve antibiotic use and
12
13 90 also to help combat antimicrobial resistance [1]. Streamlining or de-escalation of
14
15 91 antimicrobial therapy is a strategy proposed to reduce the unnecessary use of
16
17 92 broad-spectrum antimicrobials (BSA) [1,2]. This can be carried out by changing
18
19 93 from combination therapy to monotherapy or by replacing the empirical
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21 94 antibiotic with one with a narrower spectrum of activity, irrespective of the
22
23 95 microbiology results [1].
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26

27 96 Bloodstream infections (BSI) are known to be major causes of morbidity and
28
29 97 mortality. They represent suitable organisms for carrying out a de-escalation
30
31 98 strategy because they are very frequent, a high proportion of patients are
32
33 99 treated with BSA and the susceptibility of the causative organisms is known.
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35

36 100 The *Enterobacteriaceae* as a group, is the most common cause of community-
37
38 101 and nosocomial BSI, with a crude associated mortality of around 15% [3]. The
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40 102 empirical treatment for nosocomial and some healthcare-associated BSI
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42 103 frequently includes a beta-lactam antibiotic with antipseudomonal activity in
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44 104 monotherapy or in combination. This imposes strong selection pressure,
45
46 105 particularly on *Pseudomonas aeruginosa* isolates, and maybe selecting
47
48 106 multidrug resistant *Enterobacteriaceae* isolates. De-escalation according to
49
50 107 microbiological results is assumed as standard-of-care by most infectologists;
51
52 108 however, the reality is that de-escalation is much less frequent than is desirable
53
54 109 [4,5]. Some of the possible reasons for this phenomenon [6-8] include the fact
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3 110 that the safety and efficacy of this treatment strategy are based only on a few
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5 111 observational studies [9,10] and expert recommendations [11,12]. This was
6
7 112 supported by a recent Cochrane review [13] conducted among adults with
8
9 113 sepsis, severe sepsis or septic shock, whose authors concluded that there is no
10
11 114 adequate direct evidence that de-escalation of antimicrobial agents is effective
12
13 115 and safe in this scenario. Randomized clinical trials of their safety and efficacy
14
15 116 are needed, in order to establish “proof of concept” and help make clinical
16
17 117 decisions.
18
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21 118

22 119 **METHODS/DESIGN**

23 120

24 121 **Study hypothesis**

25 122 The aim of the trial is to demonstrate that de-escalation from empirical therapy
26
27 123 with an antipseudomonal beta-lactam to a targeted therapy is as effective and
28
29 124 safe in patients with BSI due to *Enterobacteriaceae* as continuing with the
30
31 125 empirical regimen.
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39 127 **Design**

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41 128 The SIMPLIFY trial is a multicenter, open-label, phase III randomized
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43 129 controlled clinical trial, powered to demonstrate the non-inferiority of de-
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45 130 escalation with respect to continuing with the antipseudomonal agent and
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47 131 designed as a real-world pragmatic trial. It was developed in accordance with
48
49 132 an extension of the SPIRIT statement for reporting non-inferiority, superiority
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51 133 and equivalence trials [14,15].
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3 135 **Participants and settings**
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5 136 The trial will be conducted at 19 public and tertiary Spanish hospitals with the
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7 137 support of the Spanish Network for Research in Infectious Diseases
8
9 138 (REIPI) and the Spanish Clinical Research Network (SCReN). Thirteen of
10
11 139 them are University hospitals. Patients will be evaluated for eligibility
12
13 140 once *Enterobacteriaceae* is isolated from blood cultures and
14
15 141 susceptibility data are available. Detection of eligible patients will be by
16
17 142 daily review of blood culture results by Infectious Disease specialists
18
19 143 from the bacteremia team at each center. To be enrolled, participants will
20
21 144 need to fulfill all inclusion and exclusion criteria (Table 1) plus give
22
23 145 written informed consent (the patient or a legally authorized
24
25 146 representative).
26
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32 148 **Table 1. Inclusion and exclusion criteria**
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34 **Inclusion criteria**

- 35
36 1. Written informed consent has been obtained from the patient or the
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38 legally authorised representative.
39
40 2. Age \geq 18 years, not legally incapacitated.
41
42 3. Hospitalised patients with monomicrobial bacteremia due to
43
44 *Enterobacteriaceae* from any source.
45
46 4. The patient has received active empiric antibiotic therapy with an
47
48 antipseudomonal beta-lactam (imipenem, meropenem, piperacillin-
49
50 tazobactam, cefepime, ceftazidime, aztreonam), alone or in combination
51
52 with another antimicrobial agent, which started in the first 24 hours after
53
54 the first positive blood culture was taken.
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5. The isolate is susceptible to at least one of antibiotics included in the experimental arm.
6. Intravenous antimicrobial treatment is planned for at least 5 days once *Enterobacteriaceae* is isolated from the blood culture.

Exclusion criteria

1. Life expectancy <30 days.
2. Pregnancy or nursing. For included women: failure to use a highly effective contraceptive method.
3. Isolation of carbapenemase-producing *Enterobacteriaceae* (because most hospitals do not use monotherapy in these cases).
4. Inclusion is delayed >48 h after susceptibility data of the isolate are available.
5. Severe neutropenia (<500 cells/mm³) on the day of randomization.
6. Planned duration of treatment >28 days (e.g. osteomyelitis, endocarditis).

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151 Randomization

152 Stratified randomization in a 1:1 ratio will be achieved using a centralized, web-
153 based automated randomization system integrated with the eCRF (electronic
154 Case Report Form) to manage assignment to the treatment arms. A copy of the
155 randomization list will be kept in a safe place in case technical problems arise.
156 The only criterion for stratification will be source of bloodstream infection
157 (urinary tract vs any other) in order to ensure that the percentage of patients
158 with urinary tract infections is similar in the two groups being compared. To

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3 159 guarantee an appropriate allocation concealment in an open trial, randomization
4
5 160 will not be stratified by site.
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9 162 **Intervention**

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11 163 A decision tree of enrolment to the study is included in Figure 1. As stated
12
13 164 above, all included patients will already be receiving an antipseudomonal beta-
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15 165 lactam (meropenem, imipenem, piperacillin-tazobactam, cefepime, ceftazidime
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17 166 or aztreonam) before randomization occurs. Patients will be allocated to one of
18
19 167 the following treatment arms:
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25 169 Experimental group:

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27 170 The patient will change to an intravenous therapy with an active narrow-
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29 171 spectrum antibiotic according to the susceptibility results (EUCAST or CLSI
30
31 172 criteria); the antibiotic will be chosen in the following order (the first active drug
32
33 173 will be used): (1) ampicillin, 2 g q6h; (2) trimethoprim/sulfamethoxazole,
34
35 174 160/800 mg q8-12h; (3) cefuroxime, 750-1500 mg q8h; (4) cefotaxime 1-2g q8h
36
37 175 or ceftriaxone, 1 g q12-24h; (5) amoxicillin/clavulanate, 1g/125 mg q8h; (6)
38
39 176 ciprofloxacin, 400 mg q12h; and (7) ertapenem, 1g q24h.
40
41 177 Trimethoprim/sulfamethoxazole will only be used in urinary tract infections in the
42
43 178 absence of an undrained renal abscess. Ciprofloxacin is included because,
44
45 179 apart from being active against *P. aeruginosa*, it is not a beta-lactam.
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51 181 Control group:

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53 182 Continuation of the antipseudomonal beta-lactam that was being administered
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55 183 on an empirical basis: meropenem, 1-2 g q8h; imipenem, 0.5-1g q6h;
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3 184 piperacillin-tazobactam, 4/0.5 g q6-8h; cefepime, 2 g q8-12h; ceftazidime, 1-2 g
4
5 185 q8h; and aztreonam, 1-2 g q8h.

6
7 186

8
9 187 Exceptions to the above rule:

10 188 Third-generation cephalosporins should be avoided where there are inducible

11 189 AmpC β -lactamase-producing *Enterobacteriaceae* (*Enterobacter* spp.,

12 190 *Providencia* spp., *Morganella morganii*, *Serratia marcescens*, and *Citrobacter*

13 191 *freundii*); hence, even if the isolates are strictly susceptible, for patients in the

14 192 control group, ceftazidime may be changed to any other antipseudomonal beta-

15 193 lactam on the day of randomization. For patients allocated to the experimental

16 194 arm, the options will be limited to trimethoprim/sulfamethoxazole, ciprofloxacin

17 195 or ertapenem.

18 196 ESBL producers could be included in the study based on attending physician's

19 197 criteria; in this cases, maximum doses of susceptible antibiotics are

20 198 recommended.

21 199

22 200 Dose adjustment

23 201 Due to the nature of the study design as a real-world clinical practice trial,

24 202 antimicrobial dosage will be as deemed by the treating clinician, dependent on

25 203 pharmacokinetic and pharmacodynamic (PK/PD) characteristics (such as higher

26 204 doses for septic shock or high body mass). Dose adjustment will be made for all

27 205 drugs as necessary in the case of renal or hepatic dysfunction, following

28 206 Summary of Product Characteristics (SmPC) recommendations.

29 207

30 208 Concomitant therapy

1
2
3 209 Even if the BSI is monomicrobial, the attending physician may consider the
4
5 210 infection to be polymicrobial at source. If additional anaerobic or gram-positive
6
7 211 coverage is needed, concomitant use of oral metronidazole, clindamycin,
8
9 212 vancomycin, teicoplanin, daptomycin or linezolid is allowed in both arms.
10
11 213 Concomitant treatment with any other systemic antibiotic with intrinsic activity
12
13 214 against gram-negative bacilli is not allowed. The administration of any of these
14
15 215 drugs while the patient is receiving the study drug will be deemed a criterion for
16
17 216 withdrawal. There are no absolute contraindications for the use of any other
18
19 217 drug during the study. However, contraindications, warnings and precautions for
20
21 218 use and possible interactions with study drugs are to be taken into account.
22
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26 219

27 220 Duration of therapy

28
29 221 The appropriate duration of therapy is considered to be between 7 and 14 days,
30
31 222 according to the attending physician's criteria. Treatments lasting longer than
32
33 223 14 days will be allowed only when there is an undrained abscess present, in
34
35 224 which case, a 4-week treatment is permitted.
36
37
38

39 225

40 226 Route of administration

41
42 227 Switching to oral therapy is allowed after the third day of therapy after
43
44 228 randomisation if all the following conditions are fulfilled: clinical improvement
45
46 229 has been achieved, absence of fever ($>38^{\circ}\text{C}$), hemodynamic stability, adequate
47
48 230 control of the source of BSI and absence of secondary foci, adequate oral
49
50 231 intake, and no gastrointestinal conditions that might compromise drug
51
52 232 absorption.
53
54

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56 233 For patients in the experimental group, switching to oral therapy is allowed with
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1
2
3 234 the same intravenous drugs as follows: trimethoprim/sulfamethoxazole 160/800
4
5 235 mg q8 -12h, cefuroxime axetil 500 mg q8-12h, amoxicillin/clavulanate 875/125
6
7 236 mg q8h, or ciprofloxacin 500 mg q12h. If the intravenous drug is ampicillin,
8
9 237 amoxicillin 1 g q8h will be used; if cefotaxime or ceftriaxone, then ceftibuten 400
10
11 238 mg q12-24h or cefixime 400 mg q12-24h will be used; if ertapenem, this drug
12
13 239 may be switched to the intramuscular route.

14
15
16 240 For patients in the control group, the preferred oral option is ciprofloxacin 500
17
18 241 mg q12h for all patients. The protocol allows treatment with cefuroxime-axetil
19
20 242 500 mg q8-12h or cefixime 400 mg q12-24h only in cases of resistance to
21
22 243 ciprofloxacin; finally, parenteral ertapenem 1g q24h may be used for
23
24 244 convenience if the isolate is resistant to all other oral options.

25
26
27 245

28
29 246 Rescue medication

30
31 247 No rescue medication is planned on behalf of the study if a patient has to
32
33 248 withdraw from the trial for any reason; the attending physician will follow clinical
34
35 249 guidelines for routine clinical practice and GCP (Good clinical practice) rules.

36
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38 250

39
40 251 Medication

41
42 252 As all the study drugs are recommended for BSI caused by *Enterobacteriaceae*,
43
44 253 the sponsor will not provide the study drugs [16]. Every site participating in the
45
46 254 study is authorised to use the drugs through the normal provision of its hospital
47
48 255 pharmacy.

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51 256

52
53 257 **Schedule of visits**

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56 258 Patients included in the study will be followed for 60 days (\pm 5 days) after
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3 259 diagnosis of the BSI (Figure 2). Follow-up will be organised in seven planned
4
5 260 visits at day 0 (baseline), day 1; day 3-5; day 7-14 (end of treatment); day 3-5
6
7 261 from end of treatment (test of cure, TOC); day 30 ± 5; and day 60 ± 5. Visits at
8
9 262 days 30 and 60 may be made by telephone.

10
11 263 The visit schedule is planned so as to obtain data on clinical status, sample
12
13 264 collection, efficacy and safety variables, and adverse events. At the final
14
15 265 evaluation at 60 days, data on all outcome variables will be gathered.
16
17 266 Additionally, data will be collected at unplanned visits, with special
18
19 267 consideration given to the occurrence of any adverse event or recurrence.
20
21
22

23 268

24 269 **Outcomes**

25
26
27 270 The primary outcome is clinical cure, which will be assessed at the TOC visit (3-
28
29 271 5 days after the end of antibiotic treatment). Death during treatment, change of
30
31 272 antibiotic therapy due to clinical failure, or need to prolong the treatment will be
32
33 273 considered as failures (Table 2). Secondary outcomes include early (5 days
34
35 274 after end of treatment) and late (60-day) clinical and microbiological response,
36
37 275 all-cause mortality (days 7, 14, and 30), length of hospital stay, recurrence rates
38
39 276 (relapse or reinfection) (day 60), safety of antibiotic treatment, including
40
41 277 *Clostridium difficile* infections and number of antibiotic treatments with an
42
43 278 antipseudomonal beta-lactam; in a subgroup of patients, the rate of intestinal
44
45 279 colonization by *P. aeruginosa* resistant to carbapenemase or piperacillin /
46
47 280 tazobactam, *Stenotrophomonas* spp., multiresistant *A. baumannii* and
48
49 281 enterobacteria producing ESBL, carbapenemase and chromosomal AmpC
50
51 282 (hyperproduction) or plasmid will be sought. Some of these secondary
52
53 283 outcomes will be analyzed as composite variables, following the DOOR/RADAR
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284 methodology. Outcome definitions, assessment, and time frames for
 285 measurement are described in

286 **Table 2. Outcome definitions and time frames**

Primary End Point and Time Frame	Definition and Assessment
CLINICAL CURE Day 3-5 after treatment*	TOC, the situation where all the following conditions are met: survival at the time of the evaluation; complete resolution of all symptoms and signs of infection (or return to the situation prior to current infection); no need for prolonged antibiotic treatment beyond the recommended duration* and no need for treatment modification due to unfavorable clinical response.
*7-14 days according to IDSA, except in the presence of undrained or late-draining abscesses, when up to 4 weeks are allowed.	
Secondary End Point and Time Frame	Definition and Assessment
CLINICAL RESPONSE After 5 days of treatment (early response)	Same as clinical cure

Until Day 60 of follow-up (late response)	
MICROBIOLOGICAL CURE After 5 days of treatment (early response) Until Day 60 of follow-up (late response)	Negative blood cultures and where applicable, negative cultures from samples taken from initial infection focus. 'PRESUMPTIVE MICROBIOLOGIC CURE' is accepted in those cases where it is not possible to prove the negativization of isolates from initial focus.
ALL-CAUSE MORTALITY 7, 14 and 60-day of follow-up	Death for any reason
LENGTH OF HOSPITAL STAY	Time from randomisation to hospital discharge
CLINICAL RECURRENCE (RELAPSE OR REINFECTION) RATES 60-day of follow-up	Recurrence of at least one clinical and one analytical sepsis criterion, with presence or absence of bacteraemia
MICROBIOLOGICAL RECURRENCE (RELAPSE OR REINFECTION) RATES 60-day of follow-up	New BSI episode with the same isolate as initial cultures with previously clinical and microbiological cure

<p>NUMBER OF DAYS OF APBL AVOIDED</p> <p>Until end of treatment</p>	<p>Number of days of antibiotic treatment with an antipseudomonal beta-lactam (APBL) avoided</p>
<p>ECOLOGICAL IMPACT</p> <p>7-14,12-21,30 days</p>	<p>Intestinal colonization by multidrug-resistant Gram-negative bacilli</p>
<p>SAFETY OF DRUGS - adverse events</p> <p>Until Day 60 of follow-up</p>	<p>Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related.</p>
<p>COMPOSITE SECONDARY VARIABLES</p> <p>7-14, 60-day follow up</p>	<p>Survival on day 14, number of days with an antipseudomonal beta-lactam avoided, presence or absence of side effects, including <i>C. difficile</i> infections, secondary MDRO infections and all drug-related adverse events</p>

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288

289 **Data collection, management and monitoring**

290 The coordinating center for this study is the Hospital Universitario Virgen

291 Macarena, Seville, Spain, and the Clinical Trials Unit (CTU-Hospital

292 Universitario Virgen del Rocío) has delegated sponsor functions on behalf of

1
2
3 293 the Fundación Pública Andaluza para la Gestión de la Investigación en Salud
4
5 294 de Sevilla (FISEVI - <http://www.fisevi.com>). Clinical research associates (CRAs)
6
7 295 connected to the Spanish Clinical Research Network (SCReN) in public
8
9 296 hospitals will carry out monitoring activities. Data collection will be conducted by
10
11 297 trained staff at each participating center and entered into a restricted access
12
13 298 electronic case report form (eCRF). These forms will be available at the eCRF
14
15 299 web platform. Outstanding queries regarding the completion of the CRF will be
16
17
18 300 sent to all participating centers as necessary to ensure accuracy of data.
19

20
21 301 In order to avoid any association with personal data, all study samples will be
22
23 302 anonymous and identifiable only by the patient's alphanumeric study code. The
24
25 303 objective and management of these samples are included in the patient's
26
27 304 information sheet and informed consent form.

28
29 305 The quality of all data collected will be carefully supervised by the CTU and
30
31 306 specific visits for source data verification are organized according to the
32
33 307 monitoring plan. Furthermore, in order to minimize bias, at the interim analysis
34
35 308 (when 50% of the sample has been included), an independent committee (3
36
37 309 independent investigators from the REIPI) blinded to treatment assignment will
38
39 310 review all accumulated data. This committee will advise the sponsor on the
40
41 311 appropriateness of continuing the clinical trial as designed.
42
43
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45 312

46 313 **Isolates**

47
48 314 All isolates will be sent to the central laboratory in the Hospital Universitario
49
50 315 Virgen Macarena in Seville for susceptibility testing using reference methods
51
52 316 and PCR characterisation and sequencing if necessary.
53
54

55 317 Eight selected hospitals will participate in the study of rectal carriage of ESBL-

1
2
3 318 AmpC- and carbapenemase-producing *Enterobacteriaceae*, by taking rectal
4
5 319 swabs from participants at different times (as set out in the schedule of visits).
6
7 320 To do this, samples will be taken by rectal swab from the patients of both
8
9 321 treatment arms on the day of randomization, the day when treatment finish, the
10
11 322 day of test of cure, and visit of day 30. The presence of *P. aeruginosa* resistant
12
13 323 to carbapenemase or piperacillin / tazobactam, *Stenotrophomonas* spp.,
14
15 324 multiresistant *A. baumannii* and enterobacteria producing ESBL,
16
17 325 carbapenemase and chromosomal AmpC (hyperproduction) or plasmid will be
18
19 326 sought. A written consent form for samples, approved by the ECs (Ethics
20
21 327 Committees), is also provided for the study.
22
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328

329 **Definition of analysis population and outcome measures**

330 The following populations will be considered: the intention-to-treat population
31
32 331 (ITTP) includes all randomized patients; the modified ITTP (mITTP) includes
33
34 332 randomized patients who have received at least one dose of intravenous
35
36 333 antibiotics; the clinically evaluable population (CEP) includes patients who have
37
38 334 completed 5 days of the intravenous study drug, or who die but have received
39
40 335 at least one dose of intravenous antibiotics. The clinically and microbiologically
41
42 336 evaluable population (CMEP) includes those in the CEP who have had
43
44 337 microbiological tests (at least one blood culture 48 hours after randomization).
45

46
47 338 The local principal investigator in the centre where the patient was included will
48
49 339 assess the primary outcome (clinical cure) in the clinically evaluable population
50
51 340 (CEP) at TOC. Due to the intrinsic characteristics of the primary outcome (soft
52
53 341 outcome) and the study methodology (non-blinded), this evaluation done will be
54
55 342 reviewed later on the basis of clinical data recovered on two occasions by an
56
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3 343 external blinded investigator: firstly, during the interim analysis to monitor
4
5 344 safety; secondly before the complete cleaning and closure of the eCRF. For
6
7 345 secondary end points, the CMEP will be eligible for early (day 5) and late (day
8
9 346 60) microbiological responses, the m-ITTP for all-cause mortality and length of
10
11 347 hospital stay, and the CEP for the evaluation of recurrence rates and drug
12
13 348 safety.
14

15
16 349

17 18 350 **Sample size**

19
20 351 The sample size was calculated using Epidat 4.0. Some of the data used to
21
22 352 calculate it was derived from the study published by Retamar *et al* [17].
23
24 353 Assuming estimated clinical cure rates of 85% in both groups, a non-inferiority
25
26 354 margin of 10% difference between the 2 groups, and treatment assignment in a
27
28 355 1:1 ratio, 344 patients in total (172 per study arm) are needed to achieve 80%
29
30 356 power with a significance level of 5%. This allows for a 5% dropout rate. The
31
32 357 10% non-inferiority margin was chosen as in recent trials of complicated urinary
33
34 358 tract and intraabdominal infections [18,19].
35
36 359

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39 360

40 360 **Statistical analysis**

41
42 361 Absolute differences will be calculated with 95% confidence intervals for the
43
44 362 clinical cure rate between the two arms of the study at TOC. Multivariate
45
46 363 analysis using logistic regression for the main outcome will be performed in
47
48 364 order to ensure the independence of the treatment effect. Special consideration
49
50 365 will be given in the multivariate analysis to the center of origin of the study
51
52 366 sample. A Cox regression analysis of mortality until 60 days will be performed
53
54 367 on the mITTP. For the superiority analysis, logistic regression will be used
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3 368 sequentially, using the methodology recently published by Evans et al [20] for
4
5 369 the composite variable (DOOR and RADAR analysis using survival at day 14,
6
7 370 number of days of antipseudomonal beta-lactam treatment avoided, presence
8
9 371 or absence of side effects, including *C. difficile* infections, secondary MDRO
10
11 372 infections, and all drug-related adverse events). Antimicrobial doses are not
12
13 373 fixed and sensitivity analyses will therefore be applied to control potential bias.
14
15

16 374

17 18 375 **Protocol violations**

19
20
21 376 All protocol violations occurring after randomization will be listed in the Clinical
22
23 377 Study Report, tabulated by subject and by recruitment center.
24

25 378

26 27 379 **ETHICS AND DISSEMINATION**

28
29 380 Each of the participating centers has obtained the approval of an Ethics
30
31 381 Review Committee, the agreement of the Directors of the Institutions (who
32
33 382 signed the contract of agreement with the sponsor of the study) and
34
35 383 authorisation from the Spanish Regulatory Agency (AEMPS, Agencia Española
36
37 384 del Medicamento y Productos Sanitarios). All the patients have to sign the
38
39 385 informed consent previous to the randomization (Supplementary data). Patients
40
41 386 may withdraw from the study at any time without prejudice, as is documented
42
43 387 and explained at the time of providing consent. The study will be carried out
44
45 388 according to the principles of the Declaration of Helsinki, and Directive
46
47 389 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on
48
49 390 the harmonization of the laws, regulations and administrative provisions of the
50
51 391 Member States relating to the implementation of Good Clinical Practice in the
52
53 392 conduct of clinical trials on medicinal products for human use until the
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3 393 new Clinical Trials Regulation (CTR) EU No 536/2014 becomes applicable,
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5 394 which will be no earlier than 28 May 2016. The confidentiality of records that
6
7 395 might identify subjects in this study will be protected in accordance with EU
8
9 396 Directive 2001/20/EC. All laws for the control and protection of personal
10
11 397 information will be carefully followed. The identities of patients will not be
12
13 398 disclosed in the e-CRF; names will be replaced by an alphanumeric code and
14
15 399 any material related to the trial, such as samples, will be identified in the same
16
17 400 way, so that no personal information will be revealed.
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20
21 401 Regarding to the dissemination plan, three communications with preliminary
22
23 402 clinical data to national and international conferences (ASM/IDSA or ECCMID)
24
25 403 are proposed during the second year of the study. For the third year, a further
26
27 404 presentation will be given at a national conference, and two other presentations
28
29 405 at international conferences with final or advanced data. Once we obtain the
30
31 406 final results of the study, at least three publications are expected: one in a D1
32
33 407 journal and two in Q1 journals.
34
35

36 408

37 38 409 **DISCUSSION**

39
40 410 The extensive use of BSA and the dramatic increase in infections due to
41
42 411 multidrug-resistant organisms are forcing the scientific community to look for
43
44 412 strategies to combat this situation. In the real world, the application of de-
45
46 413 escalation to serious infections is less frequent than is desirable. The
47
48 414 arguments against de-escalation include: (1) the MIC of some narrow-spectrum
49
50 415 drugs are closer to susceptibility breakpoints than carbapenems, for example,
51
52 416 and some physicians may therefore feel safer using the latter; (2)
53
54 417 subpopulations resistant to narrow-spectrum drugs may be selected and appear
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3 418 after some days of empirical treatment, leading to treatment failure in case of
4
5 419 de-escalation; (3) in the case of polymicrobial infections, it is not uncommon for
6
7 420 only one of the pathogens to be isolated in blood cultures, so that simplification
8
9 421 of treatment may be less safe and effective than a broad-spectrum treatment;
10
11 422 (4) there is some doubt about the real effectiveness of certain drugs against
12
13 423 isolates producing specific mechanisms of resistance. Furthermore, although it
14
15 424 is assumed that BSA has a greater impact on the selection of multidrug-
16
17 425 resistant strains, some studies suggest that it may depend more on the duration
18
19 426 of the treatment than the spectrum [16]. While none of these arguments have
20
21 427 been proven, it is also true that there is no strong evidence for the safety of de-
22
23 428 escalation strategies in these scenarios.

24
25
26
27 429 To the best of our knowledge, three randomized trials on de-escalation
28
29 430 strategies, none of them specifically focused on bacteremia, have been
30
31 431 published, which show significant differences from this study [21-23]. The one
32
33 432 published by Falguera *et al* [22] compared the efficacy of empirical versus
34
35 433 targeted treatment on the basis of urine antigen results in hospitalized patients
36
37 434 with community-acquired pneumonia. The article published by Kim *et al* [23]
38
39 435 evaluated the efficacy of early use of imipenem/cilastatin and vancomycin
40
41 436 followed by de-escalation versus conventional antimicrobials without de-
42
43 437 escalation for patients with hospital-acquired pneumonia in ICUs. The last one,
44
45 438 published recently by Leone *et al* [24], included a limited number (n=116) of
46
47 439 ICU-admitted patients with severe sepsis; Its primary outcome was duration of
48
49 440 ICU stay, and not effectiveness of both treatment strategies. In that study, de-
50
51 441 escalation followed the recommendations of guidelines, not a pre-specified
52
53 442 protocol based on the clinical impact of the antibiotics. There was no significant
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3 443 difference in mortality, although unexpectedly, patients in the experimental arm
4
5 444 had a higher rate of superinfections (27% vs 11%, $P = 0.03$). These results
6
7 445 contrast with a recent systematic review and meta-analysis that included 25
8
9 446 studies with data on de-escalation based on culture results, which showed a
10
11 447 significant reduction in the relative risk of death (RR 0.44, 95% CI: 0.30–0.66;
12
13 448 $p < 0.0001$). It is important to note that many of the included studies in the meta-
14
15 449 analysis were observational, retrospective and had a high degree of
16
17 450 heterogeneity [25].

18
19
20 451 Several authors have warned about the considerable inconsistencies in
21
22 452 definitions of de-escalation. In 2015, Weiss *et al* [26] elaborated a consensual
23
24 453 definition of de-escalation that allowed beta-lactams to be ranked according to
25
26 454 both their spectra and their ecological impact. The authors underlined
27
28 455 the difficulty of reaching consensus on the relative ecological impact of each
29
30 456 individual drug. In 2014, Madaras-Kelly *et al.* [27] used the Delphi approach to
31
32 457 develop an antibiotic spectrum score to measure de-escalation. We shall
33
34 458 therefore include both concepts in our analysis, using Outcome Ranking
35
36 459 (DOOR) and Response Adjusted for Duration of Antibiotic Risk (RADAR)
37
38 460 analyses [20].

39
40 461 Switching from intravenous to oral therapy as soon as the patient is clinically
41
42 462 stable can reduce the risk of adverse events related to intravenous therapy,
43
44 463 length of hospitalization, and cost. It can be applied regardless of the source of
45
46 464 infection and underlying conditions whenever a good option that achieves the
47
48 465 PK/PD targets is available [28]. In our study, switching to oral therapy is allowed
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50 466 in both arms to avoid exposing patients in the control arm to unnecessary risks.
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3 467 The SIMPLIFY trial has several strengths. In the first place, it will be the first trial
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5 468 on de-escalation specifically in patients with bacteremia due to
6
7 469 *Enterobacteriaceae*. Second, it will include patients independently of the source
8
9 470 of bacteraemia or severity of clinical presentation. Third, it was designed with
10
11 471 daily clinical practice in mind. We hope that, if there is reasonable evidence to
12
13 472 reject the null hypothesis, it will encourage implementation of this type of
14
15 473 strategy in daily practice.
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475 **TRIAL STATUS**

- 476 • Funding for the study was approved on 15/08/2015 and available for
477 study expenses in 01/01/2016.
- 478 • EC approval for the 19 sites included was obtained on 15th March 2016.
- 479 • Authorization from the Spanish Regulatory Authority was obtained on
480 18th March 2016.
- 481 • The study has been approved for a recruitment period of 2 years.
- 482 • Dissemination of results directed to patients will be channeled through
483 the Spanish Clinical Studies Registry (Agencia Española del
484 Medicamento y Productos Sanitarios), whose content is adapted to
485 patients.

486

487 **SPONSOR INFORMATION**

488 Name: Fundación Pública Andaluza para la Gestión de la Investigación en
489 Salud de Sevilla (FISEVI).

490 Contact: claram.rosso.sspa@juntadeandalucia.es

491

1
2
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4
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6
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14
15 498 Clinical Research Network and funded by ISCII: study number 16.001.
16
17
18
19

20
21 499

22 500 **ROLE OF THE STUDY SPONSOR/ FUNDING SOURCE**

23 501 The sponsor and funders of the study had no role in the study design or in
24
25 502 manuscript development.
26

27 503

28
29 504 **COMPETING INTERESTS ESTATEMENT**

30
31 505 The authors have no competing interests to declare.
32
33

34 506

35
36 507 **CONTRIBUTORSHIP STATEMENT**

37
38 508 JR-B and LEL-C were responsible for formulating the overall research questions
39
40 509 and for the methodological design of the study. CR-F, BA and LL-A collaborated
41
42 510 in the submission of the project for the Spanish funding, and collaborated in the
43
44 511 methodological aspects of the study. JR-B is the coordinating investigator and
45
46 512 leader of the Coordination Team. CR-F is responsible for the CTU. MN-N
47
48 513 collaborated with writing of the manuscript and with the pharmacovigilance
49
50 514 design, and JB-F, PR-G, and CL collaborated in the organisation of the study.
51
52 515 MD contributed in all the microbiological details of the study. JR-B and LEL-C
53
54 516 participated in its design and supervised the project. All authors read and
55
56
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3 517 approved the final manuscript.
4

5 518
6

7 519 **DATA SHARING STATEMENT**
8

9 520 No additional unpublished data from the study are available
10

11 521
12

13
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34 532 Universitario de Cruces, Barakaldo); ; G. Bou and I. Torres (Hospital
35

36 533 Universitario A Coruña); S. Pérez-Cortés and M.D. López-Prieto (Hospital
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38 534 Universitario de Jerez); B. Loeches and M. Romero (Hospital Universitario La
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40 535 Paz, Madrid); M. Ibarguren, M. A. Goenaga-Sánchez and J. M. García-
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42 536 Arenzana (Hospital Universitario Donostia); J. R. Yuste and J. Leiva-León
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44 537 (Clínica Universitaria de Navarra); A. Salas-Aparicio and C. de las Cuevas
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46 538 (Hospital Universitario La Princesa, Madrid); J.M. Guerra-Laso and I.
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48 539 Fernández-Natal (Complejo Asistencial Universitario de León); M. T. Pérez and
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50 540 F. Vasallo (Xerencia de Xestión Integrada de Vigo); G. Cuervo and C. Ardanuy
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9 545 Universitario Virgen Macarena).
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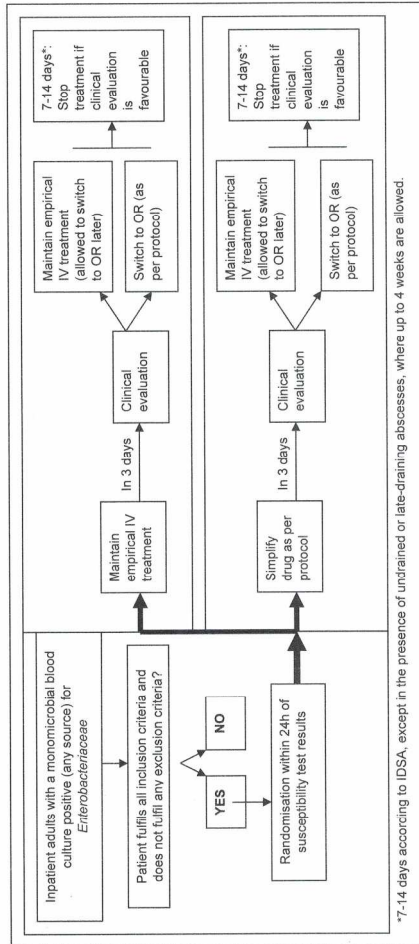
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645 Figure 1. SIMPLIFY – Decision tree of patient enrolment
646 Figure 2. Schedule of visits and assessments. Except where otherwise
647 specified, these refer to days from randomization.
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Figure 1.



203x290mm (300 x 300 DPI)

Figure 2.

Procedures	Selecti on visit (Day 0)	Visit 1 (Day 1)	Visit 2 (Day 3-5)	End of treatment (Day 7-14) ^{2,3}	Test of cure (Day 12-21) ¹	Follow-up visit (Day 30±5) ²	End of study (Day 60) ²
Randomization	X						
Informed consent	X						
Check in/exclusion criteria	X						
Pregnancy test	X						
Demographic data/ medical history	X	X	X	X	X	X	X
Physical examination	X	X	X	X ²	X	X ²	X ²
Laboratory data		X	X	X ²	X		
Blood culture	X		X	X ³			
Rectal swab ⁴	X			X	X	X	
Ancillary drugs	X	X	X	X		X	X
Drug dispensing control	X	X	X	X			
Adverse events		X	X	X	X	X	X

(1) In the presence of an undrained abscess, TOC will be performed on day 28 or if drainage occurs after day 7 of treatment, TOC is to be done 7 days after that day; (2) This visit may be made by telephone if the patient has been discharged. In this scenario, no physical examination or lab tests are requested; (3) Only if previous blood cultures or symptoms remain positive; (4) Only in selected hospitals and face-to-face scheduled visits

203x290mm (300 x 300 DPI)

NAME OF THE STUDY: Phase III randomized, multi-center, open-label, controlled clinical trial to demonstrate the non-inferiority of the narrow-spectrum directed antibiotic therapy versus a broad-spectrum antipseudomonal beta-lactam therapy in the treatment of patients with *Enterobacter* bacteremia.

SPONSOR'S CODE: SIMPLIFY

SPONSOR: Fundación Pública Andaluza para la Gestión de la Investigación en Salud de Sevilla (FISEVI), "*Andalusian Public Foundation for the Management of Clinical Research of Seville*".

INTRODUCTION

Through this document we invite you to participate in a research study. The study has been approved by the Ethics Committee of Clinical Research of your hospital and the Spanish Agency of Pharmaceuticals and Health Products, according to the current legislation, Royal Decree 1090/2015, of December 4th, which regulates clinical trials with pharmaceuticals, the Ethics Committees of Research with Pharmaceuticals and the Spanish Registry of Clinical Trials.

WHY DO WE ASK FOR YOUR PARTICIPATION?

You must know that your participation in this study is voluntary and that you can decide not to participate or change your decision and terminate your participation whenever you want to, with no questions asked, and without that altering the relationship between you and your GP or jeopardizing your treatment in any way.

GENERAL DESCRIPTION OF THE STUDY

You have been diagnosed with bacteremia (an infection caused by a bacterium that reaches the bloodstream), which requires antibiotic treatment. The number of bacteria resistant to several antibiotics is increasing significantly. Thereby, there is a series of programs that aim to improve the way in which antibiotics are used, since that is directly related to the emergence of antibiotic resistances.

This study is absolutely not intended for testing the efficacy of new antibiotics.

PURPOSE OF THE STUDY

The main goal of the study is to demonstrate that the use of an antibiotic treatment, selected according to microbiological data (of the bacterium), in patients with *Enterobacter* bacteremia, is safe and efficient enough to meet the first standard of broad-spectrum antibiotics (i.e., an antibiotic capable of curing infections by many types of bacteria). This would improve the use of antibiotics, since we would use specific antibiotics for the isolated bacterium.

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4 It is important to highlight that any of the treatment options you will receive if you
5 participate in the study will be used in the standard-of-care, with a comparable efficacy
6 in terms of experience gathered, although no other studies have done this before,
7 which is why this trial was designed.
8
9

10 **WHAT DO WE OFFER YOU?**

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13 This study is a clinical trial, which means that the treatment you will receive will be
14 randomly selected by a computer; you will have the same probability to receive one of
15 the two treatments (experimental or control) and we will compare the effects in both
16 groups.
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18

19 **WHAT DOES THE TREATMENT CONSIST OF?**

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22 All the antibiotics included in the study are regularly used in patients with the same
23 infection you suffer from. None of them is a new antibiotic and they will be used for the
24 indications approved. You may receive one of the following treatment groups:
25
26

27 - **Experimental group:** following the criteria of your physician and according to the
28 evolution of the disease, you may receive one of these antibiotics intravenously at the
29 usual doses: ampicillin, trimethoprim/sulfamethoxazol, cefuroxime, cefotaxime,
30 amoxicillin/clavulanic, ciprofloxacin, ertapenem.
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33 It does not mean you will receive all of them, but you will be administered one of them
34 in that order until your infection has been controlled.
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36

37 - **Control group:** in this case you will continue to be administered the same antibiotic
38 you are currently receiving (only one of them) at the usual dose:
39 piperacillin/tazobactam, meropenem, imipenem, aztreonam, ceftazidime, cefepime.
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41

42 In both cases, if your GP estimates that you suffer from a polymicrobial infection
43 (caused by several bacteria), the previous antibiotic could be combined with one of the
44 following: vancomycin, teicoplanin, daptomycin, linezolid, clindamycin or
45 metronidazole.
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48 The duration of the treatment will be the usual for the infection you suffer from
49 (between 7 and 14 days).
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52 After completing at least 5 days of intravenous treatment, your physician will decide
53 whether it is possible to switch from intravenous (vein) to oral (mouth) medication.
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56 During the study, the research staff will carry out a series of visits. The day the
57 antibiotic treatment ends (if you are still in the hospital) and approximately one week
58 after, a revision visit will be conducted. We will phone you to check how you feel,
59 approximately 30 days after the antibiotic treatment started.
60

Then, after 60 days from the beginning of the treatment, you will have a new and final follow-up to see how you are feeling.

The number and type of analytical samples that we are going to collect are very similar to those of any patient with the same infection you are suffering from. At the beginning of the study and in some of the subsequent visits, we will take blood samples from you to evaluate how your infection is evolving.

In some centers, in order to assess the impact that the antibiotics could have on your intestinal flora, a rectal smear will be collected from you (a cotton swab is introduced in the anus, gently rotated and removed) at the moment you are included in the study, at the end-of-the-treatment visit, at the recovery-check visit, and at the 30th day visit. Agreeing to have a rectal smear performed is not required to be able to participate in the rest of the study. Your GP will tell you if this part of the study is carried out in your hospital.

We only ask you to indicate here if you agree to have a rectal smear collected from you:

I ACCEPT

I DO NOT ACCEPT

HOW CAN YOU BENEFIT FROM THIS?

If the hypothesis is proven correct, this trial will help improve the antibiotic treatment of patients who have the same type of infections that you have, which will prevent them from receiving antibiotic treatments with spectra broader than the essential range. You may not get any benefit for your health from participating in this study; however, the data obtained from it could be very helpful for future patients that may find themselves in your current condition.

WHAT ARE THE RISKS INVOLVED IN YOUR PARTICIPATION?

The treatments and the tests conducted in this study are part of the standard-of-care.

In the case of **participating women of childbearing age**, these must have a negative pregnancy test as a previous requirement to be included in the trial.

All the pharmaceuticals that will be used in this study have been approved by the Spanish Agency of Pharmaceuticals and Health Products, duly commercialized, and they are among the antibiotics that are used in the regular clinical practice.

Most of these antibiotics may present side effects of different severity. The adverse effects that you could suffer as a consequence of the administration of these

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4 pharmaceuticals include the following: digestive discomfort, skin eruption, allergic
5 reactions, muscular discomfort, blood and hepatobiliary alterations, kidney problems
6 (including kidney failure), and neurological alterations. In any case, the risk of suffering
7 from any of these adverse effects as a consequence of your participation in this study
8 is not higher than the risk you would have if you received the regular treatment
9 established for your disease. Moreover, all the side effects or undesired episodes that
10 take place during the study will be monitored and followed up; therefore, we ask you to
11 let the physicians of the study know if you find any discomfort or other new find.
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16 In addition to these effects, blood draw and the intravenous administration of
17 pharmaceuticals could cause pain or hematomas at the puncture site, among other
18 things.
19

20 **INSURANCE**

21
22
23 The sponsor of this study has an insurance policy with Zurich Insurance PLC
24 (insurance number: 00000084548718), which complies with the current legislation and
25 will provide you with a compensation in case your health is impaired or if you suffer
26 from lesions that could result from your participation in the study.
27
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29 **CONFIDENTIALITY**

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31
32 The treatment, communication and transfer of the personal data of all the participating
33 subjects will comply with the Organic Law 15/1999, of December 13th, on personal data
34 protection, and the Royal Decree 1720/2007, of December 21st, by which the
35 development Regulation of such law is approved. According to what is established by
36 the mentioned legislation, you have the right to access, modify, oppose and cancel
37 data, for which you will have to refer to your study physician.
38
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41 The data collected for the study will be identified through a code and only your study
42 GP/collaborators will be able to relate such data with you and your medical history.
43 Therefore, your identity will not be revealed to anybody, except in some cases, such as
44 a medical emergency or legal requirement.
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48 Access to your personal information will be limited to the study physician/collaborators,
49 health authorities (Spanish Agency of Pharmaceuticals and Health Products), the
50 Ethics Committee of Clinical Research and the staff authorized by the sponsor, when
51 they need it to check the data and the procedures of the study, but always
52 confidentially, complying with the current legislation.
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56 The results of the study will be presented in scientific meetings, medical conferences
57 and scientific publications; however, the identity of the participating patients will be kept
58 strictly confidential.
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FINANCIAL COMPENSATION

The sponsor is in charge of managing the funding of the study. For the realization of the study, the sponsor has signed a contract with the center in which it will be carried out and with the study physician, who in this case will not receive any financial compensation.

Your participation in the study will not incur any extraordinary cost for you for the pharmaceuticals used in the study.

OTHER RELEVANT INFORMATION

Any new information about the pharmaceuticals used in the study and other information that could affect your availability to participate in the study, which may be discovered during your participation, will be given to you by your GP as soon as possible.

If you decide to cancel your consent to participate in this study, no new data will be added to the database, and you can also request the destruction of all the identifiable samples, previously retained, to avoid the realization of new analyses.

You must also know that you may be excluded from the study if the sponsor and the researchers consider it appropriate to do so, either for safety reasons, any adverse event caused by the study medication or because they consider that you are not complying with the established procedures. In any of these cases, you will receive an appropriate explanation for the reason that caused your dismissal from the study.

By signing the attached consent form, you agree to comply with the study procedures that have been explained to you. When your participation in this study is over, you will receive the best treatment available, which will also be the one that your GP considers most appropriate for your disease.

QUESTIONS

If you have any questions related to the study or the disease, do not hesitate to tell your physician or his/her team. You can contact Dr. _____ through the following phone number: _____.

They will be willing to answer all your questions before, during and after the study.

INFORMED CONSENT OF THE PATIENT

Name of the study: Phase III randomized, multi-center, open-label, controlled clinical trial to demonstrate the non-inferiority of the narrow-spectrum directed antibiotic therapy versus a broad-spectrum antipseudomonal beta-lactam therapy in the treatment of patients with Enterobacter bacteremia.

I, _____
(Full name of the patient, hand written by him/herself, in capital letters)

- I have read and understood the information sheet about the study
- I was able to ask questions about the study and these were answered
- I spoke with (Name of the researcher)
- I understand that my participation is voluntary
- I understand that I can leave the study:
 - at any time
 - with no questions asked
 - without my decision affecting my medical care

I authorize the use of my personal data for the realization of this study, according to the information sheet.

I freely agree to participate in the study.

Patient's signature

Date (dd/mm/yy)

Patient's name

Researcher's signature

Date (dd/mm/yy)

Researcher's name

INFORMED CONSENT OF THE LEGAL REPRESENTATIVE OF THE CONSENTIMIENTO INFORMADO DEL REPRESENTANTE LEGAL

Name of the study: Phase III randomized, multi-center, open-label, controlled clinical trial to demonstrate the non-inferiority of the narrow-spectrum directed antibiotic therapy versus a broad-spectrum antipseudomonal beta-lactam therapy in the treatment of patients with Enterobacter bacteremia.

I (name and surname of the representative) _____,
as _____ (specify the relation with the patient) of _____
_____ (name of the patient).

DECLARE THAT:

- I have read the informative document attached to this consent form (the information sheet is for the patient) (please, keep a copy for yourself)
- I was able to ask questions about the study
- I received enough information about the study. I spoke with the informing health professional: (name of the researcher) _____
- I understand that participation is voluntary and that the patient can leave the study
- at any time
 - with no questions asked
 - without that affecting his/her future medical care

IN MY PRESENCE, (name of the patient) _____
was given all the pertinent information adapted to his/her level of understanding and he/she agrees to participate; thereby, I GIVE MY CONSENT for him/her to participate in the study.

Legal/family representative's signature

Date (dd/mm/yy)

Legal/family representative's name

Researcher's signature

Date (dd/mm/yy)

Researcher's name



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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 3
	2b	All items from the World Health Organization Trial Registration Data Set	Page 3
Protocol version	3	Date and version identifier	Page 3
Funding	4	Sources and types of financial, material, and other support	Pages 24 and 25
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Pages 1 and 26
	5b	Name and contact information for the trial sponsor	Page 25
	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	Page 25
	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)	Pages 16,17 and 26

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Pages 5 and 6
	6b	Explanation for choice of comparators	Page 5
Objectives	7	Specific objectives or hypotheses	Page 6
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, non-inferiority, exploratory)	Page 6

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Page 7
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)	Pages 7 and 8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Pages 9 to 12
	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)	Page 12
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	NA
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Pages 10 to 12
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	Pages 13 to 17
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)	Page 13 and Figure 2

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3	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	Page 19
4				
5				
6	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	N/A
7				

8 **Methods: Assignment of interventions (for controlled trials)**

9 Allocation:

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11				
12	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Pages 8 and 9
13				
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17				
18	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Pages 8 and 9
19				
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21				
22	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Page 8
23				
24				
25	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
26				
27				
28		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
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32 **Methods: Data collection, management, and analysis**

33				
34	Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Page 17
35				
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39		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Pages 16 and 17
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3	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	<i>Pages 17 and 18</i>
4				
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7	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	<i>Pages 13,14,19 and 20</i>
8				
9				
10		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	<i>Pages 13,14,19 and 20</i>
11				
12		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	<i>Pages 18 and 19</i>
13				
14				
15				

16 **Methods: Monitoring**

17				
18	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	<i>Pages 16 and 17</i>
19				
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23		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	<i>Pages 17 to 19</i>
24				
25				
26	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	<i>Page 16 and 19</i>
27				
28				
29	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	<i>Page 17</i>
30				
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33 **Ethics and dissemination**

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

38 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.
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