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:	*BMJ Open*
Manuscript ID	bmjopen-2016-015439
Article Type:	Protocol
Date Submitted by the Author:	05-Dec-2016
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; University Hospital Virgen Macarena-Virgen del Rocío, Unit of Infectious Disease, Microbiology, and Preventive Medicine 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 Rodriguez-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

Title: 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

AUTHORS

Luis Eduardo López-Cortés[1], Clara Rosso-Fernández[2,3], María Núñez-Núñez[1], Lucía Lavín-Alconero[2], José Bravo-Ferrer[1], Ángel Barriga[2], Mercedes Delgado[1], Carmen Lupión[1], Pilar Retamar[1], Jesús Rodríguez-Baño[1], and the SIMPLIFY Study Group*.

Affiliations

1. Unidad Clínica de Enfermedades Infecciosas, Microbiología y Medicina Preventiva, Instituto de Biomedicina de Sevilla, IBiS/Hospitales Universitarios Virgen Macarena y Virgen del Rocío/CSIC/Universidad de Sevilla. Sevilla, Spain.
2. Unidad de Investigación Clínica y Ensayos Clínicos (UICEC-HUVR), Hospitales Universitario Virgen del Rocío y Virgen Macarena, Sevilla, Spain.
3. Farmacología Clínica, Hospital Universitario Virgen del Rocío, Sevilla, Spain.

* Members of the Simplify Study Group are listed in Acknowledgements.

Author for correspondence: Luis Eduardo López Cortés
Email: luiselopezcortes@gmail.com

KEY WORDS: De-escalation, *Enterobacteriaceae*, bloodstream infection, broad-spectrum antibiotics, antimicrobial stewardship.

ABSTRACT

Introduction: Within the context of antimicrobial stewardship programs, de-escalation of antimicrobial therapy is one of the proposed strategies for reducing the unnecessary use of broad-spectrum antibiotics (BSA). The empirical treatment of nosocomial and some health-care associated bloodstream infections (BSI) frequently includes a beta-lactam with antipseudomonal activity as monotherapy or in combination with other drugs, so there is a great opportunity to optimize the empirical therapy based on microbiological data. De-escalation is assumed as standard-of-care for experts in infectious diseases; However, it is less frequent than it would desirable.

Methods and analysis: The SIMPLIFY trial is a multicenter, open-label, phase III randomized controlled clinical trial, designed as a pragmatic 'real-practice' trial. The aim of this trial is to demonstrate the non-inferiority of de-escalation from an empirical beta-lactam with antipseudomonal activity to a targeted narrow-spectrum antimicrobial in patients with BSI due to *Enterobacteriaceae*. It will be conducted at 19 Spanish public and university hospitals.

Ethics and dissemination: Each participating center has obtained the approval of the Ethics Review Committee, the agreement of the Directors of the Institutions, and authorization from the Spanish Regulatory Agency (AEMPS, Agencia Española del Medicamento y Productos Sanitarios). Data will be presented at international conferences and published in peer-reviewed journals.

Discussion: Strategies to reduce the use of BSA should be a priority. Most of the studies that support de-escalation are observational, retrospective, and heterogeneous. A recent Cochrane review stated that well-designed clinical trials should be conducted to assess the safety and efficacy of de-escalation.

STRENGTHS OF THIS STUDY

It will be the first trial on de-escalation specifically in patients with bacteremia due to *Enterobacteriaceae*.

It will include patients independently of the source of bacteraemia or severity of clinical presentation.

It has been designed with daily clinical practice in mind.

LIMITATIONS OF THIS STUDY

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

Switching to oral therapy is allowed from the fourth day of randomization. This could potentially reduce the number of days in which patients are assigned to one or other arm, but we decided to include this possibility to avoid unnecessary days of admission.

BACKGROUND

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

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

METHODS/DESIGN

Study hypothesis

The aim of the trial is to demonstrate that de-escalation from empirical therapy with an antipseudomonal beta-lactam to a targeted therapy is as effective and safe in patients with BSI due to *Enterobacteriaceae* as continuing with the empirical regimen.

Design

The SIMPLIFY trial is a multicenter, open-label, phase III randomized controlled clinical trial, powered to demonstrate the non-inferiority of de-escalation with respect to continuing with the antipseudomonal agent and designed as a real-world pragmatic trial. It was developed in accordance with an extension of the CONSORT statement for reporting non-inferiority, superiority and equivalence trials [14].

Participants and settings

The trial will be conducted at 19 public and academic hospitals with the support of the Spanish Network for Research in Infectious Diseases (REIPI) and the Spanish Clinical Research Network (SCReN). Patients will be evaluated for eligibility once *Enterobacteriaceae* is isolated from blood cultures and susceptibility data are available. Detection of eligible patients will be by daily review of blood culture results by the bacteremia team at each center. To be enrolled, participants will need to fulfill all inclusion and exclusion criteria (Table 1) plus give written informed consent (the patient or a legally authorized representative).

Randomization

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

with urinary tract infections is similar in the two groups being compared.

Intervention

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

Experimental group:

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

Control group:

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

Exceptions to the above rule:

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

arm, the options will be limited to trimethoprim/sulfamethoxazole, ciprofloxacin or ertapenem.

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

Dose adjustment

Due to the nature of the study design as a real-world clinical practice trial, antimicrobial dosage will be as deemed by the treating clinician, dependent on pharmacokinetic and pharmacodynamic (PK/PD) characteristics (such as higher doses for septic shock or high body mass). Dose adjustment will be made for all drugs as necessary in the case of renal or hepatic dysfunction, following Summary of Product Characteristics (SmPC) recommendations.

Concomitant therapy

Even if the BSI is monomicrobial, the attending physician may consider the infection to be polymicrobial at source. If additional anaerobic or gram-positive coverage is needed, concomitant use of oral metronidazole, clindamycin, vancomycin, teicoplanin, daptomycin or linezolid is allowed in both arms. Concomitant treatment with any other systemic antibiotic with intrinsic activity against gram-negative bacilli is not allowed. The administration of any of these drugs while the patient is receiving the study drug will be deemed a criterion for withdrawal. There are no absolute contraindications for the use of any other drug during the study. However, contraindications, warnings and precautions for use and possible interactions with study drugs are to be taken into account.

Duration of therapy

The appropriate duration of therapy is considered to be between 7 and 14 days, according to the attending physician's criteria. Treatments lasting longer than 14 days will be allowed only when there is an undrained abscess present, in which case, a 4-week treatment is permitted.

Route of administration

Switching to oral therapy is allowed from the sixth day of treatment if all the

following conditions are fulfilled: clinical improvement has been achieved, absence of fever (>38ºC), hemodynamic stability, adequate control of the source of BSI and absence of secondary foci, adequate oral intake, and no gastrointestinal conditions that might compromise drug absorption.

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

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

Rescue medication

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

Medication

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

Schedule of visits

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

The visit schedule is planned so as to obtain data on clinical status, sample collection, efficacy and safety variables, and adverse events. At the final evaluation at 60 days, data on all outcome variables will be gathered. Additionally, data will be collected at unplanned visits, with special consideration given to the occurrence of any adverse event or recurrence.

Outcomes

The primary outcome is clinical cure, which will be assessed at the TOC visit (3-5 days after the end of antibiotic treatment). Secondary outcomes include early (5 days after end of treatment) and late (60-day) clinical and microbiological response, all-cause mortality (days 7, 14, and 30), length of hospital stay, recurrence rates (relapse or reinfection) (day 60), safety of antibiotic treatment, including *Clostridium difficile* infections and number of antibiotic treatments with an antipseudomonal beta-lactam; in a subgroup of patients, the rate of intestinal colonization by ESBL, AmpC- and carbapenemase-producing *Enterobacteriaceae* will also be assessed by rectal swab. Some of these secondary outcomes will be analyzed as composite variables, following the DOOR/RADAR methodology. Outcome definitions, assessment, and time frames for measurement are described in Table 2.

Data collection, management and monitoring

The coordinating center for this study is the Hospital Universitario Virgen Macarena, Seville, Spain, and the Clinical Trials Unit (CTU-Hospital Universitario Virgen del Rocío) has delegated sponsor functions on behalf of the Fundación Pública Andaluza para la Gestión de la Investigación en Salud de Sevilla (FISEVI). Clinical research associates (CRAs) connected to the Spanish Clinical Research Network (SCReN) in public hospitals will carry out monitoring activities. Data collection will be conducted by trained staff at each participating center and entered into a restricted access electronic case report form (eCRF). Outstanding queries regarding the completion of the CRF will be sent to all participating centers as necessary to ensure accuracy of data.

In order to avoid any association with personal data, all study samples will be anonymous and identifiable only by the patient's alphanumeric study code. The objective and management of these samples are included in the patient's

information sheet and informed consent form.

The quality of all data collected will be carefully supervised by the CTU and specific visits for source data verification are organized according to the monitoring plan. Furthermore, in order to minimize bias, at the interim analysis (when 50% of the sample has been included), an independent committee (3 independent investigators from the REIPI) blinded to treatment assignment will review all accumulated data. This committee will advise the sponsor on the appropriateness of continuing the clinical trial as designed.

Isolates

All isolates will be sent to the central laboratory in the Hospital Universitario Virgen Macarena in Seville for susceptibility testing using reference methods and PCR characterisation and sequencing if necessary.

Eight selected hospitals will participate in the study of rectal carriage of ESBL-AmpC- and carbapenemase-producing *Enterobacteriaceae*, by taking rectal swabs from participants at different times (as set out in the schedule of visits). A written consent form for samples, approved by the ECs (Ethics Committees), is also provided for the study.

Definition of analysis population and outcome measures

The following populations will be considered: the intention-to-treat population (ITTP) includes all randomized patients; the modified ITTP (mITTP) includes randomized patients who have received at least one dose of intravenous antibiotics; the clinically evaluable population (CEP) includes patients who have completed 5 days of the intravenous study drug, or who die but have received at least one dose of intravenous antibiotics. The clinically and microbiologically evaluable population (CMEP) includes those in the CEP who have had microbiological tests (at least one blood culture 48 hours after randomization).

The principal investigator will assess the primary outcome (clinical cure) in the clinically evaluable population (CEP) at TOC. Due to the intrinsic characteristics of the primary outcome (soft outcome) and the study methodology (non-blinded), the primary outcome will be reviewed on the basis of clinical data recovered on two occasions by the external blinded investigator: firstly, during the interim analysis to monitor safety; secondly before the complete cleaning

and closure of the eCRF. For secondary end points, the CMEP will be eligible for early (day 5) and late (day 60) microbiological responses, the m-ITTP for all-cause mortality and length of hospital stay, and the CEP for the evaluation of recurrence rates and drug safety.

Sample size

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

Statistical analysis

Absolute differences will be calculated with 95% confidence intervals for the clinical cure rate between the two arms of the study at TOC. Multivariate analysis using logistic regression for the main outcome will be performed in order to ensure the independence of the treatment effect. Special consideration will be given in the multivariate analysis to the center of origin of the study sample. A Cox regression analysis of mortality at 5-7, 14, 30 and 60 days will be performed on the mITTP. For the superiority analysis, logistic regression will be used sequentially, using the methodology recently published by Evans et al [16] for the composite variable (DOOR and RADAR analysis using survival at day 14, number of days of antipseudomonal beta-lactam treatment avoided, presence or absence of side effects, including *C. difficile* infections, secondary MDRO infections, and all drug-related adverse events). Antimicrobial doses are not fixed and sensitivity analyses will therefore be applied to control potential bias.

Protocol violations

All protocol violations occurring after randomization will be listed in the Clinical Study Report, tabulated by subject and by recruitment center.

ETHICAL ISSUES

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

DISCUSSION

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

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

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

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

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

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

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

TRIAL STATUS

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

REGISTRATION

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

FUNDING

This project is a non-commercial, investigator-driven clinical trial, funded through public competitive call by the Instituto de Salud Carlos III (ISCIII), document number: PI15/00439. The ISCIII is the main public research entity in Spain and reports directly to the Ministry of Economy and Competitiveness and in operational terms to both this Ministry and to the Ministry of Health, Social Services and Equality. The Spanish Network for Research in Infectious Diseases (REIPI) is funded by the Ministerio de Economía y Competitividad, the Instituto de Salud Carlos III, integrated in the national I+D+i 2013-2016 and co-funded by European Union (ERDF/ESF, "Investing in your future"). This study is supported by the Spanish Clinical Research Network and funded by ISCII: study number 16.001.

COMPETING INTERESTS ESTATEMENT

The authors have no competing interests to declare.

CONTRIBUTORSHIP STATEMENT

JR-B and LEL-C were responsible for formulating the overall research questions and for the methodological design of the study. CR-F, BA and LL-A collaborated in the submission of the project for the Spanish funding, and collaborated in the methodological aspects of the study. JR-B is the coordinating investigator and leader of the Coordination Team. CR-F is responsible for the CTU. MN-N and is the pharmacovigilance monitor, and JB-F, PR-G, and CL collaborated in the organisation of the study. MD contributed in all the microbiological details of the study. JR-B and LEL-C participated in its design and supervised the project. All authors read and approved the final manuscript.

DATA SHARING STATEMENT

No additional unpublished data from the study are available

ACKNOWLEDGEMENTS: P. Aguilar, I.J. de la Calle, and A. Romero (Hospital Universitario Puerto Real, Cádiz); E. Merino, V. Boix, L.Giner, J.C. Rodríguez and A. Gimeno (Hospital Universitario de Alicante); F. Guerrero-Sánchez, A. Martin-Aspas and F. Galán-Sánchez (Hospital Universitario Puerta del Mar, Cádiz); D. Diez, V. Pérez-Carral and M.I. Paz (Complexo Hospitalario Universitario de Ourense); C. Fariñas, C. Armiñanzas, C. González and C. Ruiz de Alegría-Puig (Hospital Universitario Marqués de Valdecilla, Santander); L. Gómez, E. Calbo and M. Xercavins-Valls (Hospital Universitario Mutua Terrassa, Terrassa); F. García-Colchero and M. Chávez (Hospital San Juan de Dios, Sevilla); J. Goikoetxea-Agirre, M. Montejo and L. López (Hospital Universitario de Cruces, Barakaldo); R. Fernández, C. Pereira, S. Corral and M. Chávez (Hospital San Juan de Dios, Aljarafe); G. Bou and I. Torres (Hospital Universitario A Coruña); S. Pérez-Cortés and M.D. López-Prieto (Hospital Universitario de Jerez); B. Loeches and M. Romero (Hospital Universitario La Paz, Madrid); M. Ibarguren, M. A. Goenaga-Sánchez and J. M. García-Arenzana (Hospital Universitario Donostia); J. R. Yuste and J. Leiva-León (Clínica Universitaria de Navarra); A. Salas-Aparicio and C. de las Cuevas (Hospital Universitario La Princesa, Madrid); J.M. Guerra-Laso and I. Fernández-Natal (Complejo Asistencial Universitario de León); M. T. Pérez and F. Vasallo (Xerencia de Xestión Integrada de Vigo); G. Cuervo and C. Ardanuy (Hospital Universitario de Bellvitge); J.R. Paño and S. Salvo (Hospital Clínico Universitario Lozano Blesa, Zaragoza); M. L. Martin-Pena and E. Ruiz de Gospegui (Hospital Universitario Son Espases); M. Coronel-Janeiro, M.P. Alarcón-González, and A. González-Herrero (Hospital Universitario Virgen Macarena).

REFERENCES

1. Rodríguez-Baño J, Paño-Pardo JR, Alvarez-Rocha L, *et al*. Programs for optimizing the use of antibiotics (PROA) in Spanish hospitals: GEIH-SEIMC, SEFH and SEMPSPH consensus document. *Enferm Infecc Microbiol Clin* 2012; 30:22.e1-22.e23.

2. Dellit TH, Owens RC, McGowan JE Jr, *et al*; Infectious Diseases Society of America; Society for Healthcare Epidemiology of America. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clin Infect Dis* 2007; 44(2):159-77.

3. Rodríguez-Baño J, López-Prieto MD, Portillo MM, *et al*; SAEI/SAMPAC Bacteraemia Group. Epidemiology and clinical features of community-acquired, healthcare-associated and nosocomial bloodstream infections in tertiary-care and community hospitals. *Clin Microbiol Infect* 2010; 16(9):1408-13.

4. Paterson DL, Rice LB. Empirical antibiotic choice for the seriously ill patient: are minimization of selection of resistant organisms and maximization of individual outcome mutually exclusive? *Clin Infect Dis* 2003; 36(8):1006-12

5. Livermore DM. Has the era of untreatable infections arrived? *J Antimicrob Chemother* 2009; 64 Suppl 1:i29-36.

6. Khasawneh FA, Karim A, Mahmood T, *et al*. Antibiotic de-escalation in bacteremic urinary tract infections: potential opportunities and effect on outcome. Infection. 2014; 42(5):829-34.

7. Heenen S, Jacobs F, Vincent JL. Antibiotic strategies in severe nosocomial sepsis: why do we not de-escalate more often?. *Crit Care Med* 2012; 40:1404-9.

8. Bal AM, Gould IM. Antibiotic stewardship: overcoming implementation barriers. *Curr Opin Infect Dis* 2011; 24:357-62.

9. De Bus L, Denys W, Catteeuw J, *et al*. Impact of de-escalation of beta-lactam antibiotics on the emergence of antibiotic resistance in ICU patients: a retrospective observational study. *Intensive Care Med* 2016; 42(6):1029-39.

10. Mokart D, Slehofer G, Lambert J, *et al*. De-escalation of antimicrobial treatment in neutropenic patients with severe sepsis: results from an observational study. *Intensive Care Med* 2014; 40(1):41-9.

11. Kaye KS. Antimicrobial de-escalation strategies in hospitalized patients with pneumonia, intra-abdominal infections, and bacteremia. *J Hosp Med* 2012;7 Suppl 1:S13-21.

12. Montravers P, Piednoir P, Allou N. De-escalation: in drug we trust. *Crit Care Med* 2012 ; 40(5):1645-6.

13. Silva BN, Andriolo RB, Atallah AN, *et al*. De-escalation of antimicrobial treatment for adults with sepsis, severe sepsis or septic shock. *Cochrane Database Syst Rev* 2013; (3):CD007934.

14. Piaggio G, Elbourne DR, Pocock SJ, *et al*; CONSORT Group. Reporting of noninferiority and equivalence randomized trials: extension of the CONSORT 2010 statement. *JAMA* 2012; 308(24):2594-604.

15. Retamar P, Portillo MM, López-Prieto MD, *et al*; SAEI/SAMPAC. Impact of inadequate empirical therapy on the mortality of patients with bloodstream infections: a propensity score-based analysis. *Antimicrob Agents Chemother* 2012; 56:472.

16. Evans SR, Rubin D, Follmann D, *et al*. Desirability of Outcome Ranking (DOOR) and Response Adjusted for Duration of Antibiotic Risk (RADAR). *Clin Infect Dis* 2015; 61(5):800-6.

17. DiNubile MJ, Chow JW, Satishchandran V, *et al*. Acquisition of resistant bowel flora during a double-blind randomized clinical trial of ertapenem versus piperacillin-tazobactam therapy for intraabdominal infections. *Antimicrob Agents Chemother* 2005; 49:3217-21.

18. Falguera M, Ruiz-Gonzalez A, Schoenenberger JA, *et al*. Prospective, randomised study to compare empirical treatment versus targeted treatment on the basis of the urine antigen results in hospitalised patients with community-acquired pneumonia. *Thorax* 2010; 65(2):101-106.

19. Kim JW, Chung J, Choi SH, *et al*. Early use of imipenem/cilastatin and vancomycin followed by de-escalation versus conventional antimicrobials without de-escalation for patients with hospital-acquired pneumonia in a medical ICU: a randomized clinical trial. *Crit Care* 2012; 16(1):R28.

20. Leone M, Bechis C, Baumstarck K, *et al*; AZUREA Network Investigators. De-escalation versus continuation of empirical antimicrobial treatment in severe sepsis: a multicenter non-blinded randomized noninferiority trial. *Intensive Care Med* 2014; 40(10):1399-408.

21. Paul M, Dickstein Y, Raz-Pasteur A. Antibiotic de-escalation for bloodstream infections and pneumonia: systematic review and meta-analysis. *Clin Microbiol Infect* 2016. Ahead of print.

22. Weiss E, Zahar JR, Lesprit P, *et al*; De-escalation Study Group. Elaboration of a consensual definition of de-escalation allowing a ranking of β-lactams. *Clin Microbiol Infect* 2015; 21(7):649.e1-10.

23. Madaras-Kelly K, Jones M, Remington R, *et al*. Development of an antibiotic spectrum score based on veterans affairs culture and susceptibility data for the purpose of measuring antibiotic de-escalation: a modified Delphi approach. *Infect Control Hosp Epidemiol* 2014; 35(9):1103-13.

24. Mertz D, Koller M, Haller P, *et al*. Outcomes of early switching from intravenous to oral antibiotics on medical wards. *J Antimicrob Chemother* 2009; 64(1):188-99.

Table 1. Inclusion and exclusion criteria

Inclusion criteria
1. Written informed consent has been obtained from the patient or the legally authorised representative.
2. Age ≥ 18 years, not legally incapacitated.
3. Hospitalised patients with monomicrobial bacteremia due to *Enterobacteriaceae* 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 *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/mm^3) on the day of randomization.
6. Planned duration of treatment >28 days (e.g. osteomyelitis, endocarditis).

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) 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 *C. difficile* infections, secondary MDRO infections and all drug-related adverse events

Figure 1. SIMPLIFY – Decision tree of patient enrolment

Figure 2. Schedule of visits and assessments. Except where otherwise specified, these refer to days from randomization.

Figure 1.

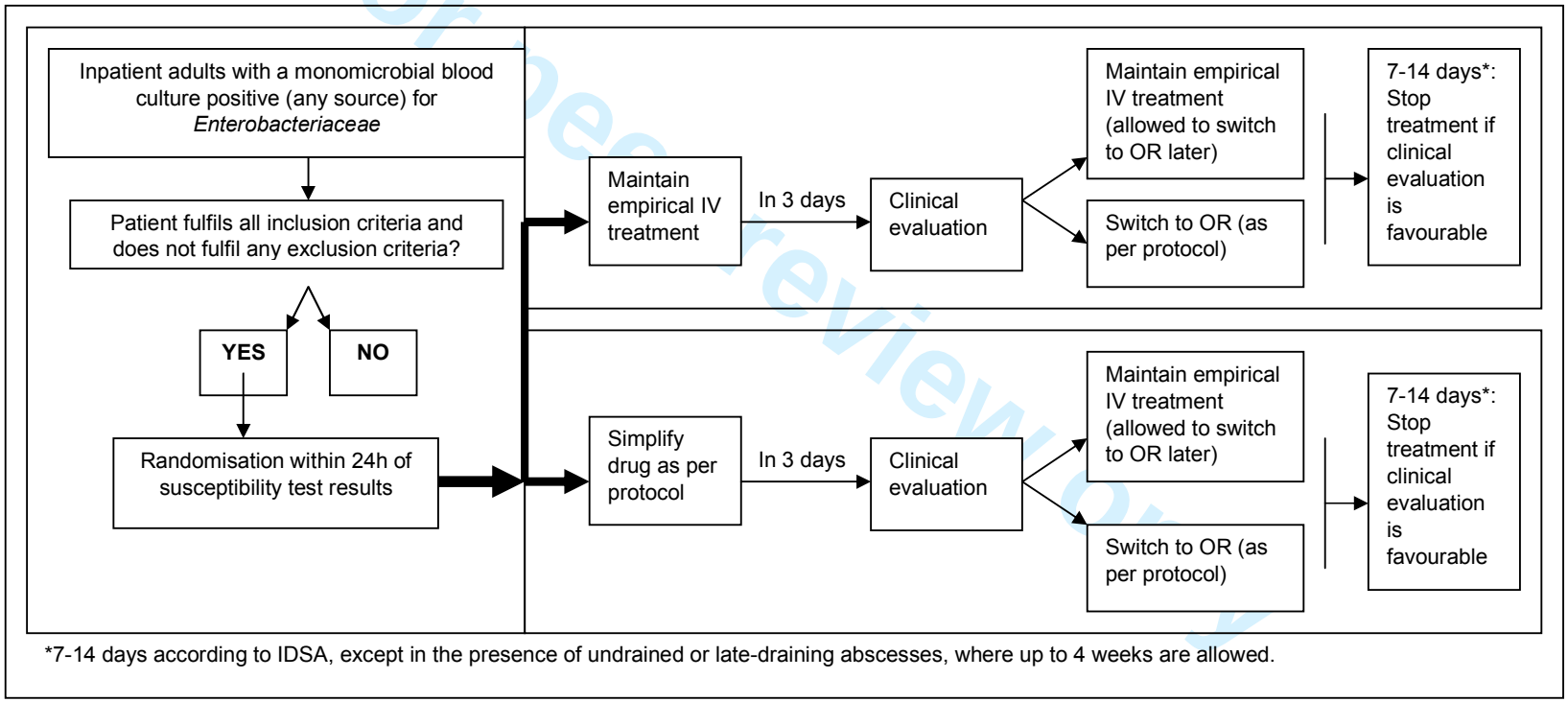

Figure 2.

Procedures	Selection 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	---

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

*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 recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

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:	*BMJ Open*
Manuscript ID	bmjopen-2016-015439.R1
Article Type:	Protocol
Date Submitted by the Author:	28-Feb-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 Lupión, Carmen; Hospital Universitario Virgen Macarena, Enfermedades Infecciosas y Microbiología Clínica Retamar, Pilar; Hospital Universitario Virgen Macarena, Enfermedades Infecciosas y Microbiología Clínica Rodriguez-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

Title: 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

AUTHORS

Luis Eduardo López-Cortés[1], Clara Rosso-Fernández[2,3], María Núñez-Núñez[1,4], Lucía Lavín-Alconero[2], José Bravo-Ferrer[1], Ángel Barriga[2], Mercedes Delgado[1], Carmen Lupión[1], Pilar Retamar[1], Jesús Rodríguez-Baño[1], and the SIMPLIFY Study Group*.

Affiliations

1. Unidad Clínica de Enfermedades Infecciosas, Microbiología y Medicina Preventiva, Instituto de Biomedicina de Sevilla (IBiS)/Hospital Universitario Virgen Macarena /CSIC/Universidad de Sevilla. Sevilla, Spain.
2. Unidad de Investigación Clínica y Ensayos Clínicos (UICEC-HUVR), Hospitales Universitario Virgen del Rocío y Virgen Macarena, Sevilla, Spain.
3. Farmacología Clínica, Hospital Universitario Virgen del Rocío, Sevilla, Spain.
4. Unidad Clínica de Farmacia. Hospitales Universitarios Virgen Macarena, Sevilla, Spain.

* Members of the Simplify Study Group are listed in Acknowledgements.

Author for correspondence: Luis Eduardo López Cortés

Email: luiselopezcortes@gmail.com

ABSTRACT

Introduction: Within the context of antimicrobial stewardship programs, de-escalation of antimicrobial therapy is one of the proposed strategies for reducing the unnecessary use of broad-spectrum antibiotics (BSA). The empirical treatment of nosocomial and some health-care associated bloodstream infections (BSI) frequently includes a beta-lactam with antipseudomonal activity as monotherapy or in combination with other drugs, so there is a great opportunity to optimize the empirical therapy based on microbiological data. De-escalation is assumed as standard-of-care for experts in infectious diseases; However, it is less frequent than it would desirable.

Methods and analysis: The SIMPLIFY trial is a multicenter, open-label, non-inferiority phase III randomized controlled clinical trial, designed as a pragmatic 'real-practice' trial. The aim of this trial is to demonstrate the non-inferiority of de-escalation from an empirical beta-lactam with antipseudomonal activity to a targeted narrow-spectrum antimicrobial in patients with BSI due to *Enterobacteriaceae*. The primary outcome is clinical cure, which will be assessed at the test of cure visit. It will be conducted at 19 Spanish public and university hospitals.

Ethics and dissemination: Each participating center has obtained the approval of the Ethics Review Committee, the agreement of the Directors of the Institutions, and authorization from the Spanish Regulatory Agency (AEMPS, Agencia Española del Medicamento y Productos Sanitarios). Data will be presented at international conferences and published in peer-reviewed journals.

Discussion: Strategies to reduce the use of BSA should be a priority. Most of the studies that support de-escalation are observational, retrospective, and heterogeneous. A recent Cochrane review stated that well-designed clinical trials should be conducted to assess the safety and efficacy of de-escalation.

REGISTRATION

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

STRENGTHS OF THIS STUDY

- It will be the first trial on de-escalation specifically in patients with bacteremia due to *Enterobacteriaceae*.
- It will include patients independently of the source of bacteraemia or severity of clinical presentation.
- A remote automatic randomisation system and external evaluation by blinded investigators were used to avoid bias.
- It has been designed with daily clinical practice in mind.

LIMITATIONS OF THIS STUDY

- The open-label design is theoretically more prone to bias.

- Switching to oral therapy could potentially reduce the number of days in which patients are assigned to one or other arm.

KEYWORDS:

De-escalation, *Enterobacteriaceae*, bloodstream infection, broad-spectrum antibiotics, antimicrobial stewardship.

BACKGROUND

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

Bloodstream infections (BSI) are known to be major causes of morbidity and mortality. They represent suitable organisms for carrying out a de-escalation strategy because they are very frequent, a high proportion of patients are treated with BSA and the susceptibility of the causative organisms is known. The *Enterobacteriaceae* as a group, is the most common cause of community- and nosocomial BSI, with a crude associated mortality of around 15% [3]. The empirical treatment for nosocomial and some healthcare-associated BSI frequently includes a beta-lactam antibiotic with antipseudomonal activity in monotherapy or in combination. This imposes strong selection pressure, particularly on *Pseudomonas aeruginosa* isolates, and maybe selecting multidrug resistant *Enterobacteriaceae* isolates. De-escalation according to microbiological results is assumed as standard-of-care by most infectologists; however, the reality is that de-escalation is much less frequent than is desirable [4,5]. Some of the possible reasons for this phenomenon [6-8] include the fact

that the safety and efficacy of this treatment strategy are based only on a few observational studies [9,10] and expert recommendations [11,12]. This was supported by a recent Cochrane review [13] conducted among adults with sepsis, severe sepsis or septic shock, whose authors concluded that there is no adequate direct evidence that de-escalation of antimicrobial agents is effective and safe in this scenario. Randomized clinical trials of their safety and efficacy are needed, in order to establish “proof of concept” and help make clinical decisions.

METHODS/DESIGN

Study hypothesis

The aim of the trial is to demonstrate that de-escalation from empirical therapy with an antipseudomonal beta-lactam to a targeted therapy is as effective and safe in patients with BSI due to *Enterobacteriaceae* as continuing with the empirical regimen.

Design

The SIMPLIFY trial is a multicenter, open-label, phase III randomized controlled clinical trial, powered to demonstrate the non-inferiority of de-escalation with respect to continuing with the antipseudomonal agent and designed as a real-world pragmatic trial. It was developed in accordance with an extension of the SPIRIT statement for reporting non-inferiority, superiority and equivalence trials [14,15].

Participants and settings

The trial will be conducted at 19 public and tertiary hospitals with the support of the Spanish Network for Research in Infectious Diseases (REIPI) and the Spanish Clinical Research Network (SCReN). Thirteen of them are Universitary hospitals. Patients will be evaluated for eligibility once *Enterobacteriaceae* is isolated from blood cultures and susceptibility data are available. Detection of eligible patients will be by daily review of blood culture results by the bacteremia team at each center. To be enrolled, participants will need to fulfill all inclusion and exclusion criteria (Table 1) plus give written informed consent (the patient or a legally authorized representative).

Table 1. Inclusion and exclusion criteria

Inclusion criteria

1. Written informed consent has been obtained from the patient or the legally authorised representative.
2. Age ≥ 18 years, not legally incapacitated.
3. Hospitalised patients with monomicrobial bacteremia due to *Enterobacteriaceae* 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 *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/mm^3) on the day of randomization.
6. Planned duration of treatment >28 days (e.g. osteomyelitis, endocarditis).

Randomization

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

will not be stratified by site.

Intervention

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

Experimental group:

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

Control group:

Continuation of the antipseudomonal beta-lactam that was being administered on an empirical basis: meropenem, 1-2 g q8h; imipenem, 0.5-1g q6h; piperacillin-tazobactam, 4/0.5 g q6-8h; cefepime, 2 g q8-12h; ceftazidime, 1-2 g

q8h; and aztreonam, 1-2 g q8h.

Exceptions to the above rule:

Third-generation cephalosporins should be avoided where there are inducible AmpC β-lactamase-producing *Enterobacteriaceae* (*Enterobacter* spp., *Providencia* spp., *Morganella morganii*, *Serratia marcescens*, and *Citrobacter freundii*); hence, even if the isolates are strictly susceptible, for patients in the control group, ceftazidime may be changed to any other antipseudomonal beta-lactam on the day of randomization. For patients allocated to the experimental arm, the options will be limited to trimethoprim/sulfamethoxazole, ciprofloxacin or ertapenem.

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

Dose adjustment

Due to the nature of the study design as a real-world clinical practice trial, antimicrobial dosage will be as deemed by the treating clinician, dependent on pharmacokinetic and pharmacodynamic (PK/PD) characteristics (such as higher doses for septic shock or high body mass). Dose adjustment will be made for all drugs as necessary in the case of renal or hepatic dysfunction, following Summary of Product Characteristics (SmPC) recommendations.

Concomitant therapy

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

infection to be polymicrobial at source. If additional anaerobic or gram-positive coverage is needed, concomitant use of oral metronidazole, clindamycin, vancomycin, teicoplanin, daptomycin or linezolid is allowed in both arms. Concomitant treatment with any other systemic antibiotic with intrinsic activity against gram-negative bacilli is not allowed. The administration of any of these drugs while the patient is receiving the study drug will be deemed a criterion for withdrawal. There are no absolute contraindications for the use of any other drug during the study. However, contraindications, warnings and precautions for use and possible interactions with study drugs are to be taken into account.

Duration of therapy

The appropriate duration of therapy is considered to be between 7 and 14 days, according to the attending physician's criteria. Treatments lasting longer than 14 days will be allowed only when there is an undrained abscess present, in which case, a 4-week treatment is permitted.

Route of administration

Switching to oral therapy is allowed after the third day of therapy after randomisation if all the following conditions are fulfilled: clinical improvement has been achieved, absence of fever (>38ºC), hemodynamic stability, adequate control of the source of BSI and absence of secondary foci, adequate oral intake, and no gastrointestinal conditions that might compromise drug absorption.

For patients in the experimental group, switching to oral therapy is allowed with the same intravenous drugs as follows: trimethoprim/sulfamethoxazole 160/800

mg q8 -12h, cefuroxime axetil 500 mg q8-12h, amoxicillin/clavulanate 875/125 mg q8h, or ciprofloxacin 500 mg q12h. If the intravenous drug is ampicillin, amoxicillin 1 g q8h will be used; if cefotaxime or ceftriaxone, then ceftibuten 400 mg q12-24h or cefixime 400 mg q12-24h will be used; if ertapenem, this drug may be switched to the intramuscular route.

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

Rescue medication

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

Medication

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

Schedule of visits

Patients included in the study will be followed for 60 days (± 5 days) after diagnosis of the BSI (Figure 2). Follow-up will be organised in seven planned

visits at day 0 (baseline), day 1; day 3-5; day 7-14 (end of treatment); day 3-5 from end of treatment (test of cure, TOC); day 30 ± 5; and day 60 ± 5. Visits at days 30 and 60 may be made by telephone.

The visit schedule is planned so as to obtain data on clinical status, sample collection, efficacy and safety variables, and adverse events. At the final evaluation at 60 days, data on all outcome variables will be gathered. Additionally, data will be collected at unplanned visits, with special consideration given to the occurrence of any adverse event or recurrence.

Outcomes

The primary outcome is clinical cure, which will be assessed at the TOC visit (3-5 days after the end of antibiotic treatment). Death during treatment, change of antibiotic therapy due to clinical failure, or need to prolong the treatment will be considered as failures. Secondary outcomes include early (5 days after end of treatment) and late (60-day) clinical and microbiological response, all-cause mortality (days 7, 14, and 30), length of hospital stay, recurrence rates (relapse or reinfection) (day 60), safety of antibiotic treatment, including *Clostridium difficile* infections and number of antibiotic treatments with an antipseudomonal beta-lactam; in a subgroup of patients, the rate of intestinal colonization by *P. aeruginosa* resistant to carbapenemase or piperacillin / tazobactam, *Stenotrophomonas* spp., multiresistant *A. baumannii* and enterobacteria producing ESBL, carbapenemase and chromosomal AmpC (hyperproduction) or plasmid will be sought. Some of these secondary outcomes will be analyzed as composite variables, following the DOOR/RADAR methodology. Outcome definitions, assessment, and time frames for measurement are described in

281 Table 2.

282 **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) 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

Until Day 60 of follow-up (late response)	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 *C. difficile* infections, secondary MDRO infections and all drug-related adverse events

Data collection, management and monitoring

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

electronic case report form (eCRF). Outstanding queries regarding the completion of the CRF will be sent to all participating centers as necessary to ensure accuracy of data.

In order to avoid any association with personal data, all study samples will be anonymous and identifiable only by the patient's alphanumeric study code. The objective and management of these samples are included in the patient's information sheet and informed consent form.

The quality of all data collected will be carefully supervised by the CTU and specific visits for source data verification are organized according to the monitoring plan. Furthermore, in order to minimize bias, at the interim analysis (when 50% of the sample has been included), an independent committee (3 independent investigators from the REIPI) blinded to treatment assignment will review all accumulated data. This committee will advise the sponsor on the appropriateness of continuing the clinical trial as designed.

Isolates

All isolates will be sent to the central laboratory in the Hospital Universitario Virgen Macarena in Seville for susceptibility testing using reference methods and PCR characterisation and sequencing if necessary.

Eight selected hospitals will participate in the study of rectal carriage of ESBL-AmpC- and carbapenemase-producing *Enterobacteriaceae*, by taking rectal swabs from participants at different times (as set out in the schedule of visits). To do this, samples will be taken by rectal swab from the patients of both treatment arms on the day of randomization, the day when treatment finish, the day of test of cure, and visit of day 30. The presence of *P. aeruginosa* resistant

to carbapenemase or piperacillin / tazobactam, *Stenotrophomonas* spp., multiresistant *A. baumannii* and enterobacteria producing ESBL, carbapenemase and chromosomal AmpC (hyperproduction) or plasmid will be sought. A written consent form for samples, approved by the ECs (Ethics Committees), is also provided for the study.

Definition of analysis population and outcome measures

The following populations will be considered: the intention-to-treat population (ITTP) includes all randomized patients; the modified ITTP (mITTP) includes randomized patients who have received at least one dose of intravenous antibiotics; the clinically evaluable population (CEP) includes patients who have completed 5 days of the intravenous study drug, or who die but have received at least one dose of intravenous antibiotics. The clinically and microbiologically evaluable population (CMEP) includes those in the CEP who have had microbiological tests (at least one blood culture 48 hours after randomization).

The local principal investigator in the centre where the patient was included will assess the primary outcome (clinical cure) in the clinically evaluable population (CEP) at TOC. Due to the intrinsic characteristics of the primary outcome (soft outcome) and the study methodology (non-blinded), this evaluation done will be reviewed later on the basis of clinical data recovered on two occasions by an external blinded investigator: firstly, during the interim analysis to monitor safety; secondly before the complete cleaning and closure of the eCRF. For secondary end points, the CMEP will be eligible for early (day 5) and late (day 60) microbiological responses, the m-ITTP for all-cause mortality and length of hospital stay, and the CEP for the evaluation of recurrence rates and drug

safety.

Sample size

The sample size was calculated using Epidat 4.0. Some of the data used to calculate it was derived from the study published by Retamar *et al* [17]. Assuming estimated clinical cure rates of 85% in both groups, a non-inferiority margin of 10% difference between the 2 groups, and treatment assignment in a 1:1 ratio, 344 patients in total (172 per study arm) are needed to achieve 80% power with a significance level of 5%. This allows for a 5% dropout rate. The 10% non-inferiority margin was chosen as in recent trials of complicated urinary tract and intraabdominal infections [18,19].

Statistical analysis

Absolute differences will be calculated with 95% confidence intervals for the clinical cure rate between the two arms of the study at TOC. Multivariate analysis using logistic regression for the main outcome will be performed in order to ensure the independence of the treatment effect. Special consideration will be given in the multivariate analysis to the center of origin of the study sample. A Cox regression analysis of mortality until 60 days will be performed on the mITTP. For the superiority analysis, logistic regression will be used sequentially, using the methodology recently published by Evans et al [20] for the composite variable (DOOR and RADAR analysis using survival at day 14, number of days of antipseudomonal beta-lactam treatment avoided, presence or absence of side effects, including *C. difficile* infections, secondary MDRO

infections, and all drug-related adverse events). Antimicrobial doses are not fixed and sensitivity analyses will therefore be applied to control potential bias.

Protocol violations

All protocol violations occurring after randomization will be listed in the Clinical Study Report, tabulated by subject and by recruitment center.

ETHICAL ISSUES

Each of the participating centers has obtained the approval of an Ethics Review Committee, the agreement of the Directors of the Institutions (who signed the contract of agreement with the sponsor of the study) and authorisation from the Spanish Regulatory Agency (AEMPS, Agencia Española del Medicamento y Productos Sanitarios). Patients may withdraw from the study at any time without prejudice, as is documented and explained at the time of providing consent. The study will be carried out according to the principles of the Declaration of Helsinki, and Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the harmonization of the laws, regulations and administrative provisions of the Member States relating to the implementation of Good Clinical Practice in the conduct of clinical trials on medicinal products for human use until the new Clinical Trials Regulation (CTR) EU No 536/2014 becomes applicable, which will be no earlier than 28 May 2016. The confidentiality of records that might identify subjects in this study will be protected in accordance with EU Directive 2001/20/EC. All laws for the control and protection of personal information will be carefully followed. The identities of

patients will not be disclosed in the e-CRF; names will be replaced by an alphanumeric code and any material related to the trial, such as samples, will be identified in the same way, so that no personal information will be revealed.

DISCUSSION

The extensive use of BSA and the dramatic increase in infections due to multidrug-resistant organisms are forcing the scientific community to look for strategies to combat this situation. In the real world, the application of de-escalation to serious infections is less frequent than is desirable. The arguments against de-escalation include: (1) the MIC of some narrow-spectrum drugs are closer to susceptibility breakpoints than carbapenems, for example, and some physicians may therefore feel safer using the latter; (2) subpopulations resistant to narrow-spectrum drugs may be selected and appear after some days of empirical treatment, leading to treatment failure in case of de-escalation; (3) in the case of polymicrobial infections, it is not uncommon for only one of the pathogens to be isolated in blood cultures, so that simplification of treatment may be less safe and effective than a broad-spectrum treatment; (4) there is some doubt about the real effectiveness of certain drugs against isolates producing specific mechanisms of resistance. Furthermore, although it is assumed that BSA has a greater impact on the selection of multidrug-resistant strains, some studies suggest that it may depend more on the duration of the treatment than the spectrum [16]. While none of these arguments have been proven, it is also true that there is no strong evidence for the safety of de-escalation strategies in these scenarios.

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

Several authors have warned about the considerable inconsistencies in definitions of de-escalation. In 2015, Weiss *et al* [26] elaborated a consensual definition of de-escalation that allowed beta-lactams to be ranked according to

both their spectra and their ecological impact. The authors underlined the difficulty of reaching consensus on the relative ecological impact of each individual drug. In 2014, Madaras-Kelly *et al*. [27] used the Delphi approach to develop an antibiotic spectrum score to measure de-escalation. We shall therefore include both concepts in our analysis, using Outcome Ranking (DOOR) and Response Adjusted for Duration of Antibiotic Risk (RADAR) analyses [20].

Switching from intravenous to oral therapy as soon as the patient is clinically stable can reduce the risk of adverse events related to intravenous therapy, length of hospitalization, and cost. It can be applied regardless of the source of infection and underlying conditions whenever a good option that achieves the PK/PD targets is available [28]. In our study, switching to oral therapy is allowed in both arms to avoid exposing patients in the control arm to unnecessary risks.

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

TRIAL STATUS

- Funding for the study was approved on 15/08/2015 and available for study expenses in 01/01/2016.
- EC approval for the 19 sites included was obtained on 15th March 2016.

- Authorization from the Spanish Regulatory Authority was obtained on 18th March 2016.
- The study has been approved for a recruitment period of 2 years.
- Dissemination of results directed to patients will be channeled through the Spanish Clinical Studies Registry (Agencia Española del Medicamento y Productos Sanitarios), whose content is adapted to patients.

FUNDING

This project is a non-commercial, investigator-driven clinical trial, funded through public competitive call by the Instituto de Salud Carlos III (ISCIII), document number: PI15/00439. The ISCIII is the main public research entity in Spain and reports directly to the Ministry of Economy and Competitiveness and in operational terms to both this Ministry and to the Ministry of Health, Social Services and Equality. The Spanish Network for Research in Infectious Diseases (REIPI) is funded by the Ministerio de Economía y Competitividad, the Instituto de Salud Carlos III, integrated in the national I+D+i 2013-2016 and co-funded by European Union (ERDF/ESF, "Investing in your future"). This study is supported by the Spanish Clinical Research Network and funded by ISCII: study number 16.001.

Role of the funding source

The funders of the study had no role in the study design or in manuscript development.

COMPETING INTERESTS ESTATEMENT

The authors have no competing interests to declare.

CONTRIBUTORSHIP STATEMENT

JR-B and LEL-C were responsible for formulating the overall research questions and for the methodological design of the study. CR-F, BA and LL-A collaborated in the submission of the project for the Spanish funding, and collaborated in the methodological aspects of the study. JR-B is the coordinating investigator and leader of the Coordination Team. CR-F is responsible for the CTU. MN-N collaborated with writing of the manuscript and with the pharmacovigilance design, and JB-F, PR-G, and CL collaborated in the organisation of the study. MD contributed in all the microbiological details of the study. JR-B and LEL-C participated in its design and supervised the project. All authors read and approved the final manuscript.

DATA SHARING STATEMENT

No additional unpublished data from the study are available

ACKNOWLEDGEMENTS: P. Aguilar, I.J. de la Calle, and A. Romero (Hospital Universitario Puerto Real, Cádiz); E. Merino, V. Boix, L.Giner, J.C. Rodríguez and A. Gimeno (Hospital Universitario de Alicante); F. Guerrero-Sánchez, A. Martin-Aspas and F. Galán-Sánchez (Hospital Universitario Puerta del Mar, Cádiz); D. Diez, V. Pérez-Carral and M.I. Paz (Complexo Hospitalario Universitario de Ourense); C. Fariñas, C. Armiñanzas, C. González and C. Ruiz de Alegría-Puig (Hospital Universitario Marqués de Valdecilla, Santander);

L. Gómez, E. Calbo and M. Xercavins-Valls (Hospital Universitario Mutua Terrassa, Terrassa); F. García-Colchero and M. Chávez (Hospital San Juan de Dios, Sevilla); J. Goikoetxea-Agirre, M. Montejo and L. López (Hospital Universitario de Cruces, Barakaldo); ; G. Bou and I. Torres (Hospital Universitario A Coruña); S. Pérez-Cortés and M.D. López-Prieto (Hospital Universitario de Jerez); B. Loeches and M. Romero (Hospital Universitario La Paz, Madrid); M. Ibarguren, M. A. Goenaga-Sánchez and J. M. García-Arenzana (Hospital Universitario Donostia); J. R. Yuste and J. Leiva-León (Clínica Universitaria de Navarra); A. Salas-Aparicio and C. de las Cuevas (Hospital Universitario La Princesa, Madrid); J.M. Guerra-Laso and I. Fernández-Natal (Complejo Asistencial Universitario de León); M. T. Pérez and F. Vasallo (Xerencia de Xestión Integrada de Vigo); G. Cuervo and C. Ardanuy (Hospital Universitario de Bellvitge); J.R. Paño and S. Salvo (Hospital Clínico Universitario Lozano Blesa, Zaragoza); M. L. Martin-Pena and E. Ruiz de Gospegui (Hospital Universitario Son Espases); M. del Barrio, S. Sadyrbaeva, M. Coronel-Janeiro, M.P. Alarcón-González, and A. González-Herrero (Hospital Universitario Virgen Macarena).

REFERENCES

1 Rodríguez-Baño J, Paño-Pardo JR, Álvarez-Rocha L, *et al*. Programs for optimizing the use of antibiotics (PROA) in Spanish hospitals: GEIH-SEIMC, SEFH and SEMPSPH consensus document. *Enferm Infecc Microbiol Clin* 2012; 30:22.e1-22.e23.

2 Dellit TH, Owens RC, McGowan JE Jr, *et al*; Infectious Diseases Society of America; Society for Healthcare Epidemiology of America. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clin Infect Dis* 2007; 44(2):159-77.

3 Rodríguez-Baño J, López-Prieto MD, Portillo MM, *et al*; SAEI/SAMPAC Bacteraemia Group. Epidemiology and clinical features of community-acquired, healthcare-associated and nosocomial bloodstream infections in tertiary-care and community hospitals. *Clin Microbiol Infect* 2010; 16(9):1408-13.

4 Paterson DL, Rice LB. Empirical antibiotic choice for the seriously ill patient: are minimization of selection of resistant organisms and maximization of individual outcome mutually exclusive? *Clin Infect Dis* 2003; 36(8):1006-12

5 Livermore DM. Has the era of untreatable infections arrived? *J Antimicrob Chemother* 2009; 64 Suppl 1:i29-36.

6 Khasawneh FA, Karim A, Mahmood T, *et al*. Antibiotic de-escalation in bacteremic urinary tract infections: potential opportunities and effect on outcome. Infection. 2014; 42(5):829-34.

7 Heenen S, Jacobs F, Vincent JL. Antibiotic strategies in severe nosocomial sepsis: why do we not de-escalate more often?. *Crit Care Med* 2012; 40:1404-

9.

8 Bal AM, Gould IM. Antibiotic stewardship: overcoming implementation barriers. *Curr Opin Infect Dis* 2011; 24:357-62.

9 De Bus L, Denys W, Catteeuw J, *et al*. Impact of de-escalation of beta-lactam antibiotics on the emergence of antibiotic resistance in ICU patients: a retrospective observational study. *Intensive Care Med* 2016; 42(6):1029-39.

10 Mokart D, Slehofer G, Lambert J, *et al*. De-escalation of antimicrobial treatment in neutropenic patients with severe sepsis: results from an observational study. *Intensive Care Med* 2014; 40(1):41-9.

11 Kaye KS. Antimicrobial de-escalation strategies in hospitalized patients with pneumonia, intra-abdominal infections, and bacteremia. *J Hosp Med* 2012;7 Suppl 1:S13-21.

12 Montravers P, Piednoir P, Allou N. De-escalation: in drug we trust. *Crit Care Med* 2012 ; 40(5):1645-6.

13 Silva BN, Andriolo RB, Atallah AN, *et al*. De-escalation of antimicrobial treatment for adults with sepsis, severe sepsis or septic shock. *Cochrane Database Syst Rev* 2013; (3):CD007934.

14 Chan A-W, Tetzlaff JM, Altman DG, et al D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. *Ann Intern Med* 2013;158:200-207.

15 Chan A-W, Tetzlaff JM, Gøtzsche PC, et al. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ 2013;346:e7586.16 Cisneros-Herreros JM, Cobo-Reinoso J, Pujol-Rojo M, et al. Guidelines for the diagnosis and treatment of patients with bacteriemia. Guidelines of the Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica].

Enferm Infecc Microbiol Clin 2007; 25(2):111-30.

17 Retamar P, Portillo MM, López-Prieto MD, *et al*; SAEI/SAMPAC. Impact of inadequate empirical therapy on the mortality of patients with bloodstream infections: a propensity score-based analysis. *Antimicrob Agents Chemother* 2012; 56:472.

18 Solomkin J, Hershberger E, Miller B, et al. Ceftolozane/tazobactam plus metronidazole for complicated intra-abdominal infections in an era of multidrug resistance: Results from a randomized, double-blind, phase 3 trial (ASPECT-cIAI). *Clin Infect Dis* 2015; 60(10):1462-71.

19 Wagenlehner FM, Sobel JD, Newell P, et al. Ceftazidime-avibactam versus doripenem for the treatment of complicated urinary tract infections, including acute pyelonephritis: RECAPTURE, a phase 3 randomized trial program. *Clin Infect Dis* 2016; 63(6):754-62.

20 Evans SR, Rubin D, Follmann D, *et al*. Desirability of Outcome Ranking (DOOR) and Response Adjusted for Duration of Antibiotic Risk (RADAR). *Clin Infect Dis* 2015; 61(5):800-6.

21 DiNubile MJ, Chow JW, Satishchandran V, *et al*. Acquisition of resistant bowel flora during a double-blind randomized clinical trial of ertapenem versus piperacillin-tazobactam therapy for intraabdominal infections. *Antimicrob Agents Chemother* 2005; 49:3217-21.

22 Falguera M, Ruiz-Gonzalez A, Schoenenberger JA, *et al*. Prospective, randomised study to compare empirical treatment versus targeted treatment on the basis of the urine antigen results in hospitalised patients with community-acquired pneumonia. *Thorax* 2010; 65(2):101-106.

23 Kim JW, Chung J, Choi SH, *et al*. Early use of imipenem/cilastatin and

vancomycin followed by de-escalation versus conventional antimicrobials without de-escalation for patients with hospital-acquired pneumonia in a medical ICU: a randomized clinical trial. *Crit Care* 2012; 16(1):R28.

24 Leone M, Bechis C, Baumstarck K, *et al*; AZUREA Network Investigators. De-escalation versus continuation of empirical antimicrobial treatment in severe sepsis: a multicenter non-blinded randomized noninferiority trial. *Intensive Care Med* 2014; 40(10):1399-408.

25 Paul M, Dickstein Y, Raz-Pasteur A. Antibiotic de-escalation for bloodstream infections and pneumonia: systematic review and meta-analysis. *Clin Microbiol Infect* 2016. Ahead of print.

26 Weiss E, Zahar JR, Lesprit P, *et al*; De-escalation Study Group. Elaboration of a consensual definition of de-escalation allowing a ranking of β-lactams. *Clin Microbiol Infect* 2015; 21(7):649.e1-10.

27 Madaras-Kelly K, Jones M, Remington R, *et al*. Development of an antibiotic spectrum score based on veterans affairs culture and susceptibility data for the purpose of measuring antibiotic de-escalation: a modified Delphi approach. *Infect Control Hosp Epidemiol* 2014; 35(9):1103-13.

28 Mertz D, Koller M, Haller P, *et al*. Outcomes of early switching from intravenous to oral antibiotics on medical wards. *J Antimicrob Chemother* 2009; 64(1):188-99.

Figure 1. SIMPLIFY – Decision tree of patient enrolment

Figure 2. Schedule of visits and assessments. Except where otherwise specified, these refer to days from randomization.

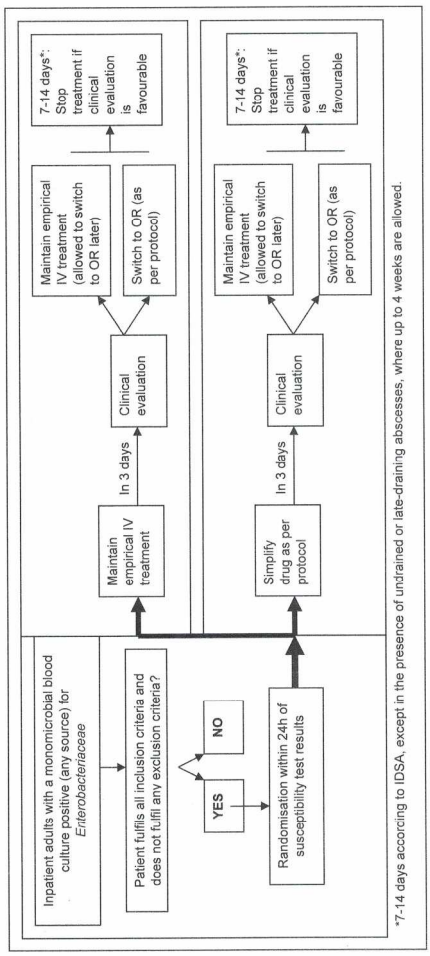

Figure 1.

203x290mm (300 x 300 DPI)

Figure 2.

Procedures	Selection 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)

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 _

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	__Page 5 _
	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, noninferiority, 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)	__Page 7 _
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	__Page 9 _
	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)	__Page 9 _
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	__Page 10 _
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	__Page 13 _
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 14 _

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 _
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	__ N/A _
Methods: Assignment of interventions (for controlled trials)			
Allocation:			__Page 8 _
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	__Page 8 _
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	__Page 8 _
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	__Page 8 _
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	__Page 8 _
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	__Page 8 _
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	__Page 16 _
	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	__Page 16 _

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 _
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 _
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	__Page 14/19 _
	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 _
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	__Page 16 _
	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 _
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 _
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 _
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	__Page 20 _
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 _

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 _
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	__Page 20 _
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 _
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	__Page 25 _
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 _
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 _
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 _
	31b	Authorship eligibility guidelines and any intended use of professional writers	__N/A _
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	__Page 20 _
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	__N/A _
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 _

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

BMJ Open

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:	*BMJ Open*
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 Lupión, Carmen; Hospital Universitario Virgen Macarena, Enfermedades Infecciosas y Microbiología Clínica Retamar, Pilar; Hospital Universitario Virgen Macarena, Enfermedades Infecciosas y Microbiología Clínica Rodriguez-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

Title: 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

AUTHORS

Luis Eduardo López-Cortés[1], Clara Rosso-Fernández[2,3], María Núñez-Núñez[1,4], Lucía Lavín-Alconero[2], José Bravo-Ferrer[1], Ángel Barriga[2], Mercedes Delgado[1], Carmen Lupión[1], Pilar Retamar[1], Jesús Rodríguez-Baño[1], and the SIMPLIFY Study Group*.

Affiliations

1. Unidad Clínica de Enfermedades Infecciosas y Microbiología Clínica , Instituto de Biomedicina de Sevilla (IBiS)/Hospital Universitario Virgen Macarena /CSIC/Universidad de Sevilla. Sevilla, Spain.
2. Unidad de Investigación Clínica y Ensayos Clínicos (UICEC-HUVR), Hospitales Universitario Virgen del Rocío y Virgen Macarena, Sevilla, Spain.
3. Farmacología Clínica, Hospital Universitario Virgen del Rocío, Sevilla, Spain.
4. Unidad Clínica de Farmacia. Hospitales Universitarios Virgen Macarena, Sevilla, Spain.

* Members of the Simplify Study Group are listed in Acknowledgements.

Author for correspondence: Luis Eduardo López Cortés

Email: luiselopezcortes@gmail.com

ABSTRACT

Introduction: Within the context of antimicrobial stewardship programs, de-escalation of antimicrobial therapy is one of the proposed strategies for reducing the unnecessary use of broad-spectrum antibiotics (BSA). The empirical treatment of nosocomial and some health-care associated bloodstream infections (BSI) frequently includes a beta-lactam with antipseudomonal activity as monotherapy or in combination with other drugs, so there is a great opportunity to optimize the empirical therapy based on microbiological data. De-escalation is assumed as standard-of-care for experts in infectious diseases; However, it is less frequent than it would desirable.

Methods and analysis: The SIMPLIFY trial is a multicenter, open-label, non-inferiority phase III randomized controlled clinical trial, designed as a pragmatic 'real-practice' trial. The aim of this trial is to demonstrate the non-inferiority of de-escalation from an empirical beta-lactam with antipseudomonal activity to a targeted narrow-spectrum antimicrobial in patients with BSI due to *Enterobacteriaceae*. The primary outcome is clinical cure, which will be assessed at the test of cure visit. It will be conducted at 19 Spanish public and university hospitals.

Ethics and dissemination: Each participating center has obtained the approval of the Ethics Review Committee, the agreement of the Directors of the Institutions, and authorization from the Spanish Regulatory Agency (AEMPS,

Agencia Española del Medicamento y Productos Sanitarios). Data will be presented at international conferences and published in peer-reviewed journals.

Discussion: Strategies to reduce the use of BSA should be a priority. Most of the studies that support de-escalation are observational, retrospective, and heterogeneous. A recent Cochrane review stated that well-designed clinical trials should be conducted to assess the safety and efficacy of de-escalation.

REGISTRATION

The European Union Clinical Trials Register: EudraCT number 2015-004219-19.

Clinical Trials.gov: NCT02795949

Protocol version: V.2.0, dated 16 May 2016.

All items from the World Health Organization Trial Registration Data Set are included in the registry.

STRENGTHS OF THIS STUDY

- It will be the first trial on de-escalation specifically in patients with bacteremia due to *Enterobacteriaceae*.
- It will include patients independently of the source of bacteraemia or severity of clinical presentation.
- A remote automatic randomisation system and external evaluation by blinded investigators were used to avoid bias.
- It has been designed with daily clinical practice in mind.

LIMITATIONS OF THIS STUDY

- The open-label design is theoretically more prone to bias.
- Switching to oral therapy could potentially reduce the number of days in which patients are assigned to one or other arm.

KEYWORDS:

De-escalation, *Enterobacteriaceae*, bloodstream infection, broad-spectrum antibiotics, antimicrobial stewardship.

BACKGROUND

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

Bloodstream infections (BSI) are known to be major causes of morbidity and mortality. They represent suitable organisms for carrying out a de-escalation strategy because they are very frequent, a high proportion of patients are treated with BSA and the susceptibility of the causative organisms is known. The *Enterobacteriaceae* as a group, is the most common cause of community- and nosocomial BSI, with a crude associated mortality of around 15% [3]. The empirical treatment for nosocomial and some healthcare-associated BSI frequently includes a beta-lactam antibiotic with antipseudomonal activity in monotherapy or in combination. This imposes strong selection pressure, particularly on *Pseudomonas aeruginosa* isolates, and maybe selecting multidrug resistant *Enterobacteriaceae* isolates. De-escalation according to microbiological results is assumed as standard-of-care by most infectologists; however, the reality is that de-escalation is much less frequent than is desirable [4,5]. Some of the possible reasons for this phenomenon [6-8] include the fact

that the safety and efficacy of this treatment strategy are based only on a few observational studies [9,10] and expert recommendations [11,12]. This was supported by a recent Cochrane review [13] conducted among adults with sepsis, severe sepsis or septic shock, whose authors concluded that there is no adequate direct evidence that de-escalation of antimicrobial agents is effective and safe in this scenario. Randomized clinical trials of their safety and efficacy are needed, in order to establish "proof of concept" and help make clinical decisions.

METHODS/DESIGN

Study hypothesis

The aim of the trial is to demonstrate that de-escalation from empirical therapy with an antipseudomonal beta-lactam to a targeted therapy is as effective and safe in patients with BSI due to *Enterobacteriaceae* as continuing with the empirical regimen.

Design

The SIMPLIFY trial is a multicenter, open-label, phase III randomized controlled clinical trial, powered to demonstrate the non-inferiority of de-escalation with respect to continuing with the antipseudomonal agent and designed as a real-world pragmatic trial. It was developed in accordance with an extension of the SPIRIT statement for reporting non-inferiority, superiority and equivalence trials [14,15].

Participants and settings

The trial will be conducted at 19 public and tertiary Spanish hospitals with the support of the Spanish Network for Research in Infectious Diseases (REIPI) and the Spanish Clinical Research Network (SCReN). Thirteen of them are Universitary hospitals. Patients will be evaluated for eligibility once *Enterobacteriaceae* is isolated from blood cultures and susceptibility data are available. Detection of eligible patients will be by daily review of blood culture results by Infectious Disease specialists from the bacteremia team at each center. To be enrolled, participants will need to fulfill all inclusion and exclusion criteria (Table 1) plus give written informed consent (the patient or a legally authorized representative).

Table 1. Inclusion and exclusion criteria

Inclusion criteria
1. Written informed consent has been obtained from the patient or the legally authorised representative.
2. Age ≥ 18 years, not legally incapacitated.
3. Hospitalised patients with monomicrobial bacteremia due to *Enterobacteriaceae* 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 *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/mm^3) on the day of randomization. 6. Planned duration of treatment >28 days (e.g. osteomyelitis, endocarditis).

Randomization

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

guarantee an appropriate allocation concealment in an open trial, randomization will not be stratified by site.

Intervention

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

Experimental group:

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

Control group:

Continuation of the antipseudomonal beta-lactam that was being administered on an empirical basis: meropenem, 1-2 g q8h; imipenem, 0.5-1g q6h;

piperacillin-tazobactam, 4/0.5 g q6-8h; cefepime, 2 g q8-12h; ceftazidime, 1-2 g q8h; and aztreonam, 1-2 g q8h.

Exceptions to the above rule:

Third-generation cephalosporins should be avoided where there are inducible AmpC β-lactamase-producing *Enterobacteriaceae* (*Enterobacter* spp., *Providencia* spp., *Morganella morganii*, *Serratia marcescens*, and *Citrobacter freundii*); hence, even if the isolates are strictly susceptible, for patients in the control group, ceftazidime may be changed to any other antipseudomonal beta-lactam on the day of randomization. For patients allocated to the experimental arm, the options will be limited to trimethoprim/sulfamethoxazole, ciprofloxacin or ertapenem.

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

Dose adjustment

Due to the nature of the study design as a real-world clinical practice trial, antimicrobial dosage will be as deemed by the treating clinician, dependent on pharmacokinetic and pharmacodynamic (PK/PD) characteristics (such as higher doses for septic shock or high body mass). Dose adjustment will be made for all drugs as necessary in the case of renal or hepatic dysfunction, following Summary of Product Characteristics (SmPC) recommendations.

Concomitant therapy

Even if the BSI is monomicrobial, the attending physician may consider the infection to be polymicrobial at source. If additional anaerobic or gram-positive coverage is needed, concomitant use of oral metronidazole, clindamycin, vancomycin, teicoplanin, daptomycin or linezolid is allowed in both arms. Concomitant treatment with any other systemic antibiotic with intrinsic activity against gram-negative bacilli is not allowed. The administration of any of these drugs while the patient is receiving the study drug will be deemed a criterion for withdrawal. There are no absolute contraindications for the use of any other drug during the study. However, contraindications, warnings and precautions for use and possible interactions with study drugs are to be taken into account.

Duration of therapy

The appropriate duration of therapy is considered to be between 7 and 14 days, according to the attending physician's criteria. Treatments lasting longer than 14 days will be allowed only when there is an undrained abscess present, in which case, a 4-week treatment is permitted.

Route of administration

Switching to oral therapy is allowed after the third day of therapy after randomisation if all the following conditions are fulfilled: clinical improvement has been achieved, absence of fever (>38ºC), hemodynamic stability, adequate control of the source of BSI and absence of secondary foci, adequate oral intake, and no gastrointestinal conditions that might compromise drug absorption.

For patients in the experimental group, switching to oral therapy is allowed with

the same intravenous drugs as follows: trimethoprim/sulfamethoxazole 160/800 mg q8 -12h, cefuroxime axetil 500 mg q8-12h, amoxicillin/clavulanate 875/125 mg q8h, or ciprofloxacin 500 mg q12h. If the intravenous drug is ampicillin, amoxicillin 1 g q8h will be used; if cefotaxime or ceftriaxone, then ceftibuten 400 mg q12-24h or cefixime 400 mg q12-24h will be used; if ertapenem, this drug may be switched to the intramuscular route.

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

Rescue medication

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

Medication

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

Schedule of visits

Patients included in the study will be followed for 60 days (± 5 days) after

diagnosis of the BSI (Figure 2). Follow-up will be organised in seven planned visits at day 0 (baseline), day 1; day 3-5; day 7-14 (end of treatment); day 3-5 from end of treatment (test of cure, TOC); day 30 ± 5; and day 60 ± 5. Visits at days 30 and 60 may be made by telephone.

The visit schedule is planned so as to obtain data on clinical status, sample collection, efficacy and safety variables, and adverse events. At the final evaluation at 60 days, data on all outcome variables will be gathered. Additionally, data will be collected at unplanned visits, with special consideration given to the occurrence of any adverse event or recurrence.

Outcomes

The primary outcome is clinical cure, which will be assessed at the TOC visit (3-5 days after the end of antibiotic treatment). Death during treatment, change of antibiotic therapy due to clinical failure, or need to prolong the treatment will be considered as failures (Table 2). Secondary outcomes include early (5 days after end of treatment) and late (60-day) clinical and microbiological response, all-cause mortality (days 7, 14, and 30), length of hospital stay, recurrence rates (relapse or reinfection) (day 60), safety of antibiotic treatment, including *Clostridium difficile* infections and number of antibiotic treatments with an antipseudomonal beta-lactam; in a subgroup of patients, the rate of intestinal colonization by *P. aeruginosa* resistant to carbapenemase or piperacillin / tazobactam, *Stenotrophomonas* spp., multiresistant *A. baumannii* and enterobacteria producing ESBL, carbapenemase and chromosomal AmpC (hyperproduction) or plasmid will be sought. Some of these secondary outcomes will be analyzed as composite variables, following the DOOR/RADAR

methodology. Outcome definitions, assessment, and time frames for measurement are described in

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

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 *C. difficile* infections, secondary MDRO infections and all drug-related adverse events

Data collection, management and monitoring

The coordinating center for this study is the Hospital Universitario Virgen Macarena, Seville, Spain, and the Clinical Trials Unit (CTU-Hospital Universitario Virgen del Rocío) has delegated sponsor functions on behalf of

the Fundación Pública Andaluza para la Gestión de la Investigación en Salud de Sevilla (FISEVI - http://www.fisevi.com). Clinical research associates (CRAs) connected to the Spanish Clinical Research Network (SCReN) in public hospitals will carry out monitoring activities. Data collection will be conducted by trained staff at each participating center and entered into a restricted access electronic case report form (eCRF). These forms will be available at the eCRF web platform. Outstanding queries regarding the completion of the CRF will be sent to all participating centers as necessary to ensure accuracy of data.

In order to avoid any association with personal data, all study samples will be anonymous and identifiable only by the patient's alphanumeric study code. The objective and management of these samples are included in the patient's information sheet and informed consent form.

The quality of all data collected will be carefully supervised by the CTU and specific visits for source data verification are organized according to the monitoring plan. Furthermore, in order to minimize bias, at the interim analysis (when 50% of the sample has been included), an independent committee (3 independent investigators from the REIPI) blinded to treatment assignment will review all accumulated data. This committee will advise the sponsor on the appropriateness of continuing the clinical trial as designed.

Isolates

All isolates will be sent to the central laboratory in the Hospital Universitario Virgen Macarena in Seville for susceptibility testing using reference methods and PCR characterisation and sequencing if necessary.

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

AmpC- and carbapenemase-producing *Enterobacteriaceae*, by taking rectal swabs from participants at different times (as set out in the schedule of visits). To do this, samples will be taken by rectal swab from the patients of both treatment arms on the day of randomization, the day when treatment finish, the day of test of cure, and visit of day 30. The presence of *P. aeruginosa* resistant to carbapenemase or piperacillin / tazobactam, *Stenotrophomonas* spp., multiresistant *A. baumannii* and enterobacteria producing ESBL, carbapenemase and chromosomal AmpC (hyperproduction) or plasmid will be sought. A written consent form for samples, approved by the ECs (Ethics Committees), is also provided for the study.

Definition of analysis population and outcome measures

The following populations will be considered: the intention-to-treat population (ITTP) includes all randomized patients; the modified ITTP (mITTP) includes randomized patients who have received at least one dose of intravenous antibiotics; the clinically evaluable population (CEP) includes patients who have completed 5 days of the intravenous study drug, or who die but have received at least one dose of intravenous antibiotics. The clinically and microbiologically evaluable population (CMEP) includes those in the CEP who have had microbiological tests (at least one blood culture 48 hours after randomization).

The local principal investigator in the centre where the patient was included will assess the primary outcome (clinical cure) in the clinically evaluable population (CEP) at TOC. Due to the intrinsic characteristics of the primary outcome (soft outcome) and the study methodology (non-blinded), this evaluation done will be reviewed later on the basis of clinical data recovered on two occasions by an

external blinded investigator: firstly, during the interim analysis to monitor safety; secondly before the complete cleaning and closure of the eCRF. For secondary end points, the CMEP will be eligible for early (day 5) and late (day 60) microbiological responses, the m-ITTP for all-cause mortality and length of hospital stay, and the CEP for the evaluation of recurrence rates and drug safety.

Sample size

The sample size was calculated using Epidat 4.0. Some of the data used to calculate it was derived from the study published by Retamar *et al* [17]. Assuming estimated clinical cure rates of 85% in both groups, a non-inferiority margin of 10% difference between the 2 groups, and treatment assignment in a 1:1 ratio, 344 patients in total (172 per study arm) are needed to achieve 80% power with a significance level of 5%. This allows for a 5% dropout rate. The 10% non-inferiority margin was chosen as in recent trials of complicated urinary tract and intraabdominal infections [18,19].

Statistical analysis

Absolute differences will be calculated with 95% confidence intervals for the clinical cure rate between the two arms of the study at TOC. Multivariate analysis using logistic regression for the main outcome will be performed in order to ensure the independence of the treatment effect. Special consideration will be given in the multivariate analysis to the center of origin of the study sample. A Cox regression analysis of mortality until 60 days will be performed on the mITTP. For the superiority analysis, logistic regression will be used

sequentially, using the methodology recently published by Evans et al [20] for the composite variable (DOOR and RADAR analysis using survival at day 14, number of days of antipseudomonal beta-lactam treatment avoided, presence or absence of side effects, including *C. difficile* infections, secondary MDRO infections, and all drug-related adverse events). Antimicrobial doses are not fixed and sensitivity analyses will therefore be applied to control potential bias.

Protocol violations

All protocol violations occurring after randomization will be listed in the Clinical Study Report, tabulated by subject and by recruitment center.

ETHICS AND DISSEMINATION

Each of the participating centers has obtained the approval of an Ethics Review Committee, the agreement of the Directors of the Institutions (who signed the contract of agreement with the sponsor of the study) and authorisation from the Spanish Regulatory Agency (AEMPS, Agencia Española del Medicamento y Productos Sanitarios). All the patients have to sign the informed consent previous to the randomization (Supplementary data). Patients may withdraw from the study at any time without prejudice, as is documented and explained at the time of providing consent. The study will be carried out according to the principles of the Declaration of Helsinki, and Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the harmonization of the laws, regulations and administrative provisions of the Member States relating to the implementation of Good Clinical Practice in the conduct of clinical trials on medicinal products for human use until the

new Clinical Trials Regulation (CTR) EU No 536/2014 becomes applicable, which will be no earlier than 28 May 2016. The confidentiality of records that might identify subjects in this study will be protected in accordance with EU Directive 2001/20/EC. All laws for the control and protection of personal information will be carefully followed. The identities of patients will not be disclosed in the e-CRF; names will be replaced by an alphanumeric code and any material related to the trial, such as samples, will be identified in the same way, so that no personal information will be revealed.

Regarding to the dissemination plan, three communications with preliminary clinical data to national and international conferences (ASM/IDSA or ECCMID) are proposed during the second year of the study. For the third year, a further presentation will be given at a national conference, and two other presentations at international conferences with final or advanced data. Once we obtain the final results of the study, at least three publications are expected: one in a D1 journal and two in Q1 journals.

DISCUSSION

The extensive use of BSA and the dramatic increase in infections due to multidrug-resistant organisms are forcing the scientific community to look for strategies to combat this situation. In the real world, the application of de-escalation to serious infections is less frequent than is desirable. The arguments against de-escalation include: (1) the MIC of some narrow-spectrum drugs are closer to susceptibility breakpoints than carbapenems, for example, and some physicians may therefore feel safer using the latter; (2) subpopulations resistant to narrow-spectrum drugs may be selected and appear

after some days of empirical treatment, leading to treatment failure in case of de-escalation; (3) in the case of polymicrobial infections, it is not uncommon for only one of the pathogens to be isolated in blood cultures, so that simplification of treatment may be less safe and effective than a broad-spectrum treatment; (4) there is some doubt about the real effectiveness of certain drugs against isolates producing specific mechanisms of resistance. Furthermore, although it is assumed that BSA has a greater impact on the selection of multidrug-resistant strains, some studies suggest that it may depend more on the duration of the treatment than the spectrum [16]. While none of these arguments have been proven, it is also true that there is no strong evidence for the safety of de-escalation strategies in these scenarios.

To the best of our knowledge, three randomized trials on de-escalation strategies, none of them specifically focused on bacteremia, have been published, which show significant differences from this study [21-23]. The one published by Falguera *et al* [22] compared the efficacy of empirical versus targeted treatment on the basis of urine antigen results in hospitalized patients with community-acquired pneumonia. The article published by Kim et al [23] evaluated the efficacy of early use of imipenem/cilastatin and vancomycin followed by de-escalation versus conventional antimicrobials without de-escalation for patients with hospital-acquired pneumonia in ICUs. The last one, published recently by Leone *et al* [24], included a limited number (n=116) of ICU-admitted patients with severe sepsis; Its primary outcome was duration of ICU stay, and not effectiveness of both treatment strategies. In that study, de-escalation followed the recommendations of guidelines, not a pre-specified protocol based on the clinical impact of the antibiotics. There was no significant

difference in mortality, although unexpectedly, patients in the experimental arm had a higher rate of superinfections (27% vs 11%, P = 0.03). These results contrast with a recent systematic review and meta-analysis that included 25 studies with data on de-escalation based on culture results, which showed a significant reduction in the relative risk of death (RR 0.44, 95% CI: 0.30–0.66; p<0.0001). It is important to note that many of the included studies in the meta-analysis were observational, retrospective and had a high degree of heterogeneity [25].

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

Switching from intravenous to oral therapy as soon as the patient is clinically stable can reduce the risk of adverse events related to intravenous therapy, length of hospitalization, and cost. It can be applied regardless of the source of infection and underlying conditions whenever a good option that achieves the PK/PD targets is available [28]. In our study, switching to oral therapy is allowed in both arms to avoid exposing patients in the control arm to unnecessary risks.

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

TRIAL STATUS

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

SPONSOR INFORMATION

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

Contact: claram.rosso.sspa@juntadeandalucia.es

FUNDING

This project is a non-commercial, investigator-driven clinical trial, funded through public competitive call by the Instituto de Salud Carlos III (ISCIII), document number: PI15/00439, funded by Instituto de Salud Carlos III, integrated in the national I+D+i 2013-2016 and co-funded by European Union (ERDF/ESF, "Investing in your future"). This study is supported by the Spanish Clinical Research Network and funded by ISCII: study number 16.001.

ROLE OF THE STUDY SPONSOR/ FUNDING SOURCE

The sponsor and funders of the study had no role in the study design or in manuscript development.

COMPETING INTERESTS ESTATEMENT

The authors have no competing interests to declare.

CONTRIBUTORSHIP STATEMENT

JR-B and LEL-C were responsible for formulating the overall research questions and for the methodological design of the study. CR-F, BA and LL-A collaborated in the submission of the project for the Spanish funding, and collaborated in the methodological aspects of the study. JR-B is the coordinating investigator and leader of the Coordination Team. CR-F is responsible for the CTU. MN-N collaborated with writing of the manuscript and with the pharmacovigilance design, and JB-F, PR-G, and CL collaborated in the organisation of the study. MD contributed in all the microbiological details of the study. JR-B and LEL-C participated in its design and supervised the project. All authors read and

approved the final manuscript.

DATA SHARING STATEMENT

No additional unpublished data from the study are available

ACKNOWLEDGEMENTS: P. Aguilar, I.J. de la Calle, and A. Romero (Hospital Universitario Puerto Real, Cádiz); E. Merino, V. Boix, L.Giner, J.C. Rodríguez and A. Gimeno (Hospital Universitario de Alicante); F. Guerrero-Sánchez, A. Martin-Aspas and F. Galán-Sánchez (Hospital Universitario Puerta del Mar, Cádiz); D. Diez, V. Pérez-Carral and M.I. Paz (Complexo Hospitalario Universitario de Ourense); C. Fariñas, C. Armiñanzas, C. González and C. Ruiz de Alegría-Puig (Hospital Universitario Marqués de Valdecilla, Santander); L. Gómez, E. Calbo and M. Xercavins-Valls (Hospital Universitario Mutua Terrassa, Terrassa); F. García-Colchero and M. Chávez (Hospital San Juan de Dios, Sevilla); J. Goikoetxea-Agirre, M. Montejo and L. López (Hospital Universitario de Cruces, Barakaldo); ; G. Bou and I. Torres (Hospital Universitario A Coruña); S. Pérez-Cortés and M.D. López-Prieto (Hospital Universitario de Jerez); B. Loeches and M. Romero (Hospital Universitario La Paz, Madrid); M. Ibarguren, M. A. Goenaga-Sánchez and J. M. García-Arenzana (Hospital Universitario Donostia); J. R. Yuste and J. Leiva-León (Clínica Universitaria de Navarra); A. Salas-Aparicio and C. de las Cuevas (Hospital Universitario La Princesa, Madrid); J.M. Guerra-Laso and I. Fernández-Natal (Complejo Asistencial Universitario de León); M. T. Pérez and F. Vasallo (Xerencia de Xestión Integrada de Vigo); G. Cuervo and C. Ardanuy (Hospital Universitario de Bellvitge); J.R. Paño and S. Salvo (Hospital Clínico

Universitario Lozano Blesa, Zaragoza); M. L. Martin-Pena and E. Ruiz de Gospegui (Hospital Universitario Son Espases); M. del Barrio, S. Sadyrbaeva, M. Coronel-Janeiro, M.P. Alarcón-González, and A. González-Herrero (Hospital Universitario Virgen Macarena).

REFERENCES

1 Rodríguez-Baño J, Paño-Pardo JR, Álvarez-Rocha L, *et al*. Programs for optimizing the use of antibiotics (PROA) in Spanish hospitals: GEIH-SEIMC, SEFH and SEMPSPH consensus document. *Enferm Infecc Microbiol Clin* 2012; 30:22.e1-22.e23.

2 Dellit TH, Owens RC, McGowan JE Jr, *et al*; Infectious Diseases Society of America; Society for Healthcare Epidemiology of America. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clin Infect Dis* 2007; 44(2):159-77.

3 Rodríguez-Baño J, López-Prieto MD, Portillo MM, *et al*; SAEI/SAMPAC Bacteraemia Group. Epidemiology and clinical features of community-acquired, healthcare-associated and nosocomial bloodstream infections in tertiary-care and community hospitals. *Clin Microbiol Infect* 2010; 16(9):1408-13.

4 Paterson DL, Rice LB. Empirical antibiotic choice for the seriously ill patient: are minimization of selection of resistant organisms and maximization of individual outcome mutually exclusive? *Clin Infect Dis* 2003; 36(8):1006-12

5 Livermore DM. Has the era of untreatable infections arrived? *J Antimicrob Chemother* 2009; 64 Suppl 1:i29-36.

6 Khasawneh FA, Karim A, Mahmood T, *et al*. Antibiotic de-escalation in bacteremic urinary tract infections: potential opportunities and effect on outcome. Infection. 2014; 42(5):829-34.

7 Heenen S, Jacobs F, Vincent JL. Antibiotic strategies in severe nosocomial sepsis: why do we not de-escalate more often?. *Crit Care Med* 2012; 40:1404-

9.

8 Bal AM, Gould IM. Antibiotic stewardship: overcoming implementation barriers. *Curr Opin Infect Dis* 2011; 24:357-62.

9 De Bus L, Denys W, Catteeuw J, *et al*. Impact of de-escalation of beta-lactam antibiotics on the emergence of antibiotic resistance in ICU patients: a retrospective observational study. *Intensive Care Med* 2016; 42(6):1029-39.

10 Mokart D, Slehofer G, Lambert J, *et al*. De-escalation of antimicrobial treatment in neutropenic patients with severe sepsis: results from an observational study. *Intensive Care Med* 2014; 40(1):41-9.

11 Kaye KS. Antimicrobial de-escalation strategies in hospitalized patients with pneumonia, intra-abdominal infections, and bacteremia. *J Hosp Med* 2012;7 Suppl 1:S13-21.

12 Montravers P, Piednoir P, Allou N. De-escalation: in drug we trust. *Crit Care Med* 2012 ; 40(5):1645-6.

13 Silva BN, Andriolo RB, Atallah AN, *et al*. De-escalation of antimicrobial treatment for adults with sepsis, severe sepsis or septic shock. *Cochrane Database Syst Rev* 2013; (3):CD007934.

14 Chan A-W, Tetzlaff JM, Altman DG, et al D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. *Ann Intern Med* 2013;158:200-207.

15 Chan A-W, Tetzlaff JM, Gøtzsche PC, et al. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ 2013;346:e7586.16 Cisneros-Herreros JM, Cobo-Reinoso J, Pujol-Rojo M, et al. Guidelines for the diagnosis and treatment of patients with bacteriemia. Guidelines of the Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica].

Enferm Infecc Microbiol Clin 2007; 25(2):111-30.

17 Retamar P, Portillo MM, López-Prieto MD, *et al*; SAEI/SAMPAC. Impact of inadequate empirical therapy on the mortality of patients with bloodstream infections: a propensity score-based analysis. *Antimicrob Agents Chemother* 2012; 56:472.

18 Solomkin J, Hershberger E, Miller B, et al. Ceftolozane/tazobactam plus metronidazole for complicated intra-abdominal infections in an era of multidrug resistance: Results from a randomized, double-blind, phase 3 trial (ASPECT-cIAI). *Clin Infect Dis* 2015; 60(10):1462-71.

19 Wagenlehner FM, Sobel JD, Newell P, et al. Ceftazidime-avibactam versus doripenem for the treatment of complicated urinary tract infections, including acute pyelonephritis: RECAPTURE, a phase 3 randomized trial program. *Clin Infect Dis* 2016; 63(6):754-62.

20 Evans SR, Rubin D, Follmann D, *et al*. Desirability of Outcome Ranking (DOOR) and Response Adjusted for Duration of Antibiotic Risk (RADAR). *Clin Infect Dis* 2015; 61(5):800-6.

21 DiNubile MJ, Chow JW, Satishchandran V, *et al*. Acquisition of resistant bowel flora during a double-blind randomized clinical trial of ertapenem versus piperacillin-tazobactam therapy for intraabdominal infections. *Antimicrob Agents Chemother* 2005; 49:3217-21.

22 Falguera M, Ruiz-Gonzalez A, Schoenenberger JA, *et al*. Prospective, randomised study to compare empirical treatment versus targeted treatment on the basis of the urine antigen results in hospitalised patients with community-acquired pneumonia. *Thorax* 2010; 65(2):101-106.

23 Kim JW, Chung J, Choi SH, *et al*. Early use of imipenem/cilastatin and

vancomycin followed by de-escalation versus conventional antimicrobials without de-escalation for patients with hospital-acquired pneumonia in a medical ICU: a randomized clinical trial. *Crit Care* 2012; 16(1):R28.

24 Leone M, Bechis C, Baumstarck K, *et al*; AZUREA Network Investigators. De-escalation versus continuation of empirical antimicrobial treatment in severe sepsis: a multicenter non-blinded randomized noninferiority trial. *Intensive Care Med* 2014; 40(10):1399-408.

25 Paul M, Dickstein Y, Raz-Pasteur A. Antibiotic de-escalation for bloodstream infections and pneumonia: systematic review and meta-analysis. *Clin Microbiol Infect* 2016. Ahead of print.

26 Weiss E, Zahar JR, Lesprit P, *et al*; De-escalation Study Group. Elaboration of a consensual definition of de-escalation allowing a ranking of β-lactams. *Clin Microbiol Infect* 2015; 21(7):649.e1-10.

27 Madaras-Kelly K, Jones M, Remington R, *et al*. Development of an antibiotic spectrum score based on veterans affairs culture and susceptibility data for the purpose of measuring antibiotic de-escalation: a modified Delphi approach. *Infect Control Hosp Epidemiol* 2014; 35(9):1103-13.

28 Mertz D, Koller M, Haller P, *et al*. Outcomes of early switching from intravenous to oral antibiotics on medical wards. *J Antimicrob Chemother* 2009; 64(1):188-99.

Figure 1. SIMPLIFY – Decision tree of patient enrolment

Figure 2. Schedule of visits and assessments. Except where otherwise specified, these refer to days from randomization.

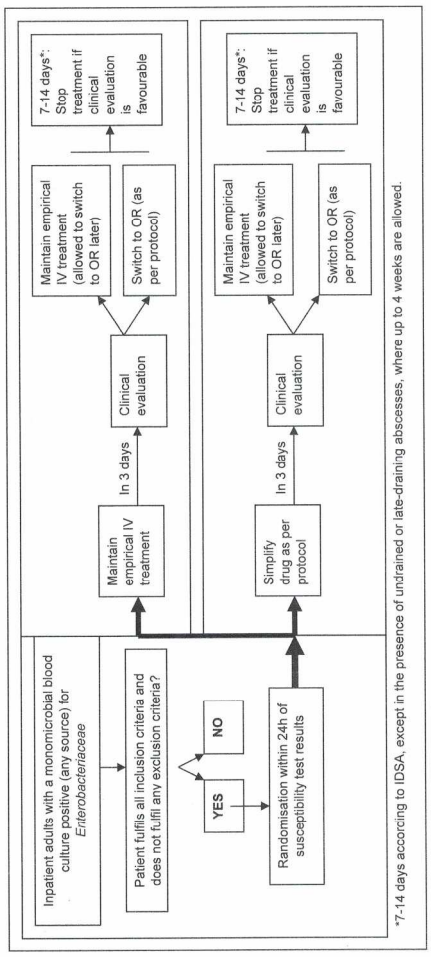

Figure 1.

203x290mm (300 x 300 DPI)

Figure 2.

Procedures	Selection 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.

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

WHAT DO WE OFFER YOU?

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

WHAT DOES THE TREATMENT CONSIST OF?

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

- Experimental group: following the criteria of your physician and according to the evolution of the disease, you may receive one of these antibiotics intravenously at the usual doses: ampicillin, trimethoprim/sulfamethoxazol, cefuroxime, cefotaxime, amoxicillin/clavulanic, ciprofloxacin, ertapenem.

It does not mean you will receive all of them, but you will be administered one of them in that order until your infection has been controlled.

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

In both cases, if your GP estimates that you suffer from a polymicrobial infection (caused by several bacteria), the previous antibiotic could be combined with one of the following: vancomycin, teicoplanin, daptomycin, linezolid, clindamycin or metronidazole.

The duration of the treatment will be the usual for the infection you suffer from (between 7 and 14 days).

After completing at least 5 days of intravenous treatment, your physician will decide whether it is possible to switch from intravenous (vein) to oral (mouth) medication.

During the study, the research staff will carry out a series of visits. The day the antibiotic treatment ends (if you are still in the hospital) and approximately one week after, a revision visit will be conducted. We will phone you to check how you feel, approximately 30 days after the antibiotic treatment started.

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

pharmaceuticals include the following: digestive discomfort, skin eruption, allergic reactions, muscular discomfort, blood and hepatobiliary alterations, kidney problems (including kidney failure), and neurological alterations. In any case, the risk of suffering from any of these adverse effects as a consequence of your participation in this study is not higher than the risk you would have if you received the regular treatment established for your disease. Moreover, all the side effects or undesired episodes that take place during the study will be monitored and followed up; therefore, we ask you to let the physicians of the study know if you find any discomfort or other new find.

In addition to these effects, blood draw and the intravenous administration of pharmaceuticals could cause pain or hematomas at the puncture site, among other things.

INSURANCE

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

CONFIDENTIALITY

The treatment, communication and transfer of the personal data of all the participating subjects will comply with the Organic Law 15/1999, of December 13th, on personal data protection, and the Royal Decree 1720/2007, of December 21st, by which the development Regulation of such law is approved. According to what is established by the mentioned legislation, you have the right to access, modify, oppose and cancel data, for which you will have to refer to your study physician.

The data collected for the study will be identified through a code and only your study GP/collaborators will be able to relate such data with you and your medical history. Therefore, your identity will not be revealed to anybody, except in some cases, such as a medical emergency or legal requirement.

Access to your personal information will be limited to the study physician/collaborators, health authorities (Spanish Agency of Pharmaceuticals and Health Products), the Ethics Committee of Clinical Research and the staff authorized by the sponsor, when they need it to check the data and the procedures of the study, but always confidentially, complying with the current legislation.

The results of the study will be presented in scientific meetings, medical conferences and scientific publications; however, the identity of the participating patients will be kept strictly confidential.

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 to12*
	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*

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*
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	*N/A*
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	*Pages 8 and 9*
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*
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	*Page 8*
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	*N/A*
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	*N/A*
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	*Page 17*
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	*Pages 16 and 17*

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	*Pages 17 and 18*
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	*Pages 13,14,19 and 20*
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	*Pages 13,14,19 and 20*
	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)	*Pages 18 and 19*
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	*Pages 16 and 17*
	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	*Pages 17 to 19*
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 16 and 19*
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*
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	*Pages 20 and 21*
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 17*

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*
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	*Pages 18 and 20*
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*
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	*Page 25*
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*
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*
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*
	31b	Authorship eligibility guidelines and any intended use of professional writers	*N/A*
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	*N/A*
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	*Annex 1*
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*

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