Non-inferiority versus superiority trial design for new antibiotics in an era of high antimicrobial resistance: the case for post-marketing, adaptive randomised controlled trials

Simone Lanini, John P A Ioannidis*, Francesco Vairo, Michel Pletschette, Gina Portella, Virginia Di Bari, Alessia Mammone, Raffaella Pisapia, Stefano Merler, Boniface Nguhuni, Martin Langer, Antonino Di Caro, Sarah J L Edwards, Nicola Petrosillo, Alimuddin Zumla*, Giuseppe Ippolito**

Antimicrobial resistance is one of the most important threats to global health security. A range of Gram-negative bacteria associated with high morbidity and mortality are now resistant to almost all available antibiotics. In this context of urgency to develop novel drugs, new antibiotics for multidrug-resistant Gram-negative bacteria (namely, ceftazidime-avibactam, plazomicin, and meropenem-vaborbactam) have been approved by regulatory authorities based on non-inferiority trials that provided no direct evidence of their efficacy against multidrug-resistant bacteria such as Enterobacteriaceae spp, *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, *Burkholderia cepacia*, and *Acinetobacter baumannii*. The use of non-inferiority and superiority trials, and selection of appropriate and optimal study designs, remains a major challenge in the development, registration, and post-marketing implementation of new antibiotics. Using an example of the development process of ceftazidime-avibactam, we propose a strategy for a new research framework based on adaptive randomised clinical trials. The operational research strategy has the aim of assessing the efficacy of new antibiotics in special groups of patients, such as those infected with multidrug-resistant bacteria, who were not included in earlier phase studies, and for whom it is important to establish an appropriate standard of care.

Lancet Infect Dis 2019; 19: e444–51

Published Online August 23, 2019 http://dx.doi.org/10.1016/S1473-3099(19)30284-1

*Authors contributed equally

National Institute for Infectious Diseases (INMI), Lazzaro Spallanzani IRCCS, Rome, Italy (S Lanini MD, F Vairo MD, V Di Bari MD, A Di Caro MD, A Mammone MD, R Pisapia PhD, N Petrosillo MD, Prof G Ippolito FRCP); **Department of Medicine, Stanford Prevention Research Center** (Prof J P A Ioannidis MD), **and Departments of Health Research and Policy and of Biomedical Data Science** (J P A Ioannidis), **Stanford University School of Medicine, Stanford, California, USA; Department of Tropical and Infectious Diseases, Medical Center of the University of Munich, Munich, Germany** (M Pletschette MD); **EMERGENCY-NGO, Milan, Italy** (G Portella MD, Prof M Langer MD); **Center for Information Technology, Bruno Kessler Foundation, Trento, Italy** (S Merler MS); **Division of Health, President's Office Regional Administration and Local Government (PORALG), Dodoma, Tanzania** (B Nguhuni MD); **Ethics and Governance** (Prof S J L Edwards PhD) **and Division of Infection and Immunity** (Prof A Zumla FRCP), **University College London; and NIHR Biomedical Research Centre, University College London Hospitals, London, UK** (A Zumla)

Correspondence to: Prof Giuseppe Ippolito, National Institute for Infectious Diseases (INMI), Lazzaro Spallanzani IRCCS, 00149 Rome, Italy **giuseppe.ippolito@inmi.it**

Introduction

Antimicrobial resistance is one of the most pressing health issues worldwide.[1,2] The mechanisms of transmission of this resistance among Gram-negative bacteria are extremely efficient and several multidrug-resistant Gram-negative bacteria are now phenotypically resistant to all available antimicrobials.[3] Carbapenem-resistant Gram-negative bacteria such as Enterobacteriaceae spp, *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, *Burkholderia cepacia*, and *Acinetobacter baumannii*, are associated with fatal human infections with no established standard of care.[4–6]

In January, 2017, WHO issued a consensus document[7] defining the priorities for research and development of new antibiotics. The document concluded that carbapenem-resistant Gram-negative bacteria are a critical threat for human welfare and that there is an urgent need for future research strategies to focus on the discovery of new antimicrobials. This document was followed by EU and US Government initiatives, including the Joint Research Programming Initiative on Antimicrobial Resistance,[8] initiatives of the National Institute for Allergy and Infectious Diseases,[9] and calls made by the European Innovative Medicines Initiative,[10] and the Antibacterial Resistance Leadership Group.[11,12]

A major challenge in the development, registration, and post-marketing implementation of new antibiotics is the selection of appropriate and efficient study designs. There is substantial ongoing debate and confusion about the use of non-inferiority and superiority designs. Using as an example the process that has led to the development and registration of the combination of ceftazidime-avibactam, we propose a strategy for developing a new methodological research framework based on adaptive, post-marketing randomised clinical trials (aRCTs), using carbapenem-resistant-Gram-negative bacteria sepsis as a case study.

Ceftazidime and avibactam

Ceftazidime is a well-established third-generation cephalosporin with enhanced activity against most Gram-negative bacteria, including Enterobacteriaceae spp and *P aeruginosa*, and was approved for human use by the US Food and Drug Administration (FDA) in 1985. By contrast with carbapenems, which are the standard of care for several multidrug-resistant Gram-negative bacteria (including those resistant to cephalosporin),[6] ceftazidime is poorly active against anaerobes *A baumannii* and *S maltophilia*, and is inactivated by extended spectrum β-lactamases.[13] Avibactam is a non-β-lactam, β-lactamase inhibitor without intrinsic antibacterial activity. Ceftazidime plus avibactam can re-establish antibacterial activity for Gram-negative bacteria producing Ambler classes A, C, and D β-lactamases, which inactivate cephalosporins and carbapenems. However, ceftazidime-avibactam has no activity against Gram-negative bacteria that have become resistant to ceftazidime for mechanisms other than production of β-lactamases[4,14,15] and for Gram-negative bacteria that produce metallo-β-lactamases (ie, Ambler class B β-lactamases), which are associated with high level resistance to all β-lactams, including carbapenems.[16]

The safety and efficacy of ceftazidime-avibactam have been assessed in eight randomised controlled trials (RCTs), providing evidence that ceftazidime-avibactam is non-inferior to carbapenems for treatment of Gram-negative bacterial infections.[17–23] These studies included

adults with either urinary tract infections, hospital acquired pneumonia, or intra-abdominal infections. The proportion of randomly assigned participants who had a microbiological diagnosis of the infection ranged between 44% and 92%. Among them, the prevalence of cephalosporin resistance was between 13% and 100%, whereas prevalence of resistance to either carbapenems or ceftazidime-avibactam was between 0% and 10%. The aims behind the trials were to define the preliminary efficacy and safety profile (two phase 2 RCTs)[22,23] and to find alternative drugs that are suitable for carbapenem-sparing regimens (six non-inferiority, phase 3 RCTs).[17–21] Ceftazidime-avibactam was not expected to be more convenient than the comparator in terms of administration route or safety profile. In addition, results of individual RCTs have been pooled into secondary research studies, including meta-analyses[6,24–26] and post-hoc analyses,[27,28] for supporting the hypothesis that ceftazidime-avibactam is superior to standard of care for infections caused by bacteria with special antimicrobial resistance profiles. As it is typical when multiple meta-analyses are done, the conclusions and the emphasis placed on the results vary among them and their results can become conflicting and even misleading.[27,28] In particular, some studies[29,30] confirmed no significant difference between treatment groups, some studies[25,26] claimed better efficacy of the experimental intervention for multidrug-resistant bacteria than the comparator, whereas other studies[24] showed that the experimental intervention was more toxic than the comparator.

Ethical and practical implications of non-inferiority RCTs

Non-inferiority-RCTs are typically presented as a pragmatic design that can compare a new intervention against an established standard of care.[31] By contrast to superiority RCTs, which assess whether the new intervention performs better than the old ones, non-inferiority-RCTs are designed for excluding an unacceptable loss in efficacy. Due to this inherent feature, interpreting non-inferiority RCTs can be a challenge. Indeed, several ethical and analytical concerns are still a matter of debate.[32] Remarkable ethical issues include how to establish a reasonable (and ethically acceptable) non-inferiority margin,[33] and how to inform and convince patients to receive a treatment that is expected to be (somehow) worse than a consolidated standard of care.[34] In addition, from a methods point of view, non-inferiority-RCTs are very susceptible to the effects of incomplete information on outcomes. By contrast with superiority RCTs, where there is substantial consensus that they can best be interpreted by intention-to-treat analysis, guidance on how to deal with missing and censored observations in non-inferiority-RCTs is variable and includes:[32] multiple imputation analysis (which could be biased because of the arbitrary imputation framework); intention-to-treat analysis (which could bias toward a false positive conclusion of non-inferiority); analysis modified on inclusion criteria, such as modified intention-to-treat analysis (which could introduce selection bias); or sensitivity analysis of the different approaches (where inconsistent results would provide no evidence for clinical decision). The proportion of non-inferiority RCTs that successfully claim non-inferiority is so high that it suggests a bias in design, analysis, or interpretation often leads to spuriously favourable conclusions.[35–37]

Despite these structural complexities, non-inferiority-RCTs are of substantial value because they can show unacceptable loss in efficacy of a tested drug for specific clinical conditions, such as eravacycline for therapy of urinary tract infection[38] and daptomycin for treatment of pneumonia.[39] Also relevant is the excess deaths associated with approval based on non-inferiority RCTs of tigecycline for severe infections.[37] Moreover, non-inferiority RCTs are pivotal for choosing an alternative intervention that, in comparison with the standard of care, is better in terms of tolerability, safety, and delivery or cost (ie, the tradeoff decision).[40] An appropriate example can be seen in a non-inferiority RCT[41] from 2017 that assessed efficacy of oral azithromycin versus intramuscular penicillin for treatment of yaws in African children. The advantage of oral therapy is self-evident (ie, averting injections in a low-resource setting).[41] Tradeoff decisions are also relevant in affluent settings. Several non-inferiority RCTs have been done for ascertaining whether antibiotics could be a reasonable alternative to the surgical standard of care for acute appendicitis. In this case as well, the rationale for non-inferiority was clear (ie, sparing surgery).[42,43]

However, methodological and ethical concerns emerge when non-inferiority-RCTs are used to infer conclusions beyond the actual results and stakeholders suggest that this is appropriate.[44] In particular, concerns rise when surrogate (in vitro) evidence of efficacy is merged with results of non-inferiority RCTs to draw new evidence of superiority. For example, ceftazidime-avibactam was assessed as a non-inferior alternative to carbapenem in clinical settings with high prevalence of cephalosporin resistant Gram-negative bacteria for which standard of care was, in fact, a carbapenem. When non-inferiority was shown, indirect (in vitro) evidence was used to support the use of ceftazidime-avibactam for several clinical conditions caused by susceptible microorganisms, including those resistant to the standard of care used in the non-inferiority RCTs (eg, Enterobacteriaceae that produce *Klebsiella pneumoniae* carbapenemase).[45,46]

There are several flaws in such an approach. First, in-vitro studies do not prove in-vivo efficacy. For example, a superiority RCT[47] that assessed the in-vivo effects of the in-vitro synergy between meropenem and colistin on carbapenem-resistant-Gram-negative bacteria showed no significant effect.[47] Second, using RCT results to infer conclusions outside of the scope of the study compromises the integrity of the evidence and can create confusion among health-care workers who change practice on the

basis of the results. The most obvious clinical consequence of non-inferiority of ceftazidime-avibactam versus carbapenems is to include ceftazidime-avibactam within antimicrobial stewardship programmes for carbapenem-sparing regimens aimed to contain the diffusion of carbapenem-resistant-Gram-negative bacteria in settings with high prevalence of cephalosporin resistance. Third, ethical issues would need to be raised if non-inferiority RCTs were designed, instead of superiority RCTs, for accelerating marketing of alternative compounds with no expected greater efficacy, no self-evident advantage, and no evident biosimilarity compared to a consolidated standard of care. These limitations were evident in two systematic reviews[33,48] that showed that most non-inferiority RCT protocols contain no rationale for the non-inferiority hypothesis, no rationale for establishing the efficacy margin, and poor information given to patients about the final purpose of the study (including the real meaning of non-inferiority).

Adaptive RCTs for assessment of superiority in the post-marketing phase

The challenge for research on carbapenem-resistant-Gram-negative bacteria infections is to find alternate innovations that are ethical and effective without over-interpreting data from non-inferiority RCTs. Experience in operational research for other severe infections, such as Ebola virus disease, shows that adaptive RCTs (aRCTs) could provide a solution.[49] Adaptation is a carefully considered investigational procedure for modifying study parameters while the aRCT is ongoing, on the basis of a review of the interim data analyses.[50] Thus, it might be possible to build on available evidence from existing non-inferiority RCTs for producing new, solid, evidence and for providing all patients with the best treatment as soon as possible.[51]

To assess the performance of putative aRCTs in this field, we used a proprietary simulator package (ADDPLAN-TM, Cologne, version 6.1) that is approved by the main regulatory agencies in Europe (European Medicines Agency), USA (FDA), and Japan (Pharmaceuticals and Medical Devices Agency). The aim of this simulated aRCT is to assess the efficacy (superiority) of a new antibiotic (the experimental arm) versus a standard of care (the control arm) for treatment of bacterial sepsis due to carbapenem-resistant Gram-negative bacteria (the condition). The experimental arm will include an antibiotic that has already received market authorisation by non-inferiority RCT for treatment of infections due to drug-resistant bacteria, according to guidelines for evaluation of new antimicrobials.[52,53] The primary end-point will be 14 days reduction of all-cause mortality after randomisation from an expected 30% to less than 20% with a power of 80% and an one-sided α error of 5%. This expectation is, indeed, a conservative assumption because mortality for bloodstream infections due to certain carbapenem-resistant Gram-negative bacteria, such as *Klebsiella* spp, might be higher than 30%.[54] One-sided significance has been chosen because the experimental arm will include an approved drug, which proved to be non-inferior to standard of care, and has (yet unproven) potential for superiority in selected subsets of patients, such as those with carbapenem-resistant Gram-negative bacteria infections.[6,24–26] To optimise statistical power, all analyses are done on all participants for whom eligibility criteria can be ascertained after randomisation (ie, a carbapenem-resistant Gram-negative bacteria has been isolated from a blood sample taken before treatment allocation). The adaptation strategy consists of a three-stage sequential design (ie, stage 1 is the first interim analysis, stage 2 is the second interim analysis, and stage 3 is the final analysis stage) allowing for sample size recalculation and early stopping for efficacy.[55] As a result of the superiority design, this study will have advantages compared with a non-inferiority RCT. In particular, intention-to-treat analyses of all participants who meet the enrollment criteria will prevent bias towards rejection of the null hypothesis due to incomplete outcome information. Moreover, censored observation, such as lost to follow-up, will not significantly affect the chance of type 2 error, because a no futility stopping rule will be implemented. Finally, the expected inflation of type 1 error due to group sequential design is controlled by the implementation of an α spending function, minimal sample size at stage 1, and minimal sample size for subsequent stages. The basic aRCT parameters are reported in the panel.[58–60]

Panel A of the figure shows the probability of early stopping and expected sample size for different levels of efficacy of the experimental versus the control arm. Panel B of the figure shows the aRCT sequence, including participant enrollment and the interpretation of results after each analysis. In particular, if the previous hypothesis is confirmed (ie, all-cause mortality is 30% and 20% in the control and experimental groups, respectively), the expected sample size for this aRCT will be, on average, 278. By contrast, a standard non-adaptive RCT would have required a sample size of about 460 patients; the reduction of the sample size is driven by the chance of early stopping and the optimisation of statistical power obtained through recalculation of sample size.

The aRCT design can become a pragmatic study[61] when implemented with point-of-care randomisation in real life settings with high prevalence of carbapenem-resistant Gram-negative bacteria, high standards of care, and access to the most up-to-date diagnostics (eg, hospitals in high-income countries[2,62,63] or settings in low-income and middle-income countries where a high standard of care can be guaranteed).[64] At best, this aRCT would be part of an ongoing integrated intervention for infection control that also includes hospital-based surveillance of multidrug-resistant bacteria and antimicrobial stewardship programmes.[65] The aRCT is expected to enroll patients with

***Panel*: The basic parameters for adaptive, post-marketing randomised clinical trials (aRCTs)**

- The maximum number of stages is three (ie, first interim analysis, second interim analysis, and final analysis).
- α=0·050 one-sided should be used as the significance level.
- The O'Brien and Fleming design should be used for the α spending function.[56,57]
- Information rate per stage should be 0·333 at stage 1, 0·667 at stage 2, and 1·000 at stage 3 (uniform).
- The measure of effect should be by risk difference.
- The overall conditional power should be 80% for assessing reduction of all-cause mortality from 30% to 20% (all-cause mortality is the study primary outcome).
- The allocation ratio should be 1:1.
- At each stage the sample size should be recalculated using Fisher's exact test and maximum likelihood ratio estimates for observed effect (ie, it should be assumed that the observed risk difference at previous interim analysis is the true effect). Fisher's exact test should be considered because it yields an exact level α testing procedure that is quite conservative.
- For sample size constraint per stage there are 70 participants at stage 1, and ten to 180 participants at stage 2 and 3. Depending on the assumed risk difference at interim analyses that influence the calculation of the overall conditional power, a varying number of participants will be required to be enrolled in stage 2 and 3.
- The sample size range should be 70–430 participants.
- For the average sample size range according to observed effect, see panel A of the figure.
- The number of simulation iterations should be 10 000.
- The software specification used for the simulation was ADDPLANTM 6.1.1 ADDPLAN (approved by the US Food and Drug Administration, European Medicines Agency, and the Pharmaceuticals and Medical Devices Agency, Japan).

complex characteristics that are potentially in need of multiple simultaneous empirical therapies.[66] Thus, the experimental compound will need to be administered on top of all other therapies and might include a combination of several antimicrobials.[67] To increase pragmatism, double-blinding would not be introduced, as providing placebos would make the trial deviate substantially from routine practice. In our opinion, these studies can be implemented within international research networks[8,11,12] and primarily funded through public sector grants for independent medical research. Unfortunately, much recruitment for antimicrobial trials in the past decade has happened in centres without a strong tradition of clinical research or questionable quality of care, but this trend needs to be reversed if studies with more complex designs are to be done. This improvement would help to overcome scepticism about aRCTs feasibility. Decision-making funding bodies and other stakeholders (eg, patients associations) might become more supportive if they are familiarised with these trials with comprehensive explanation of the experimental design, study aims, potential risks, expected advantages, and how to manage the effects of adaptation on economic issues.[55,68]

We have described our adaptive strategy as simply as possible to best convey the essential mechanism of this approach. However, composite designs could be tailored on the actual ethical and economic issues that might arise locally. Exposing patients to suboptimal treatment can be reduced by a stopping rule for futility while more interim analyses could be considered to detect earlier a potentially extraordinary efficacy of the experimental compound. Use of composite primary endpoints might reduce the required sample size but caveats also exist on their use. For example, for sepsis, treatment success definition could include parameters for improved haemodynamic stability or some validated clinical score (eg, the sequential organ failure assessment [SOFA] score) in addition to all-cause mortality.[69] Composite endpoints have also been proposed for hospital pneumonia and ventilator-associated pneumonia.[70,71] A major disadvantage with composite endpoints, however, is that the components have very different clinical significance. Moreover, the results might differ across the components of the composite.[72–74] Finally, if the proposed RCT is meant to simultaneously assess efficacy of more than one new therapeutic option, multiarm study designs are feasible.[50,51,75]

aRCTs are remarkably flexible study designs but their advantages come at the cost of increasing complexity. Indeed, the proposed aRCTs also have unavoidable practical limitations. First, advantages of each further adaptive component or surrogate endpoint introduce additional complexity for study management and might reduce the ability to interpret results.[55] Second, aRCTs always need a careful selection of statistical analyses tailored on the specific adaptive components chosen for preventing potential inflation of the statistical error and bias on effect estimates.[55] However, regulatory agencies in Europe and the USA have already issued detailed guidelines[76,77] and statistical features for the most common adaptive designs, which have already been validated and implemented in specific software packages.[55] Third, there is a need to combine sufficient clinical and methodological expertise to pick the best adaptation parameters and to be able to implement the trials faithfully to the original intention. Fourth, innovative aRCTs in the field of antimicrobial resistance need access to the most up-to-date techniques in molecular microbiology for timely selection of participants according to the antimicrobial resistance profile of the infecting organism. Indeed, the feasibility and the gains in statistical power of enrolling participants according to antimicrobial resistance profile have been shown in the MERINO study.[69] Finally, there are still no formal recommendations on how to report aRCTs in the peer-reviewed literature and how to appraise evidence from aRCTs in evidence synthesis. The CONSORT collaboration[78] has started a consensus process for producing guidelines for reporting aRCTs. However, there is no reason to think that aRCTs are less reliable than other RCTs. Although regulatory agencies, such as the European Medicines Agency and FDA, have already considered aRCTs instead of standard RCTs for market authorisations,[79] there is a need for regulators and methodologists alike to devise suitable research designs for

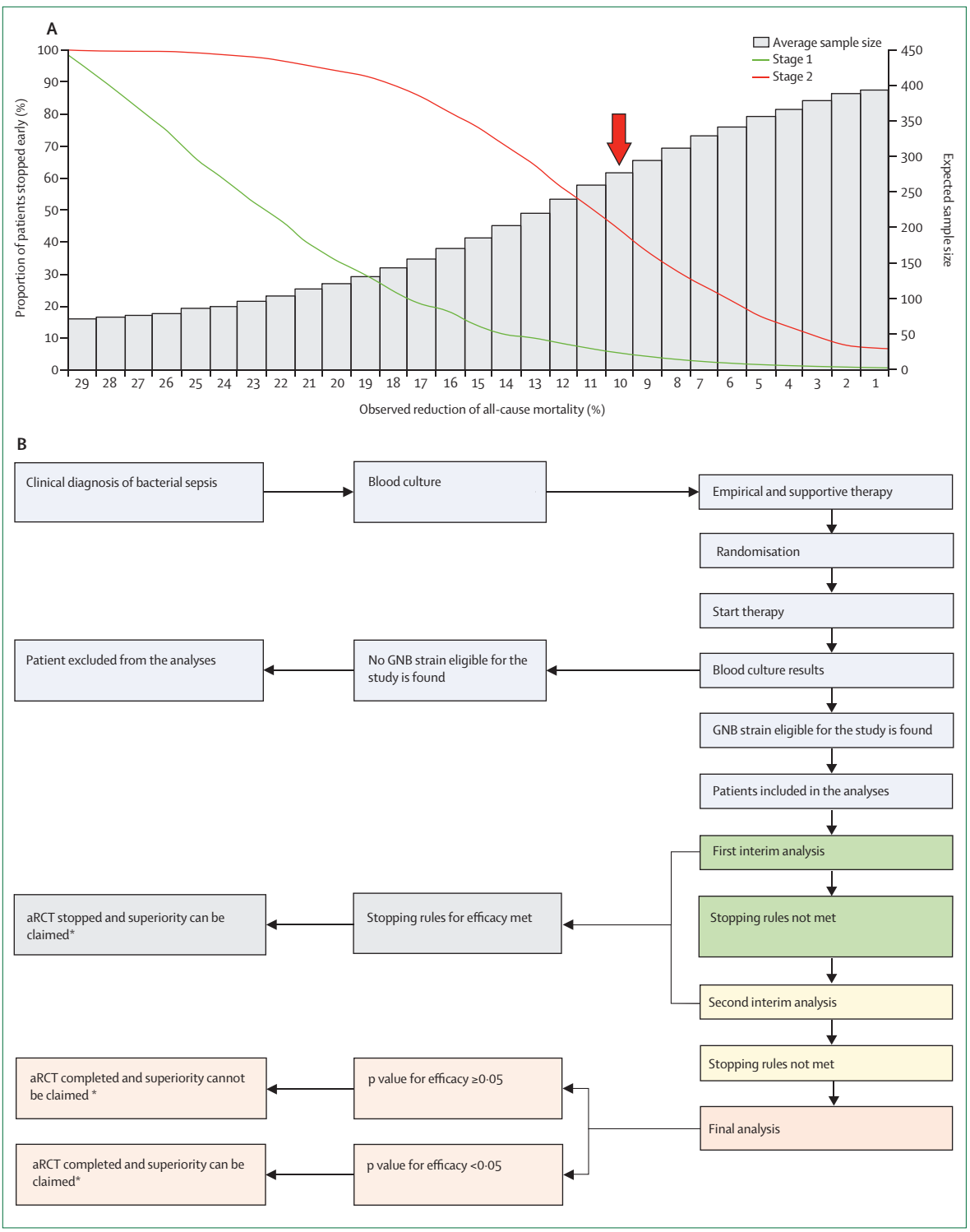

Figure: **Adaptive trial simulation**
(A) The probability of early stopping of the aRCT (lines) and expected sample size (bars) for observed reduction in all-mortality between the control (assumed at 30%) and experimental group (variable between 1% and 29%). Red arrow represents sample size (n=278) for the main aRCT assumption, including power 80%, α=0·05, and efficacy (risk difference) of 10%. (B) Different phases of the aRCT, including participant enrollment and selection (blue), first interim analysis (green), second interim analysis (yellow), binding decision on early aRCT termination (grey), and final analysis (red). aRCT=adaptive, post-marketing randomised clinical trial. GNB=Gram-negative bacteria. *As one or multiple aRCTs are completed, their results can be added to the results of other existing trials in cumulative meta-analyses that provide new, comprehensive views of the developing evidence.

post-marketing analyses of treatments provided under early access schemes.

Conclusions

During the past decade, antimicrobial resistance has become a major global health priority. Despite ongoing scientific research and increasing efforts from pharmaceutical industries and funding agencies, antimicrobial resistance continues to spread worldwide. Carbapenem resistance in Gram-negative bacteria is of particular concern. Non-inferiority RCTs appear to have deviated from their primary field of application and are being used to empirically inform new standard of care for multidrug-resistant pathogens. The case for ceftazidime-avibactam is made here but similar conclusions can be drawn for other antimicrobials effective against multidrug-resistant Gram-negative bacteria, including plazomicin (approved by the FDA following evidence from a single non-inferiority RCT against meropenem)[80,81] or meropenem-vaborbactam (approved by the FDA following evidence from a single non-inferiority RCT against piperacillin-tazobactam).[81–83] The choice of developing these drugs as a result of evidence from non-inferiority, instead of superiority RCTs, is primarily a matter of convenience.[40] In terms of logistics, a superiority RCT would have required the selection of only carbapenem-resistant infections within a longer study time and higher costs for testing. Furthermore, from a drug development point of view, superiority RCTs could have led to the risk of a negative result, meaning absence of adequate data to support the approval of the drug.[81]

However, outside their proper field of application, non-inferiority RCTs are much weaker than superiority RCT in terms of scientific rationale, ethical justification, and potential for translational research outputs; in fact, they provide no evidence to establish a new solid standard of care. We suggest alternative ways to promote aRCTs, integrating them as part of infection control programmes within health-care settings with a high prevalence of multidrug resistance. In this context, aRCTs could be viewed as next generation, phase 4, post-marketing RCTs that go beyond the primary scope of surveilling infrequent side-effects and assessing effectiveness under health economics aspects. aRCTs could also include elements directly associated with drug efficacy in special groups of patients, such as those infected with multidrug-resistant bacteria who were not included in earlier phase studies and for whom it is urgent to establish the appropriate therapy.

Contributors

GI, SL, JPAI, and AZ developed the concept of this Personal View and the first draft. SL and AM did the simulations. All authors contributed to writing and final version of the manuscript.

Declaration of interests

NP has received personal fees from Pfizer, Merck and company, Shionogi, Johnson & Johnson, Cepheid, Zambon, Angelini, Takeda, and Accelerate. NP has also received a research grant from Shionogi. All other authors declare no competing interests.

Acknowledgments

This Personal View was supported by the Italian Ministry of Health ("Ricerca Corrente"), Linea 1. GI, AZ, SL, and FV receive support from the PANDORA-ID-NET, (EDCTP Reg/Grant RIA2016E-1609) grant. AZ is in receipt of a National Institutes of Health Research (NIHR) senior investigator award. SJLE and AZ receive support from the UCH/UCL NIHR Biomedical Research Centre.

References

1 Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States. Atlanta, GA: US Department of Health and Human Services, CDC, 2013. http://www.cdc.gov/drugresistance/threat-report-2013/ (accessed July 25, 2019).

2 European Centre for Disease Prevention and Control. Surveillance of antimicrobial resistance in Europe 2016. Annual Report of the European Antimicrobial Resistance Surveillance Network). Stockholm: ECDC, 2017. https://ecdc.europa.eu/en/publications-data/antimicrobial-resistance-surveillance-europe-2016 (accessed July 25, 2019).

3 de Man TJB, Lutgring JD, Lonsway DR, et al. Genomic analysis of a pan-resistant isolate of *Klebsiella pneumoniae*, United States 2016. *MBio* 2018; **9:** e00440–18.

4 Codjoe FS, Donkor ES. Carbapenem resistance: a review. *Med Sci (Basel)* 2017; **6:** 1.

5 Falagas ME, Tansarli GS, Karageorgopoulos DE, Vardakas KZ. Deaths attributable to carbapenem-resistant Enterobacteriaceae infections. *Emerg Infect Dis* 2014; **20:** 1170–75.

6 Chen M, Zhang M, Huang P, et al. Novel β-lactam/β-lactamase inhibitors versus alternative antibiotics for the treatment of complicated intra-abdominal infection and complicated urinary tract infection: a meta-analysis of randomized controlled trials. *Expert Rev Anti Infect Ther* 2018; **16:** 111–20.

7 WHO. Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. 2017. http://www.who.int/medicines/publications/global-priority-list-antibiotic-resistant-bacteria/en/ (accessed Aug 18, 2018).

8 Joint Programming Initiative on Antimicrobial Resistance. Global Coordination of Antimicrobial Resistance Research. http://www.jpiamr.eu (accessed Sept 1, 2018).

9 National institute of Allergy and Infectious Diseases. Antimicrobial (Drug) Resistance. https://www.niaid.nih.gov/research/antimicrobial-resistance (accessed Feb 25, 2019).

10 Innovative Medicine Initiative. New antimicrobial resistance accelerator programme part of latest IMI calls for proposals. https://www.imi.europa.eu/news-events/press-releases/new-antimicrobial-resistance-accelerator-programme-part-latest-imi-calls (accessed Feb 25, 2019).

11 Centers for Diseases Control and prevention. Federal engagement in antimicrobial resistance. 2018. https://www.cdc.gov/drugresistance/federal-engagement-in-ar/index.html (accessed Aug 15, 2018).

12 National Institute for Allergy and Infectious Diseases. Antibacterial Resistance Leadership Group (ARLG). https://www.niaid.nih.gov/research/antibacterial-resistance-leadership-group (accessed Sept 1, 2018).

13 Mulvey MR, Bryce E, Boyd D, et al. Ambler class A extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella spp.* in Canadian hospitals. *Antimicrob Agents Chemother* 2004; **48:** 1204–14.

14 Lister PD, Wolter DJ, Hanson ND. Antibacterial-resistant *Pseudomonas aeruginosa*: clinical impact and complex regulation of chromosomally encoded resistance mechanisms. *Clin Microbiol Rev* 2009; **22:** 582–610.

15 Nikaido H, Pagès JM. Broad-specificity efflux pumps and their role in multidrug resistance of Gram-negative bacteria. *FEMS Microbiol Rev* 2012; **36:** 340–63.

16 Abboud MI, Damblon C, Brem J, et al. Interaction of avibactam with class B metallo-β-lactamases. *Antimicrob Agents Chemother* 2016; **60:** 5655–62.

17 Qin X, Tran BG, Kim MJ, et al. A randomised, double-blind, phase 3 study comparing the efficacy and safety of ceftazidime/avibactam plus metronidazole versus meropenem for complicated intra-abdominal infections in hospitalised adults in Asia. *Int J Antimicrob Agents* 2017; **49:** 579–88.

18 Torres A, Zhong N, Pachl J, et al. Ceftazidime-avibactam versus meropenem in nosocomial pneumonia, including ventilator-associated pneumonia (REPROVE): a randomised, double-blind, phase 3 non-inferiority trial. *Lancet Infect Dis* 2018; **18:** 285–95.

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:** 754–62.

20 Mazuski JE, Gasink LB, Armstrong J, et al. Efficacy and safety of ceftazidime-avibactam plus metronidazole versus meropenem in the treatment of complicated intra-abdominal infection: results from a randomized, controlled, double-blind, phase 3 program. *Clin Infect Dis* 2016; **62:** 1380–89.

21 Carmeli Y, Armstrong J, Laud PJ, et al. Ceftazidime-avibactam or best available therapy in patients with ceftazidime-resistant Enterobacteriaceae and *Pseudomonas aeruginosa* complicated urinary tract infections or complicated intra-abdominal infections (REPRISE): a randomised, pathogen-directed, phase 3 study. *Lancet Infect Dis* 2016; **16:** 661–73.

22 Lucasti C, Popescu I, Ramesh MK, Lipka J, Sable C. Comparative study of the efficacy and safety of ceftazidime/avibactam plus metronidazole versus meropenem in the treatment of complicated intra-abdominal infections in hospitalized adults: results of a randomized, double-blind, phase II trial. *J Antimicrob Chemother* 2013; **68:** 1183–92.

23 Vazquez JA, González Patzán LD, Stricklin D, et al. Efficacy and safety of ceftazidime-avibactam versus imipenem-cilastatin in the treatment of complicated urinary tract infections, including acute pyelonephritis, in hospitalized adults: results of a prospective, investigator-blinded, randomized study. *Curr Med Res Opin* 2012; **28:** 1921–31.

24 Sternbach N, Leibovici Weissman Y, Avni T, Yahav D. Efficacy and safety ofceftazidime/avibactam: a systematic review and meta-analysis. *J Antimicrob Chemother* 2018; **73:** 2021–29.

25 Zhong H, Zhao XY, Zhang ZL, et al. Evaluation of efficacy and safety of ceftazidime-avibactam in the treatment of Gram-negative bacterial infections: a systematic review and meta-analysis. *Int J Antimicrob Agents* 2018; **52:** 443–50.

26 Zhang Y, Tao LN, Qu XY, Niu JQ, Ding YH, Zhang SX. Efficacy and safety of ceftazidime-avibactam in the treatment of complicated intra-abdominal infections (CIAIs) and complicated urinary tract infections (CUTIs): A meta-analysis of randomized controlled trials. *Rev Assoc Med Bras* 2018; **64:** 253–63.

27 Ioannidis JP. Meta-research: the art of getting it wrong. *Res Synth Methods* 2010; **1:** 169–84.

28 Ioannidis JP. The mass production of redundant, misleading, and conflicted systematic reviews and meta-analyses. *Milbank Q* 2016; **94:** 485–514.

29 Stone GG, Newell P, Gasink LB, et al. Clinical activity of ceftazidime/avibactam against MDR Enterobacteriaceae and *Pseudomonas aeruginosa*: pooled data from the ceftazidime/avibactam phase III clinical trial programme. *J Antimicrob Chemother* 2018; **73:** 2519–23.

30 Mendes RE, Castanheira M, Woosley LN, Stone GG, Bradford PA, Flamm RK. Molecular β-lactamase characterization of aerobic gram-negative pathogens recovered from patients enrolled in the ceftazidime-avibactam phase 3 trials for complicated intra-abdominal infections, with efficacies analyzed against susceptible and resistant subsets. *Antimicrob Agents Chemother* 2017; **61:** e02447–16.

31 Dal-Ré R, Janiaud P, Ioannidis JPA. Real-world evidence: how pragmatic are randomized controlled trials labeled as pragmatic? *BMC Med* 2018; **16:** 49.

32 Mauri L, D'Agostino RB Sr. Challenges in the design and interpretation of noninferiority trials. *N Engl J Med* 2017; **377:** 1357–67.

33 Rehal S, Morris TP, Fielding K, Carpenter JR, Phillips PP. Non-inferiority trials: are they inferior? A systematic review of reporting in major medical journals. *BMJ Open* 2016; **6:** e012594.

34 Doshi P, Hur P, Jones M, et al. Informed consent to study purpose in randomized clinical trials of antibiotics, 1991 through 2011. *JAMA Intern Med* 2017; **177:** 1–8.

35 Flacco ME, Manzoli L, Boccia S, et al. Head-to-head randomized trials are mostly industry sponsored and almost always favor the industry sponsor. *J Clin Epidemiol* 2015; **68:** 811–20.

36 Flacco ME, Manzoli L, Ioannidis JP. Noninferiority is almost certain with lenient noninferiority margins. *J Clin Epidemiol* 2016; **71:** 118.

37 Prasad P, Sun J, Danner RL, Natanson C. Excess deaths associated with tigecycline after approval based on noninferiority trials. *Clin Infect Dis* 2012; **54:** 1699–709.

38 US National Library of Medicine. Efficacy and safety study of eravacycline compared with levofloxacin in complicated urinary tract infections. 2019. https://clinicaltrials.gov/ct2/show/results/NCT01978938?intr=Eravacycline&rank=4 (accessed May, 2019).

39 Silverman JA, Mortin LI, Vanpraagh A, et al. Inhibition of daptomycin by pulmonary surfactant: in vitro modeling and clinical impact. *J Infect Dis* 2005; **191:** 2149–52.

40 Rex JH, Talbot GH, Goldberger MJ, et al. Progress in the fight against multidrug-resistant bacteria 2005-2016: modern noninferiority trial designs enable antibiotic development in advance of epidemic bacterial resistance. *Clin Infect Dis* 2017; **65:** 141–46.

41 Kwakye-Maclean C, Agana N, Gyapong J, et al. A single dose oral azithromycin versus intramuscular benzathine penicillin for the treatment of yaws-a randomized non inferiority trial in Ghana. *PLoS Negl Trop Dis* 2017; **11:** e0005154.

42 Wilms IM, de Hoog DE, de Visser DC, Janzing HM. Appendectomy versus antibiotic treatment for acute appendicitis. *Cochrane Database Syst Rev* 2011; **11:** CD008359.

43 Varadhan KK, Neal KR, Lobo DN. Safety and efficacy of antibiotics compared with appendicectomy for treatment of uncomplicated acute appendicitis: meta-analysis of randomised controlled trials. *Br Med J* 2012; **344:** e2156.

44 Di Nubile MJ. Noninferior antibiotics: when is "not bad" "good enough"? *Open Forum Infect Dis* 2016; published online May 25. DOI:10.1093/ofid/ofw110.

45 US Food and Drug Administration. Approved drug products: avycaz-avibactam sodium/ceftazidime. 2018. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/206494s004lbl.pdf (accessed Sep 29, 2018).

46 European Medicine Agency. Summary of product characteristics—Annex 1—Zavicefta—Avibactam Sodium/Ceftazidime. 2018. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004027/WC500210234.pdf (accessed Sept 29, 2018).

47 Paul M, Daikos GL, Durante-Mangoni E, et al. Colistin alone versus colistin plus meropenem for treatment of severe infections caused by carbapenem-resistant Gram-negative bacteria: an open-label, randomised controlled trial. *Lancet Infect Dis* 2018; **18:** 391–400.

48 Doshi P, Hur P, Jones M, et al. Informed consent to study purpose in randomized clinical trials of antibiotics, 1991 through 2011. *JAMA Intern Med* 2017; **177:** 1–8.

49 Lanini S, Zumla A, Ioannidis JP, et al. Are adaptive randomised trials or non-randomised studies the best way to address the Ebola outbreak in west Africa? *Lancet Infect Dis* 2015; **15:** 738–45.

50 Chow SC, Chang M. Adaptive design methods in clinical trials—a review. *Orphanet J Rare Dis* 2008; **3:** 11.

51 Huskins WC, Fowler VG Jr, Evans S. Adaptive designs for clinical trials: application to healthcare epidemiology research. *Clin Infect Dis* 2018; **66:** 1140–46.

52 US Food and Drug administration. Guidance, compliance, & regulatory information. Antibacterial Drug Products: use of noninferiority studies to support approval. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/antibacterial-drug-products-use-noninferiority-studies-support-approval (accessed March 1, 2019).

53 European Medicine Agencies. Guideline on the evaluation of medicinal products 5 indicated for treatment of bacterial infections, Rev. 3. https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-evaluation-medicinal-products-indicated-treatment-bacterial-infections-revision-3_en.pdf (accessed March 1, 2019).

54 Xu L, Sun X, Ma X. Systematic review and meta-analysis of mortality of patients infected with carbapenem-resistant *Klebsiella pneumoniae*. *Ann Clin Microbiol Antimicrob* 2017; **16:** 18.

55 Pallmann P, Bedding AW, Choodari-Oskooei B, et al Adaptive designs in clinical trials: why use them, and how to run and report them. *BMC Med* 2018; **16:** 29.

56 O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics* 1979; **35:** 549–56.

57 ADDPLAN. ADDPLAN Base version 6.1 user manual. http://www.biometrische-gesellschaft.de/fileadmin/AG_Daten/AdaptiveDesigns/Mielke.pdf (accessed Aug 21, 2019).

58 Mehta C, Liu L. An objective re-evaluation of adaptive sample size re-estimation: commentary on 'twenty-five years of confirmatory adaptive designs'. *Stat Med* 2016; **35:** 350–58.

59 Pritchett YL, Menon S, Marchenko O, et al. Sample size re-estimation designs in confirmatory clinical trials—current state, statistical considerations, and practical guidance. *Stat Biopharm Res* 2015; **7:** 309–21.

60 Müller HH, Schäfer H. Adaptive group sequential designs for clinical trials: combining the advantages of adaptive and of classical group sequential approaches. *Biometrics* 2001; **57:** 886–91.

61 Loudon K, Treweek S, Sullivan F, Donnan P, Thorpe KE, Zwarenstein M. The PRECIS-2 tool: designing trials that are fit for purpose. *BMJ* 2015; **350:** 2147.

62 Solter E, Adler A, Rubinovitch B, et al. Israeli national policy for carbapenem-resistant enterobacteriaceae screening, carrier isolation and discontinuation of isolation. *Infect Control Hosp Epidemiol* 2018; **39:** 85–89.

63 Lanini S, Costa AN, Puro V, et al. Donor-recipient infection (DRIn) collaborative study group. Incidence of carbapenem-resistant gram negatives in Italian transplant recipients: a nationwide surveillance study. *PLoS One* 2015; **10:** 0123706.

64 Langer M, Portella G, Finazzi S, et al. Intensive care support and clinical outcomes of patients with Ebola virus disease (EVD) in West Africa. *Intensive Care Med* 2018; **44:** 1266–75.

65 Knudsen JD, Andersen SE, Bispebjerg Intervention Group. A multidisciplinary intervention to reduce infections of ESBL- and AmpC-producing, gram-negative bacteria at a university hospital. *PLoS One* 2014; **9:** e86457.

66 Levy MM, Evans LE, Rhodes A. The surviving sepsis campaign bundle: 2018 update. *Crit Care Med* 2018; **46:** 997–1000.

67 Wright H, Bonomo RA, Paterson DL. New agents for the treatment of infections with Gram-negative bacteria: restoring the miracle or false dawn? *Clin Microbiol Infect* 2017; **23:** 704–12.

68 Collignon O, Koenig F, Koch A, et al Adaptive designs in clinical trials: from scientific advice to marketing authorisation to the European Medicine Agency. *Trials* 2018; **19:** 642.

69 Harris PNA, Tambyah PA, Lye DC, et al. Effect of piperacillin-tazobactam vs meropenem on 30-day mortality for patients with *E coli* or *Klebsiella pneumoniae* bloodstream infection and ceftriaxone resistance: a randomized clinical trial. *JAMA* 2018; **320:** 984–94.

70 Talbot GH, Das A, Cush S, Dane A, et al. Evidence-based study design for hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia. *J Infect Dis* 2019; **219:** 1536–44.

71 Talbot GH. Evolution and current status of United States Food and Drug Administration and European Medicines Agency regulatory guidance for studies of nosocomial pneumonia. *Curr Opin Crit Care* 2018; **24:** 379–84.

72 McCoy CE. Understanding the use of composite endpoints in clinical trials. *West J Emerg Med* 2018; **19:** 631–34.

73 European Network for Health Technology Assessment. European network for health technology assessment guideline for endpoints used for relative effectiveness assessment of pharmaceuticals: composite endpoints. 2013. https://www.eunethta.eu/wp-content/uploads/2018/01/Composite-endpoints.pdf (accessed Feb 25, 2019).

74 US Food and Drug administration. Multiple endpoints in clinical trials guidance for industry. 2017 https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm536750.pdf (accessed Feb 25, 2019).

75 Boeree MJ, Heinrich N, Aarnoutse R, et al. High-dose rifampicin, moxifloxacin, and SQ109 for treating tuberculosis: a multi-arm, multi-stage randomised controlled trial. *Lancet Infect Dis* 2017; **17:** 39–49.

76 European Medicines Agency. Reflection paper on methodological issues in confirmatory clinical trials planned with an adaptive design. 2007. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003616.pdf (accessed Feb 25, 2019).

77 US Food and Drug Administration. Federal drug administration guidance for industry adaptive design clinical trials for drugs and biologics center for drug evaluation and research Rockville. 2018. http://www.fda.gov/downloads/Drugs/Guidances/ucm201790.pdf (accessed Feb 25, 2019).

78 Dimairo M, Coates E, Pallmann P, et al. Development process of a consensus-driven CONSORT extension for randomised trials using an adaptive design. *BMC Med* 2018; **16:** 210.

79 Bothwell LE, Avorn J, Khan NF, Kesselheim AS. Adaptive design clinical trials: a review of the literature and ClinicalTrials.gov. *BMJ Open* 2018; **8:** 018320.

80 US Food and Drug Administration. Highlights of prescribing information Zemdri (plazomicin). 2018. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210303Orig1s000lbl.pdf (accessed Sept 29, 2018).

81 Theuretzbacher U, Paul M. Developing a new antibiotic for extensively drug-resistant pathogens—the case of plazomicin. *Clin Microbiol Infect* 2018; **24:** 1231–33.

82 Kaye KS, Bhowmick T, Metallidis S, et al. Effect of meropenem-vaborbactam vs piperacillin-tazobactam on clinical cure or improvement and microbial eradication in complicated urinary tract infection: the TANGO I randomized clinical trial. *JAMA* 2018; **319:** 788–99.

83 US Food and Drug Administration. Highlights of prescribing information Vabomere (meropenem and vaborbactam). 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209776lbl.pdf (accessed Sept 29, 2018).