VIEWPOINT

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TITLE:
Non-inferiority versus Superiority for New Antibiotics in an Era of High Antimicrobial Resistance: the case for post-marketing Adaptive Randomized Controlled Trials

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Abstract
Antimicrobial resistance (AMR) is one of the most important threats to global health security. A range of Gram-negative bacteria (GNB) associated with high morbidity and mortality rates are now resistant to virtually all available antibiotics. In this context of urgency to develop novel drugs, new antibiotics for multi drug resistant (MDR) GNB (namely, ceftazidime-avibactam, plazomicin and meropenem-varbobactam) have been approved by regulatory authorities on grounds of non-inferiority trials which provided no direct evidence of their efficacy against MDR such as Enterobacteriaceae, 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 as an example, the development process of ceftazidime-avibactam, we propose a strategy for a new research framework based on adaptive randomized clinical trials (aRCTs). The operational research strategy has the aim of assessing the efficacy of new antibiotics in special groups of patients, such as those infected with MDR bacteria, who were not included in earlier phase studies, and for whom it is important to establish an appropriate standard of care.
Introduction

Antimicrobial resistance (AMR) is currently one of the most pressing health issues worldwide. The mechanisms of AMR transmission among Gram-negative bacteria (GNB) are extremely efficient and several multidrug resistant (MDR) GNB are now phenotypically resistant to all available antimicrobials. Carbapenem-resistant GNBs (CR-GNB) such as Enterobacteriaceae, Pseudomonas aeruginosa, Stenotrophomonas maltophilia, Burkholderia cepacia and Acinetobacter baumannii are associated with fatal human infections with no established standard of care (SoC).

In January 2017, the World Health Organization (WHO) issued a consensus document defining priorities for research and development of new antibiotics. The document concluded that CR-GNBs are a critical threat for human welfare and that there is an urgent need that future research strategy focuses on the discovery of new antimicrobials. This was followed by European Union and US Government initiatives, including the Joint Research Programming Initiative on Antimicrobial Resistance (JPIAMR), initiatives of the National Institute for Allergy and Infectious Diseases, and calls made by the European Initiative for Medicine innovation (IMI) and the Antibacterial Resistance Leadership Group (ARLG).

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 which has led to the development and registration of ceftazidime/avibactam (CAZ-AVI) we propose a strategy for developing a new methodological research framework based on adaptive post-marketing randomized clinical trials (aRCTs) using CR-GNB sepsis as a case-study.

Ceftazidime/avibactam: an overview of current knowledge from RCTs

Ceftazidime is an old third-generation cephalosporin with enhanced activity against most GNBs, including Enterobacteriaceae and Pseudomonas aeruginosa and was approved for human use in the 1985. In contrast to carbapenems, that are the current SoC for several MDR GNB (including those resistant to cephalosporin), ceftazidime is poorly active against anaerobes, Acinetobacter baumannii, Stenotrophomonas maltophilia and is inactivated by extended spectrum β-lactamases. Avibactam is a non-β-lactam, β-lactamase inhibitor, without intrinsic antibacterial activity. Combination of ceftazidime with avibactam (CAZ-AVI) can re-establish antibacterial activity for GNBs producing Ambler classes A, C and D β-lactamases, which inactivate cephalosporins and carbapenems. However CAZ-AVI has no activity against GNBs that become resistant to ceftazidime for mechanisms other than production of β-lactamases, and for GNBs producing metallo-β-lactamases (i.e. Ambler class B β-lactamases) which are associated with high level resistance to all β-lactams including carbapenems.
The safety and efficacy of CAZ-AVI have been assessed in eight RCTs providing evidence that CAZ-AVI is non-inferior to carbapenems for treatment of GNBs infections.\textsuperscript{17-23} These studies included adults with either urinary tract infection (UTI), hospital acquired pneumonia (HAP) or intra-abdominal infections (IAI). The proportion of randomized participants who had a microbiological diagnosis of the infection ranged between 44-92%. Among them, the prevalence of cephalosporin resistance was between 13-100% while prevalence of resistance to either carbapenem or CAZ-AVI was between 0-10%. The aim to perform the trials were to define preliminary efficacy and safety profile (two phase II RCTs) and to find alternative drugs suitable for carbapenem-sparing regimens (six non-inferiority phase III RCTs). CAZ-AVI 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 and post-hoc analyses, for supporting the hypothesis that CAZ-AVI is superior to SoC for infection due to bacteria with special AMR profile.\textsuperscript{6,24-26} As it is typical when multiple meta-analyses are produced, the conclusions and the emphasis placed on the results vary among them and their results may become conflicting and even misleading.\textsuperscript{27-28} In particular, some studies confirmed no significant difference between treatment arms,\textsuperscript{29-30} some studies claimed better efficacy of the experimental intervention for MDR bacteria\textsuperscript{25-26} while other studies suggested that the experimental intervention was more toxic than the comparator.\textsuperscript{24}

**Non-inferiority randomized controlled trials for antibiotics: ethical and clinical practice implications**

NI-RCTs are typically presented as a pragmatic design that can compare a new intervention against an established SoC.\textsuperscript{31} In contrast to superiority RCTs, assessing whether the new intervention performs better than the old ones, NI-RCTs are designed for excluding an unacceptable loss in efficacy. Due to this inherent feature, interpreting NI-RCT can be a challenge. Indeed, several ethical and analytical concerns are still a matter of debate.\textsuperscript{32} Remarkable ethical issues include: how to establish a reasonable (and ethically acceptable) non-inferiority margin\textsuperscript{33} and how to inform and convince patients for receiving a treatment that is expected to be (somehow) worse than a consolidated SoC.\textsuperscript{34} In addition, from a methodological point of view, NI-RCT are very vulnerable to the impact of incomplete information on outcomes. In contrast to superiority RCTs where there is substantial consensus that they can best be interpreted by ITT analysis, guidance on how to deal with missing and censored observations in NI-RCTs is uneven, and includes:\textsuperscript{32} multiple imputation analysis (which may be biased due to the arbitrary imputation framework); ITT analysis (which may bias toward a false positive conclusion of non-inferiority); analysis modified on inclusion criteria, such as MITT (which may introduce selection bias); or sensitivity analysis of the different approaches (where inconsistent results would provide no evidence for clinical decision). The rate with which NI-RCT successfully claim non-inferiority is so high that it suggests that bias in design, analysis and/or interpretation often leads them to spuriously favorable conclusions.\textsuperscript{35-37}
Despite these structural complexities, NI-RCTs are of substantial value since they can reveal unacceptable loss in efficacy of a tested agent for specific clinical condition such as eravacycline for therapy of urinary tract infection and daptomycin for treatment pneumonia. Another example is the excess deaths associated with approval based NI-RCTs of tigecycline for severe infections. Moreover NI-RCTs are pivotal for choosing an alternative intervention that, in comparison with the SoC, is better in terms of tolerability, safety, delivery or cost (i.e.: tradeoff decision). An appropriate example is the recent NI-RCT to assess efficacy of oral azithromycin versus intramuscular penicillin for treatment of yaws among African children. The advantage of the oral therapy is self-evident (i.e. averting injections in a low-resource setting). Tradeoff decisions are also relevant in affluent settings. Several NI-RCTs have been carried out for ascertaining whether antibiotics could be a reasonable alternative to current surgical SoC for acute appendicitis. In this case as well, the rationale for NI was clear (i.e. sparing surgery).

Methodological and ethical concerns emerge when NI-RCTs are used to infer conclusions beyond the actual results and stakeholders suggest this is appropriate. Typically, surrogate (in vitro) evidence of efficacy is merged with results of NI-RCTs to draw new evidence of superiority. For example, CAZ-AVI was assessed as non-inferior alternative to carbapenem in clinical settings with high prevalence of cephalosporin resistant GNBs whose SoC was, in fact, a carbapenem. When non-inferiority was proved, indirect (in vitro) evidence was used to support the use of CAZ-AVI for several clinical conditions caused by susceptible microorganisms including those resistant to the SoC used in the NI-RCTs (e.g. KPC-producing Enterobacteriaceae).

There are several flaws in such an approach. First, in vitro studies do not prove in vivo efficacy. For example, a recent (superiority) RCT to assess the in vivo impact of the in vitro synergy between meropenem and colistin on CR-GNBs suggested no significant effect. Second, using RCTs results to infer conclusions outside the scope of the study blurs scientific evidence and produces misguidance. The most obvious clinical consequence of non-inferiority of CAZ-AVI versus carbapenems is to include CAZ-AVI within antimicrobial stewardship programs for carbapenem-sparing regimens aimed to contain the diffusion of CR-GNBs in settings with high prevalence of cephalosporin resistance. Third, ethical issues would need to be raised if NI-RCTs were designed, instead of superiority RCTs, for speeding-up marketing of alternative compounds with no expected greater efficacy, no self-evident advantage and no evident bio-similarity over a consolidated SoC. These limitations are pointed at by two recent systematic reviews suggesting that most NI-RCTs protocols contain no rationale for the non-inferiority hypothesis, no rationale for establishing the efficacy margin and poor information to patients about the final purpose of the study (including the real meaning of non-inferiority).

Adaptive randomized clinical trials for assessment of superiority in the post-marketing phase
The challenge for research on CR-GNBs infections is to find alternate innovations without over-interpreting data from NI-RCTs. Experience in operational research for other severe infections, such as Ebola virus disease, suggests that aRCT could provide a solution. Adaptation is a carefully thought investigational procedure for modifying study parameters while the aRCT is ongoing based on review of interim data analyses. Thus, it may be possible to build on available evidence from existing NI-RCTs for producing new, solid, evidence and for providing all patients with the best treatment the soonest.

To assess the performance of putative aRCTs in this field, we used a proprietary simulator package (ADDPLAN-TM) currently approved by the main regulatory agencies in Europe (EMA), United States (FDA) and Japan (PMDA). The aim of this simulated aRCT is to assess the efficacy (superiority) of a new antibiotic (experimental arm) versus a SoC (control arm) for treatment of bacterial sepsis due to CR-GNBs (condition). The experimental arm will include an antibiotic that has already received market authorization by NI-RCT for treatment of infections due to usually drug-resistant bacteria, according to current guidelines for evaluation of new antimicrobials. The primary endpoint will be 14 days reduction of all-cause mortality after randomization from an expected 30% to less than 20% with a power of 80% and one-sided alpha error of 5%. This is, indeed, a conservative assumption since mortality for bloodstream infections due to certain CR-GNBs, such as Klebsiella spp, may be higher than 30%. One-sided significance has been chosen as the experimental arm will include an approved drug, which proved to be non-inferior to SoC, and has (yet unproven) potential for superiority in selected sub-set of patients such as those with CR-GNBs infections. To optimize statistical power, all analyses are carried out on all participants for whom eligibility criteria can be ascertained after randomization (i.e. a CR-GNB has been isolated from a blood sample taken before treatment allocation).

Adaptation strategy consists of a 3-stage sequential design allowing for sample size recalculation and early stopping for efficacy. Due to the superiority design this study will have advantages as compared with a NI-RCT. In particular, ITT of all participants, which met enrollment criteria, will prevent bias toward rejection of 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, as no futility stopping rule is implemented. Finally, the expected inflation of type 1 error due to group sequential design is controlled through the implementation of an alpha spending function, minimal simple size at stage 1 and minimal sample size for subsequent stage. Table 1 reports basic aRCT parameters.

Figure 1 panel A shows the aRCT sequence including participant enrollment and the interpretation of results after each analysis. Figure 1 panel B shows the probability of early stopping and expected sample size for different level of efficacy of experimental arm versus control. In particular, if prior hypothesis is confirmed (i.e. all-cause mortality is 30% and 20% in control and experimental arm, respectively), the expected sample size for this aRCT will be about 278. In contrast, a standard non-adaptive RCT would have required a sample
size of about 460 subjects; the reduction of the sample size is driven by the chance of early stopping and the optimization of statistical power obtained through recalculation of sample size.

The aRCT design can become a pragmatic trial when implemented with point-of-care randomization in real-life settings with high prevalence of CR-GNBs, high standards of care and access to the state-of-art diagnostics (e.g. hospitals in high-income countries or settings in low and middle-income countries where high standard of care can be guaranteed). At best this aRCT would be a part of an ongoing integrated intervention for infection control that also includes hospital-based surveillance of MDR bacteria and antimicrobial stewardship programmes. The aRCT is expected to enroll complex patients potentially in need of multiple simultaneous empiric therapies. Thus, the experimental compound will need to be administered on top of all other therapies and may include a combination of several antimicrobials. 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 and primarily funded through public sector grants for independent medical research. Unfortunately, much recruitment for antimicrobial trials in the last decade has happened in centers without strong tradition of clinical research and/or questionable quality of care, but this trend needs to be reversed in studies with more complex designs are to be performed. This would help to overcome skepticism about aRCTs feasibility. Decision-making funding bodies and other stakeholders (e.g. patients associations) may become more supportive if they are familiarized with these trials with comprehensive explanation of the experimental design, study aims, potential risks, expected advantages and how to manage the impact of adaptation on the economic issues.

The adaptive strategy described above has been taken to be as simple as possible to illustrate the essential mechanism of this approach. However, composite designs may be tailored on the actual ethical and economic issues that may arise locally. Exposing patients to suboptimal treatment can be reduced by a stopping rule for futility while more interim analyses may be considered to detect earlier a potentially extraordinary efficacy of the experimental compound. Use of composite primary endpoints may reduce the required sample size but caveats also exist on their use. For example, for sepsis, treatment success definition may include parameters for improved hemodynamic stability or some validated clinical score (e.g. SOFA score) in addition to all-cause mortality. Composite endpoints have also been proposed for hospital pneumonia and ventilator associated pneumonia. A major disadvantage with composite endpoints, however, is that the components have very different clinical significance. Moreover, the results may differ across the components of the composite. Finally, if the proposed RCT is meant to simultaneously assess efficacy of more than one new therapeutic options, multi-arm study designs are feasible.
Adaptive RTCs are remarkably flexible study designs but their advantages come at the cost of increasing complexity. Indeed, the proposed aRCTs also has unavoidable practical limitations. Firstly, advantages of each further adaptive components and/or surrogate endpoints introduce additional complexity for study management and may reduce results interpretability. Secondly, aRCT always needs 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. However, regulatory agencies in Europe and the USA have already issued detailed guidelines and statistical features for most common adaptive designs have been already validated and implemented in specific software packages. Thirdly, 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. Fourthly, innovative aRCTs in the field of AMR need access to state-of-art molecular microbiology techniques for timely selection of participants according to the AMR profile of the infecting organism. Indeed, the feasibility and the significant gain in terms of statistical power of enrolling participants according to AMR profile has been recently demonstrated in the MERINO study. Finally, there is still no formal recommendations on how to report aRCT in the peer-reviewed literature and how to appraise evidence from aRCTs in evidence synthesis. The CONSORT collaboration 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. In fact, regulatory agencies, such as EMA and FDA, have already considered aRCTs instead of standard RCTs for market authorizations.

Conclusions
During the last decade, AMR has become a major global health priority. Despite ongoing scientific research, increasing efforts from pharmaceutical industries and funding agencies, AMR continues to spread at global level. Carbapenem resistance among GNBs is of particular concern. NI-RCTs appear to have departed from their primary field of application and are being used to empirically inform new SoC for MDR pathogens. The case for CAZ-AVI is made here, but similar conclusions can be drawn for other antimicrobials effective against MDR GNBs including plazomicin (approved on the ground of a single NI-RCT against meropenem) or meropenem-varbobactam (approved on the ground of a single NI-RCT against piperacillin-tazobactam). The choice of developing these drugs using NI-RCTs, instead of superiority RCTs, is primarily a matter of convenience. In terms of logistics, a superiority RCT would have required to select only CR infections within a longer study time and higher costs for testing. Furthermore, from a drug development point of view, superiority RCTs would have exposed the developmental endeavor to the risk of a “negative result “, meaning lack of adequate data support for any approval of the drug. However, outside their proper field of application, NI-RCT 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 SoC. We suggest alternative ways to promote aRCTs, bringing them forward as an integral part of infection control programs within healthcare settings with high prevalence of MDR. In this context, aRCT may be viewed as a next generation phase IV post-marketing RCTs that go behind the primary scope of surveilling infrequent side effects and/or assessing effectiveness under health economics aspects, but also includes elements directly associated to drug efficacy in special groups of patients such as those infected with MDR bacteria who were not included in earlier phase studies and for whom it is urgent to establish the appropriate therapy.

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All other authors declare that they have no conflicts of interest.

Contributor

Prof Giuseppe Ippolito, Dr Simone Lanini, Dr John Ioannidis and Sir Alimuddin Zumla ideated the concept and developed the first draft. Simone Lanini and Alessia Mammone performed the simulations. All other authors contributed to writing and finalization of the manuscript.

Table 1. Simulation model specification.
**Maximum number of stages**: 3

**Significance level**: $\alpha=0.050$ one-sided

**$\alpha$ spending function**: O’Brien and Fleming design

**Information rate per stage**: 0.333 at stage 1, 0.667 at stage 2, 1.000 at stage 3 (uniform);

**Measure of effect**: Risk difference

**Overall conditional power**: 80% for assessing reduction of all-cause mortality from 30% to 20% (all-cause mortality is the study primary outcome)

**Allocation ratio**: 1:1

Sample size recalculation: at each stage the sample size is recalculated using Fisher’s exact test and maximum likelihood ratio estimate for observed effect (i.e. we assume that the observed risk difference at previous interim analysis is the true effect). Fisher’s exact test was considered because yields an exact level-$\alpha$ testing procedure which typically behaves quite conservatively.

**Sample size constraint per stage**: 70 participants at stage 1 (fixed); 10 to 180 participants at stage 2 and 3 (variable). Depending on the assumed risk difference at interim analyses that influence the calculation of the overall conditional power, a varying number of participants (10-180) are required to be enrolled in stage 2 and 3. This range guarantees the applicability of Fisher’s exact test and a 80% power if the prior hypothesis if true.

**Sample size range**: 70 – 430

**Average sample size range according to observed effect**: see figure 1 panel B

**Simulation iterations**: 10,000

**Simulator specification**: Software: ADDPLANTM 6.1.1 ADDPLAN (approved by FDA, EMA, and PMDA) FDA=US Food and Drug Administration. EMA=European Medicines Agency. PMDA=Pharmaceuticals and Medical Devices Agency, Japan.
Figure 1. Adaptive trial simulation.

Panel A shows different phases of the aRCT including: participants enrollment and selection (blue); first interim analysis (green); second interim analysis (yellow), binding decision on early aRCT termination (grey) and final analysis (red).

Panel B shows the probability of early stopping of the aRCT (lines) and expected sample size (bars) for observed drop in all-mortality between control (assumed at 30%) and experimental arm (variable between 1-29%). Green line reports probability of stopping in the first interim analysis. Yellow line reports probability of stopping in the second interim analysis. Red arrow: reports sample size (N=278) for main aRCT assumption including power 80%, α=0.05 and efficacy (risk difference) of 10%.

*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 evolving evidence.


45. FDA Approved Drug Products: Avycaz-Avibactam Sodium/Ceftazidime available at [https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/206494s004lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/206494s004lbl.pdf) accessed on 29/09/2018


53. US Food and Drug administration [https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064980.htm](https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064980.htm) accessed on 01/03/2019


79. Highlights of prescribing information Zemdri™ (plazomicin) Food and Drug Administration US Approval 2018 available at [https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210303Orig1s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210303Orig1s000lbl.pdf) accessed on 29/09/2018


82. Highlights of prescribing information Vabomere™ (meropenem and vaborbactam) Food and Drug Administration US Approval 2017 available at [https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209776lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209776lbl.pdf) accessed on 29/09/2018