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Optimizing patient recruitment into clinical trials of antimicrobial-resistant pathogens

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Recruitment of patients with critical priority antimicrobial-resistant (AMR) bacteria into drug approval randomized controlled trials (RCTs) has not been successful to date. Approaching from the viewpoint of clinician-investigators and learning from the experience of AMR-focused investigator-initiated trials, we present suggestions to improve feasibility and efficiency of RCTs evaluating patients with severe infections caused by carbapenem-resistant Gram-negative or other AMR bacteria. Considerations address the trials' eligibility criteria, whether the focus of the trial is pathogen- or syndrome-targeted, trials' case report forms and monitoring, informed consent strategies for the recruitment of extremely ill patients, team dedication and incentives to run the trial and alternative trial designs. Evidence on the effects of new drugs against the AMR that these drugs target is weak and needs to be improved through better industry–academic collaboration, taking advantage of the different strengths of industry-led and investigator-initiated research.

Introduction

The increasing incidence and burden of antimicrobial-resistant (AMR) bacteria, alongside the inability of randomized controlled trials (RCTs) to recruit sufficient patients with AMR bacteria to test new antibiotics, is paradoxical. New antibiotics, targeting AMR and currently used solely for AMR bacteria, were tested nearly universally on populations different from the target population.[1] For example, ceftaroline, commonly used for severe MRSA infections was approved following two trials including patients with complicated skin and skin structure infections, with only a third due to MRSA; and two trials in patients with community-acquired pneumonia (CAP), where MRSA was an exclusion criterion.[1] The few new drug trials that did intend to focus on patients with AMR bacteria failed to achieve the target sample and were prohibitively costly.[2] Four new drug RCTs published in recent years that focused on AMR pathogens (CARE, CREDIBLE, TANGO and RESTORE-IMI) included overall only 315 patients.[3–6] In this review, we will discuss how to optimize the conduct of trials targeting infections caused by AMR pathogens.

Investigator-initiated trials have been more successful than industry trials in recruiting large samples of patients with AMR bacteria into RCTs. For example, compared with the CARE trial assessing plazomicin[7] and the CREDIBLE trial assessing cefiderocol,[5] the AIDA[8] and OVERCOME[9] trials comparing colistin alone with colistin/meropenem succeeded better in recruiting a meaningful sample size of patients (CARE 37 patients, CREDIBLE 152, AIDA 406 and OVERCOME 464), in significantly fewer recruiting sites (CARE 68 sites, CREDIBLE 95, AIDA 6, OVERCOME 21) and at much lower costs.[2,10,11] All these trials recruited patients with carbapenem-resistant Gram-negative bacteria, although CARE focused only on carbapenem-resistant Enterobacterales (CRE) while others allowed all carbapenem-resistant Gram-negative bacteria and recruited mainly patients with carbapenem-resistant *Acinetobacter baumannii* (CRAB). The investigator-initiated trials (AIDA and OVERCOME) were clinical effectiveness trials, assessing clinically available therapies aiming to answer a clinical question, while CARE and CREDIBLE assessed new drugs with the aim to gain market approval. Nevertheless, there might be details to learn from the success of investigator-initiated trials in patient recruitment for trials of critical-priority AMR bacteria.

Consider the typical patient with an infection caused by CRE, CRAB or any other resistance trait that had not yet become endemic. This is a hospitalized patient, typically following prolonged hospitalization in high-care units. The patient is likely to have multiple baseline comorbidities and multiorgan failure following the conditions that led to the hospitalization and/or complications that arose afterwards, and carries multiple devices (IV catheter, intubation for mechanical ventilation, feeding tube etc.). This patient is likely to have already received one or more courses of antibiotics (selecting for the AMR bacteria) and most likely the AMR pathogen emerged while the patient was treated with a non-covering antibiotic. Either due to this grim baseline condition or due to sepsis, many of these patients are unlikely to be able to

provide informed consent at the time of infection onset. Recruitment of such patients must consider this setting.

Eligibility

Inclusion and exclusion criteria must consider the target patient population and the alternative options available for their treatment. Exclusion criteria must be carefully tailored to the trial's specific target population and interventions. Special populations (transplant recipients, patients with septic shock, patients with neutropenia etc.) should not be excluded unless there is good reason to believe that the interventions will harm them specifically or are not optimal for them. Exclusion criteria must consider the comparator regimens in the trial sites. If the best available therapy used as the comparator is nephrotoxic, renal failure should not be an exclusion criterion, as in the comparison of plazomicin to polymyxins in the CARE trial.[7] This might require a broader Phase 1–2 programme addressing the special populations for new antibiotics targeting AMR pathogens. With AMR pathogens, prior antibiotic treatment to which the AMR pathogen is resistant (most antibiotics) should not be an exclusion criterion. Furthermore, simplifying the criteria for inclusion can increase patient recruitment. Inclusion and exclusion criteria of the CARE trial span 1361 words with 23 exclusion criteria, compared with 453 words and 6 exclusion criteria in AIDA, both assessing nephrotoxic drugs.[7,12] Imagine the willingness and time needed to identify an eligible patient in these two trials. Investigators must consider each exclusion in the exclusion criteria carefully and FDA and EMA as regulatory bodies must consider this when directing the pharmaceutical industry on their clinical trial design. Minimizing exclusion criteria to those that are absolutely necessary will allow broader recruitment and improve a trial's external validity, approximating the real-world patient population with AMR pathogens.

Time from the index eligibility event to randomization should be minimized to allow intervention assessment at the time of most need and largest antibiotic effect. Yet this time window should be reasonable to allow the recruitment of most patients with the disease and mimic the time flow of directing tailored therapy in clinical practice. With AMR pathogens, the time window from start of appropriate, *in vitro* covering therapy to inclusion is more relevant that the time between isolation of AMR bacteria to inclusion, since treatment options are limited and non-covering empirical therapy is frequent and probably not effective. In investigator-initiated RCTs, although the time window for recruitment was defined as 72–96 h from start of appropriate antibiotics, patients were recruited at a median of 0–1 days from start of appropriate antibiotics (and 3–4 days from isolation of AMR bacteria); see Table S1, available as Supplementary data at *JAC-AMR* Online. Pathogen-focused trials will profit from rapid diagnostics (pathogen identification and susceptibilities).

Trial focus

Pathogen-focused trials are easier to conduct logistically than syndrome-based trials. In a computerized setting it is easy to issue a notification for every isolation of the target organism and proceed to implement eligibility from this initial event. It is much more complicated to automate the identification of a syndrome, be it pneumonia, intra-abdominal infection or other. The timepoint of eligibility is clearer in pathogen-focused trials (time culture taken) than in syndrome-based trials. The syndrome is a less definite event than pathogen identification, introducing possible bias in the selection of eligible patients. The syndromic approach may risk recruiting patients who do not actually have the disease of interest, or allow the recruitment of patients with an organism that is non-susceptible to the study drug.[13] Post-susceptibility exclusions could be used to resolve this problem, but will be limited by wasting resources and will risk imbalance between groups. Finally, bacteraemia, the most definite severe bacterial infection, was not well represented in syndrome-based trials compared with pathogen-focused trials (Table S2, available as Supplementary data at *JAC-AMR* Online). Whether syndrome- or pathogen-based, trials should make efforts to include all eligible patients with bacteraemia. Bacteraemia without an identified source of infection can be included in pathogen-focused trials. Regulatory bodies should allow the inclusion of such patients and consider antibiotic effects among bacteraemic patients. Ultimately, pathogen-focused trials are those relevant to assess antibiotic efficacy for AMR bacteria.

The epidemiology of infectious diseases changes and is unpredictable. A local outbreak of CRE, subsequently controlled, may significantly reduce the incidence of CRE infections documented in the pre-trial survey. Trials targeting AMR bacteria should plan for such changes. Options are to focus on more than one priority AMR pathogen or mechanism of resistance[14] (e.g. all carbapenem-resistant Gram-negative bacteria covered by the tested antibiotic) or to use an adaptive design that allows shifts between AMR bacteria according to the changing epidemiology. Platform trials, allowing the evaluation of multiple interventions concomitantly, can be planned to address several pathogens simultaneously. Other than improving trial efficiency, this will address the real-time clinical needs.

Informed consent

Recruiting patients into an RCT requires informed consent, quite an impossible feat when it comes to the typical patient with an AMR infection as described above. Procedures allowing the recruitment of patients that cannot provide informed consent exist in most countries but differ significantly between countries and even between different ethics committees within a country. For example, the usual strategy in most European hospitals is to relegate the consent responsibility to a relative of the patient. In Israel, only a legal guardian appointed by court can serve as a proxy for informed consent. In Europe, a waiver for 'emergency interventions' is rare, while in Israel an ethics committee has the prerogative to defer informed consent and request the approval of the patient's caretaking physician for the patient's participation in the trial. Obviously, the aim is obtaining a balance between the need to perform large, meaningful trials for the benefit of all future patients, and the obligation to respect the individual patient's autonomy and rights.

Informed consent strategies should separate clinical effectiveness trials from new drug trials.[15] In clinical effectiveness trials, where approved antibiotics or management strategies commonly in use are formally compared, patients have difficulty understanding the concept of informed consent ('We would usually treat you with A or B, but now we're doing a trial and asking you to sign that you consent to be treated with A or B randomly').

Consenting becomes a measure of the patient's general willingness to help, acceptance to participate in research, or confidence in the recruiting physician/s, rather than a true understanding of the interventions and the rationale for the trial. For these trials, a minimal process has been previously suggested, possibly obtaining approval only for the data collection and/or relegating the decision to approve and the trial's oversight to the ethics committee.[15] Community consultation, public disclosure of a planned trial and opt-out procedures have been proposed to conserve some measure of patient autonomy.[16,17]

For new drug trials, full informed consent is required, but strategies that optimize inclusion of patients with AMR pathogens in clinical trials should be pursued. Possibly, in settings with a high incidence of the target AMR, upfront, advance consent can be obtained from all admitted patients to potential participation in the event of an infection.[18] People are usually aware of the problem of antibiotic resistance, and this can be leveraged to promote recruitment into antimicrobial resistance trials. Information on the trial can be shared with patients in advance. Presenting the trial as a video in addition to the form might be easier for patients at the timepoint of recruitment. Since severe infections are emergencies, and treatment options for AMR pathogens are limited, deferred consent procedures may be also considered for these trials.[19]

Team dedication

In trial planning and performance, involvement of physician-investigators, who raise practical questions and are familiar with the everyday clinical practice, may improve motivation to complete these trials. Investigators launching a trial are naturally dedicated to the trial. They participated in the trial's conception, they wrote the protocol, and they have the motivation to complete the trial. In AIDA, researchers from five of the six recruiting sites participated in the conception, planning and design of the trial.[12] In OVERCOME, fewer sites participated in the planning, but in both trials all the other sites had previously performed similar trials and were recruited based on their academic interest in the trial.[9] Researchers in each site had the goal of doing the trial well and achieving the required sample size.

Industry trials recruit dozens of sites per trial and, while attempting to promote researchers' identification with the trial's cause and dedication to the trial, there is typically limited academic interest in the trial sites. Typically, very few individuals are recruited per centre, limiting learning curves. This partially stems from the complicated eligibility criteria, data collection and monitoring, and the types of outcomes collected that distance the trial from clinical practice. But mainly, it is the fact that it is not the investigators' trial.

Focusing the recruitment on a few 'super-recruiting' dedicated sites, endemic for and familiar with the target AMR pathogens, has many advantages. These sites can be consulted in the final set-up of the trial to improve investigators' acquaintance with the trial and their feeling of dedication towards the trial. Are we sure of the quality of randomization in trials including a few dozen sites where each site recruits 2–3 patients? Is a patient randomized to the intervention in Israel comparable to a patient randomized to the control in France? No matter how stringent the trial's procedures are, disease characteristics, patient management and practices differ between hospitals, countries and continents. The factors differentiating between these patients' management might not be reflected in the data collected and presented. The quality of the randomization might improve with fewer centres, when centre or country strata will be meaningful. Researchers at the few centres selected for participation can develop a learning curve of trial procedures to mainstream patient identification, recruitment and data collection. Following their involvement in the trial from the protocol stage, investigators from the selected trial sites can appropriately author the articles reporting the trial.

In our experience, industry-funded trials have the capability to pay a ∼30–50 times higher fee per patient compared with investigator-initiated/trials. The incentive of participation in investigator-initiated trials is mainly academic and funding is variably given upfront or periodically during the grant's duration or per patient. Payment strategies for recruitment in RCTs have not been compared formally,[20] but economic theories point against the effectiveness of financial incentives that change relationships and paradoxically reduce volunteering spirit.[21,22] Pay per patient might paradoxically decrease physicians' motivation to recruit compared with the obligation borne from trust. The 'super-recruiting' trial centre strategy might allow for upfront payment rather than paying per recruitment, increasing dedication to the trial and allowing centres to plan research assistant recruitment and building strong research teams.

Focused data collection and risk-based monitoring can increase researchers' dedication and identification with a trial. Pragmatic case report forms and management oversight would encourage trial performance. Non-discriminatory collection of standard data in all trials and attributing equal importance to each item during monitoring undermines dedication. The typical contract research organization monitor (in our experience) values the item 'increased sodium' on a par with 'pulmonary oedema' or 'randomization'. A focused case report form focuses on the data truly necessary for the trial's analysis, based on good planning of the analysis and results presentation in advance. In prior investigator-initiated trials, if a question arose during the data analysis that could not be answered with the available data, we contacted the trial sites or were contacted by other primary investigators and requested or supplied further data, as necessary. This is possible with interested, dedicated researchers. With dedicated trial sites, monitoring can focus primarily on compliance with the ethical requirements, eligibility criteria, the randomization and the outcome data collection, stressing these over other items. This requires monitors who are well acquainted with the medical field and the trial; this is possible with few recruiting sites where a single academic monitor can cover all sites, improving the quality and efficiency of monitoring.

Alternative trial designs

Given the complexity of recruiting a sufficient sample size of patients with AMR pathogens, alternative trial designs, more efficient than the classical RCT, are appealing. Observational studies of new drugs are impossible to conduct without bias favouring the new antibiotic. No adjustment will overcome the selection of patients receiving the new, attractive and costly antibiotic. Matching or weighting procedures using propensity

Table 1. Suggested domains to optimize patient recruitment into clinical trials of AMR pathogens

Domain	Proposed strategy
Trial focus and eligibility	• Pathogen-focused trials, including bacteraemia with target AMR pathogens • Tailor carefully, minimize and justify exclusion criteria • Base the time-window for recruitment on time from start of appropriate antibiotics
Centre selection, team dedication and involvement	• Focus recruitment on few dedicated high-recruiting centres • Involve the centres' research teams at the trial planning and protocol stage
Informed consent	• Apply special procedures that will allow non-restrictive recruitment at the time of sepsis onset
Efficient trial designs	• Improve efficiency by adaptive RCT designs considering possible changing epidemiology of antimicrobial resistance • Consider how historical controls can contribute
Data collection	• Tailor carefully, minimize and justify each collected variable
Compensation for recruitment	• Upfront payment to improve motivation and support research units in high-recruiting, academic trial centres
Framework for academic involvement in approval trials of antibiotics directed against AMR pathogens	• Continue the drug development programme following antibiotic approval for non-AMR indications, by independent investigator-led, industry-funded pathogen-focused RCTs of antimicrobial resistance that will lead to drug-label extension to the treatment of the target AMR pathogens.

scores will restrict the analysis to a few unrepresentative patients or distort the data, leaving poor credibility to the adjusted analysis. Any alternative design needs to avoid the strong indication bias that will dictate who will receive the new antibiotic. Another important limitation to observational data that needs to be avoided in the study of new antibiotics is the lack of treatment standardization when simply observing patients' treatment, a bias termed adherence to the allocated intervention (or given treatment in observational studies). Antibiotic treatment in clinical practice is frequently modified, administration schedules are variable and combination therapies against AMR pathogens are very frequent, prohibiting the true evaluation of a specific antibiotic.[23]

Use of historical controls has been proposed in the planning of new RCTs, to reduce the planned sample size by the prior knowledge from the historical trial/arm through Bayesian statistics.[24] Use of historical controls as participants in a new trial distances the new study from a RCT design, but may offer advantages over the observational cohort design.[25] For example, we are currently designing a prospective trial recruiting patients with CRAB bacteraemia and pneumonia to protocolized treatment with cefiderocol. We plan to use eligibility criteria identical to AIDA and OVERCOME,[8,9] collect the same data and outcomes, including the same centres that participated in AIDA and OVERCOME, to allow a comparison with the subgroup of patients with CRAB treated with colistin in these two trials. This will be more efficient than recruiting half of the patients now again to treatment with colistin, with the limitation of comparing different time periods. Another limitation would be the expected differences between patients recruited into an RCT (following informed consent) versus 'real life' patients. It has been demonstrated that mortality rates in RCTs in infectious diseases are lower compared with observational studies, mainly due to the stringent eligibility criteria of RCTs excluding the sicker patients,[26] although specifically for AIDA we have shown that the broad inclusion criteria led to little differences in patient characteristics and outcomes between the randomized and non-randomized patients fulfilling inclusion criteria.[27]

A cluster randomized trial with crossover design might increase efficiency, if changing treatment policies in the trial clusters is possible. A cluster can be a ward, hospital or a region. This is possible with approved antibiotics that are in use in the trial centres. For example, a cluster-randomized, crossover trial compared treatment strategies for CAP, including β-lactam monotherapy, β-lactam/macrolide combination therapy, or fluoroquinolone monotherapy.[28] The policy for CAP management was rotated in the participating hospitals (clusters) according to a random scheme that included crossovers. Overall compliance with treatment strategies was high, about 90%. This design streamlined patient inclusion in the study and allowed a large number of patients to be evaluated in the comparison. This design can be borrowed to answer many pragmatic questions on management of AMR pathogens, including combination therapy, inhalation therapy, treatment durations and more. Clustering the interventions has the potential advantage of enabling the assessing of the antibiotics' impact on resistance in the unit of randomization, a measure difficult to assess in RCTs. This design would be more problematic in new, non-approved, antibiotics without

informed consent. The ethical discourse on informed consent of a cluster RCT of an individual-level intervention bases the requirement of informed consent on intervention-associated risk level, degree of intrusion in a participant's life, and other factors, quite similar to those of an individual-level RCT.[29,30] In studies of infections caused by CRAB and CRE, where treatment at the onset of infection is urgent and in a locale where only polymyxins are available for these AMR pathogens, ethics committees might consider waiving or deferring informed consent, given that protocolized treatment with new antibiotics within a cluster design, monitored within the study, can provide an advantage.[31]

Finally, not an alternative design, but an alternative drug development pathway should be considered. Much has been written on academic–industry collaboration in research. In much of the collaboration nowadays, academic investigators external to the drug company do not significantly contribute to the conception, design and analysis of new drug trials.[32] Given the good experience of the industry in conducting non-inferiority trials of new antibiotics in syndrome-based trials and their poor experience in conducting pathogen-focused trials of antimicrobials, we propose a pathway whereby industry lead the former and academic investigators lead the latter. Drug regulatory agencies can approve a new antibiotic for the syndromes assessed in the drug development programme. Once approved for use, the drug regulatory agency should require the marketing company to further support investigator-initiated pathogen-focused RCTs of the recently approved antibiotics developed for critical priority pathogens. Conducting AMR pathogen-focused RCTs of antibiotics that are already on the market is easier than prior to their approval, yet these trials can adhere to new drug approval trial standards with appropriate funding.

In summary, we provided a clinician's and an investigator's view on how to improve the evidence we need on old and mainly new antibiotics for AMR bacteria. The domains for improvement are summarized in Table 1. At this time, a gap exists in the evidence we have on the effects of the new antibiotics on infections caused by AMR pathogens.

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All authors report no conflicts of interest.

Supplementary data

Tables S1 and S2 are available as Supplementary data at *JAC-AMR* Online.

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