Modern Clinician-initiated Clinical Trials to Determine Optimal Therapy for Multidrug-resistant Gram-negative Infections

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Treatment options for multidrug-resistant (MDR) gram-negative infection are growing. However, postregistration, pragmatic, and clinician-led clinical trials in this field are few, recruit small sample sizes, and experience deficiencies in design and operations. MDR gram-negative therapeutic trials are often inefficient, only evaluating a single antibiotic or strategy at a time. Novel clinical trial designs offer potential solutions by attempting to obtain clinically meaningful conclusions at the end or during a trial, for many treatment strategies, simultaneously. An integrated, consensus approach to MDR gram-negative infection trial design is crucial.

Keywords. gram-negative resistance; clinical trials; trial design; therapeutics; MDR.

The urgency in determining the best antimicrobial treatment for resistant gram-negative infections is greater than ever before [1]. Currently, an enormous effort is being made toward developing new antibiotics active against gram-negative bacilli (GNB). Regulatory pathways for industry have been aimed at conducting trials in complicated urinary tract infections or complicated intra-abdominal infections; however, clinicians need data on how new therapies fare for a broad range of infections, including those involving multidrug resistance [2, 3]. Large pharmaceutical companies (the most equipped to conduct such trials) may have key reservations, mainly high costs of development and low financial returns [4]. Design and reporting limitations placed on academic investigators by drug companies funding studies has called into question the validity of many published trials [5, 6].

From a clinician's perspective, patient management is not based on a single decision. Rather it is dynamic, based on a sequence of decisions with adjustments of therapy made over time. This reality needs to be reflected in the way we design and interpret clinical trial data. This can be utilized to improve trial efficiency where multiple decision points of an individual's care during their trial period can be analyzed at the same time. Trial designs outside the field of infectious diseases have provided new insights and methodology whereby simultaneously analyzing multiple different therapies at different stages of the patient's clinical course is performed for the one disease process [7]. Such trial designs lend themselves well to the application of trials investigating therapies for multidrug-resistant (MDR) GNB infections.

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Barriers to Conducting Trials Investigating Therapies for MDR GNB

Investigators must overcome research, financial, and regulatory barriers to successfully conduct clinical trials. Recently, many new antibiotic compounds have been developed; however, they face significant challenges in proving their efficacy in registration trials and subsequently convincing clinicians to use them. Evidence of this is the ongoing widespread use of polymyxins for *Klebsiella pneumoniae* carbapenemase (KPC) producers. New agents are often compared against susceptible strains of bacteria instead of MDR pathogens for which they were developed, or trials only include small numbers of MDR pathogens, making it hard to ascertain their utility over and above existing antibiotics.

Conducting good-quality clinical trials is expensive. The total cost of bringing a novel antibiotic through phase 1–3 clinical trials is upwards of US $130 million, with postapproval trials often adding significantly more cost [8]. Financial return on investment for pharmaceutical companies to develop new antimicrobials is poor. There have been a number of modern trials proving noninferiority with shortened durations of antibiotic therapy that significantly limit sales volumes for drug companies [9–11]. If a novel antibiotic is brought to market, existing antibiotics will often place downward pressure on its price due to overlap in indications and efficacy. If the novel antibiotic is eventually taken

up by clinicians and used, it will almost inevitably drive its own resistance, thereby limiting its future utility [12].

Regulatory bodies, such as the US Food and Drug Administration and the European Medicines Agency, have distinctive requirements for patient selection, clinical endpoint measures, specifications of statistical parameters, and rules on expedited approvals. This puts an added expense on pharmaceutical companies and delays the time for a drug to come to market, further reducing its effective patent period. Carbapenem-resistant pathogen registration trials by Wunderink et al, McKinnell et al, Motsch et al, and Shionogi Inc evaluating meropenem-vaborbactam (targeting antibiotic non-susceptible gram-negative organisms [TANGO-2]), plazomicin (combating antibiotic resistant *Enterobacteriaceae* [CARE]), imipenem-relebactam (efficacy and safety of imipenem/relebactam versus colistin plus imipenem in patients with imipenem-nonsusceptible bacterial infections [RESTOREIMI 1]), and cefiderocol (cefiderocol versus best available therapy for the treatment of severe infections caused by carbapenem-resistant gram-negative pathogens [CREDIBLE-CR]), respectively, have faced a number of difficulties [13–16]. First, inclusion of multiple clinical syndromes in the evaluable trial population led to different endpoints for different disease states, and markedly different mortality rates between groups. Second, they faced poor study enrollment, often despite extensive protocol changes [13–16]. Recruitment of small numbers of trial participants (N = 77, N = 69, N = 47, and N = 152, respectively) limits the power of the study and makes it prone to imbalances in baseline variables and outcomes due to chance alone. Third, these trials are expensive to operate with the cost of a single enrolled patient potentially being as high as US $80,000 [17]. Fourth, carbapenem-resistant Enterobacteriaceae trials have focused on KPC producers, where these novel antimicrobials have been compared principally against polymyxins and aminoglycosides, where superiority in efficacy and safety endpoints can more easily be observed given well-known disadvantages in dosing and toxicity with these older drugs. More challenging would be the inclusion of organisms with different mechanisms of carbapenem resistance (eg, MBL, OXA-48). This is particularly true for carbapenem-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa*.

Additional sources of funding and resources are clearly needed as the public health value of effective novel antimicrobials does not currently provide significant weight in economic decision making [18]. Different economic models of antibiotic research and development have been proposed, which include government and public funding of clinical-stage antibiotic development. Proposed government incentives are estimated to be between US $1 billion and US $2 billion for each successfully developed antibiotic [19]. Alternatively, a nonprofit organization approach has been proposed with the advantages of less pressure to generate high shareholder value or to increase drug prices, with the ability to enter drug markets addressing unmet needs [19].

Recent Clinician-initiated Trials on Therapeutic Options for MDR GNB Infections

Recently, a number of investigator-led trials have been performed investigating therapies for MDR GNB (Table 1). Trials evaluating existing antimicrobials such as piperacillin-tazobactam, meropenem, and colistin have been common despite the desperate need for novel antibiotics in this field [20–25]. Continuing the search for a carbapenem-sparing agent among extended-spectrum β-lactamase (ESBL)– or AmpC-producing Enterobacteriales is a public health priority; however, only 2 trials investigating potential contenders (piperacillin-tazobactam or fosfomycin) have occurred [25, 26].

Both superiority and noninferiority trial designs have been used. When looking for a potential carbapenem-sparing agent, providing evidence for noninferiority without providing simultaneous evidence of an additional clinical benefit over and above using a carbapenem (eg, reduction in future burden of carbapenem-resistant bacterial infection) limits the impact of the study and has important ethical considerations. Indeed, Harris et al in the MERINO trial showed no difference in development of carbapenem resistance between the piperacillin-tazobactam and meropenem groups, although the trial was not designed to assess this secondary outcome with adequate power [26]. Gold-standard antibiotic susceptibility testing (eg, broth microdilution at a reference laboratory) at all trial sites may not be achievable, reflecting a "real world" setting (ie, pragmatic trial). Thus interpretation of resistance testing in such trials can be challenging as it does not always correlate with clinical success and mortality using "real world" methods. The MERINO trial initially reported no correlation between piperacillin-tazobactam minimum inhibitory concentration and clinical success or mortality, although when isolates were analyzed in a research laboratory using broth microdilution, a correlation was observed [27, 28].

MDR GNB investigator-initiated therapeutic trials vary widely in the number of sites and countries involved, with a range of 5–60 sites and 1–17 countries, respectively, in the small sample provided in Table 1. Inclusion of patients with septic shock, high sepsis severity scores, or those expected to survive more than 24 – 168 hours (depending on individual trial protocol) has excluded large numbers of sick patients from trials and limits the generalizability and between study interpretation of results. A similar point is made in those who are immunocompromised or have neutropenia. Inclusion of patients with polymicrobial infections and allowing the use of additional antibiotics while the trial drug is being administered is not uncommonly allowed in trial protocols, significantly limiting our ability to learn from the study [13].

A lack of accepted dosing strategies, including extended infusions, for many tested antibiotics, as well as the pragmatic issue of lack of therapeutic drug monitoring in many centers around the world, allows for significant variation in antimicrobial dosing between individual centers in the same trial and between different trials. Differential treatment effects seen in multicenter international trials are an issue [29]. Many MDR

Table 1. Examples of Recent Clinician-initiated Trials

Author Name (Trial)	Comparators	Population	No.	Design	Primary outcome
Harris et al (MERINO) [26]	Piperacillin-tazobactam vs meropenem	Ceftriaxone-nonsusceptible *Escherichia coli* and *Klebsiella* spp bacteremia	379	Noninferiority	30-d all-cause mortality
Paul et al [20]	Colistin vs colistin + meropenem	Carbapenem-nonsusceptible gram-negative bacteremia, pneumonia, or UTI	406	Superiority	Composite endpoint • 14-d mortality • Improved/stable SOFA score • Improved PaO_2 (pneumonia) • Microbiological cure (bacteremia)
Yahav et al [9]	7 vs 14 d of antibiotic therapy	Uncomplicated gram-negative bacteremia	604	Noninferiority	Composite endpoint • 90-d mortality • Microbiological relapse • Local suppurative or distal complications • Readmission to hospital or extended hospital stay (>14 d)
Durante-Mangoni et al [21]	Colistin vs colistin + rifampicin	XDR *Acinetobacter baumannii* bacteremia, pneumonia, or complicated intra-abdominal infection	210	Superiority	30-d all-cause mortality
Rosso-Fernandez et al (FOREST) [25]	Fosfomycin vs meropenem or ceftriaxone	ESBL-producing *E. coli* bacteremia secondary to UTI	161	Noninferiority	Composite endpoint • Clinical cure • Microbiologic cure (days 5–7)
Clinical trials not yet completed					
Kaye [22]	Colistin vs colistin + meropenem	XDR gram-negative bacteremia or pneumonia	444	Superiority	30-d all-cause mortality
Wright (GAMECHANGER) [30]	Cefiderocol vs SOC	Gram-negative bacteremia	284	Noninferiority	14-day all-cause mortality
Harris (MERINO-2) [24]	Piperacillin-tazobactam vs meropenem	AmpC-producing Enterobacteriaceae bacteremia	100	Noninferiority	Composite endpoint • 30-d mortality • Microbiological failure (days 3–5) • Microbiological relapse (days 5–30)
Oren R (PETERPEN) [23]	Piperacillin-tazobactam vs meropenem	Ceftriaxone-nonsusceptible *E. coli* and *Klebsiella* spp bacteremia	1084	Noninferiority	30-d all-cause mortality

Abbreviations: ESBL, extended-spectrum β-lactamase; FOREST, fosfomycin versus meropenem or ceftriaxone in bacteraemic infections caused by multidrug resistance in *E. coli*; GAMECHANGER, cefiderocol versus best available therapy for treatment of gram-negative bloodstream infection; MERINO, effect of piperacillin-tazobactam versus meropenem on 30-day mortality for patients with *E. coli* or *Klebsiella pneumoniae* bloostream infection and ceftriaxone resistance; PaO2, partial pressure of oxygen; PETERPEN, *Piperacillin tazobactam* versus meropenem for treatment of bloodstream infections caused by cephalosporin-resistant Enterobacteriaceae; SOC, standard of care; SOFA, Sequential Organ Failure Assessment; UTI, urinary tract infection; XDR, extensively drug-resistant.

GNB trials leave the length of therapy up to the treating clinician, with various protocols employing a minimum number of days of trial antibiotic for inclusion (4–5 days depending on individual trial protocol) [30]. As durations continue to become shorter, and with outcome assessments such as length of hospitalization, adverse events (including *Clostridioides difficile* infection), and development of resistance being analyzed, trial antibiotic stopping rules have been proposed [1].

Current Issues With Trial Design for MDR GNB Infections

Early Enrollment

Recruited patients have often received prior antimicrobial therapy for a number of days prior to enrollment. Enrollment criteria are often based on specific microbiological data that is not initially available. When these data become available and the patient is eligible for randomization, they may have already undergone substantial clinical improvement. This significantly reduces the ability to detect a difference in efficacy between treatment arms as it systematically biases toward the null hypothesis. Earlier identification of MDR GNB organisms with accompanying susceptibility data would not only allow better assessment of antibiotic efficacy but also improve patient enrollment numbers. Technologies to improve rapid diagnostic methods and susceptibility testing are in the pipeline, with one system showing a 7-hour turnaround time from a positive blood culture [31]. The intravenous sulbactam-ETX2514 in the treatment of patients with infections caused by *Acinetobacter Baumannii*-calcoaceticus complex (ATTACK) trial, a phase 3 study evaluating the efficacy and safety of ETX2514/sulbactam in patients with infections caused by *Acinetobacter baumannii-calcoaceticus* complex, is utilizing the BioFire FilmArray respiratory panel *plus*, which is a multiplex polymerase chain reaction assay able to detect 18 bacteria, 7 antibiotic resistance markers, and 9 viruses. It is a highly sensitive and specific assay with a fast turnaround time [32, 33]. The T2Bacteria Panel is another promising rapid diagnostic assay. Using nonculture methods for detection of bloodstream infection, it was able to detect 5 common bacterial pathogens more rapidly and accurately than standard culture methods in a large clinical study [34].

Microbial genome sequencing direct from sterile patient samples such as blood may provide a future of rapid identification of bacteria and antimicrobial resistance genes as this technology becomes faster and cheaper to perform [35].

Sample Size

Determination of an appropriate trial sample size that is both appropriate and feasible can be difficult. The larger the variation in outcome, the larger the sample size needed. Conversely, the more effective a study drug is, the smaller the same size needed to detect this effect [36]. Estimating treatment effects prior to a trial to accurately calculate the sample size is difficult as data on placebo-controlled antibiotic trials seldom exist. Significant differences in mortality exist between patients in observational studies vs interventional trials, further complicating the issue. Factoring in the minimally clinically relevant difference in mortality or a composite outcome creates added complexity.

Outcomes

Determining primary endpoints that are both important to clinicians and patients remains a vexing issue [37]. If validity of the endpoint is in question or not universally accepted, sufficient justification in the reporting is required. Composite endpoints have become increasingly used in trial designs but can lead to exaggerated treatment effects and difficulties in overall interpretation. Significant variation in severity and importance of individual outcomes often exists within the composite endpoint (eg, death when compared to readmission to hospital). Outcomes such as treatment success can provide a source of bias, particularly when observers are not blinded. Patient-centered outcomes focusing on quality of life and function are often difficult to measure but are crucial in decision making. A primary outcome of survival at 90 days supported by a secondary outcome of success at 7 days (composite of survival, resolution of fever and symptoms, stable or improved Sequential Organ Failure Assessment [SOFA] score, and negative blood cultures) may be most clinically relevant [37].

Pragmatic Design

Modern clinical trials have evolved to become more pragmatic in an attempt to improve generalizability. Registration and pharma-led trial results for novel antimicrobials are often difficult to generalize. Restrictive eligibility criteria, different delivery of patient care, and intensive patient follow-up are contributory [38]. Often comparison antibiotics are not recognized as standard of care. Not being able to standardize the overall delivery of care in pragmatic multicenter international trials can lead to differences in overall prognoses and treatment effects. A conflict exists whereby improved external validity of pragmatic trials comes at the expense of greater internal validity seen in mechanistic or explanatory trials [39]. If the main goal of the trial is to accurately inform current clinical practice, then a pragmatic approach seems ideal.

Proposed Ideas to Improve the Design of Clinician-initiated Trials

Frequentist Versus Bayesian Adaptive Randomization

Current trial design and analysis relies on the frequentist approach to statistical inference. This approach views a clinical trial as one of an infinite sequence of possible repetitions of the same trial, each producing statistically independent results [40]. The underlying parameters of the trial are fixed (ie, assumptions about the trial data) during the repeatable sampling process. This provides a limit (expressed as confidence intervals) of the relative frequency of a particular trial event (eg, mortality).

Bayesian adaptive randomization essentially uses the patient outcome data generated during the trial to randomize future patients to "better performing" treatment arms [41]. Parameters within the trial design are treated as random, whereas the data collected have been observed and are considered fixed. Assessing outcomes that combine safety and efficacy, predefined interim analyses are undertaken at designated time points where new randomization tables would be generated. At each update, a decision on efficacy and safety is made for each antibiotic treatment arm, and the future chance of being randomized to a respective group is influenced by its likelihood at that point on being the best drug.

Bayesian adaptive randomization (BAR) is far from universally accepted among trial statisticians [42]. Multiple undesirable properties are often quoted. Simulation studies have shown that it produces a high probability of sample size imbalance, greatly overestimates treatment effect difference, and has a smaller overall power to detect such a difference [42]. It also exaggerate biases influencing treatment effects when there are geographical or temporal differences between study participants, including differences in supportive medical care [43]. Reproducibility and differences in results between BAR and equal randomization design trials has also brought about concern. Given the above limitations, the scientific community should be cautious in the utilization and interpretation of trials incorporating BAR.

Multiarm, Multistage Design

In the multiarm element of the multiarm, multistage (MAMS) design, there is the opportunity to test multiple antimicrobial strategies simultaneously against a common control group. For EBSL producers, we may use meropenem as the standard of care against which other options are tested (Figure 1). Simultaneously tested strategies may include (1) a combination of meropenem with an antibiotic active against KPC producers (eg, plazomicin); (2) a new broad-spectrum antibiotic (eg, cefiderocol); and (3) a strategy based on knowledge of colonization status in high-risk patients.

In the multistage element of the MAMS design, new advances can be tested, even as a phase 2 trial. Seamless continuation to a phase 3 trial can occur or, using prespecified, interim analyses, recruitment to a particular arm can be discontinued because of lack of effect [44]. The MAMS design should therefore be viewed as a more efficient trial design than traditional designs.

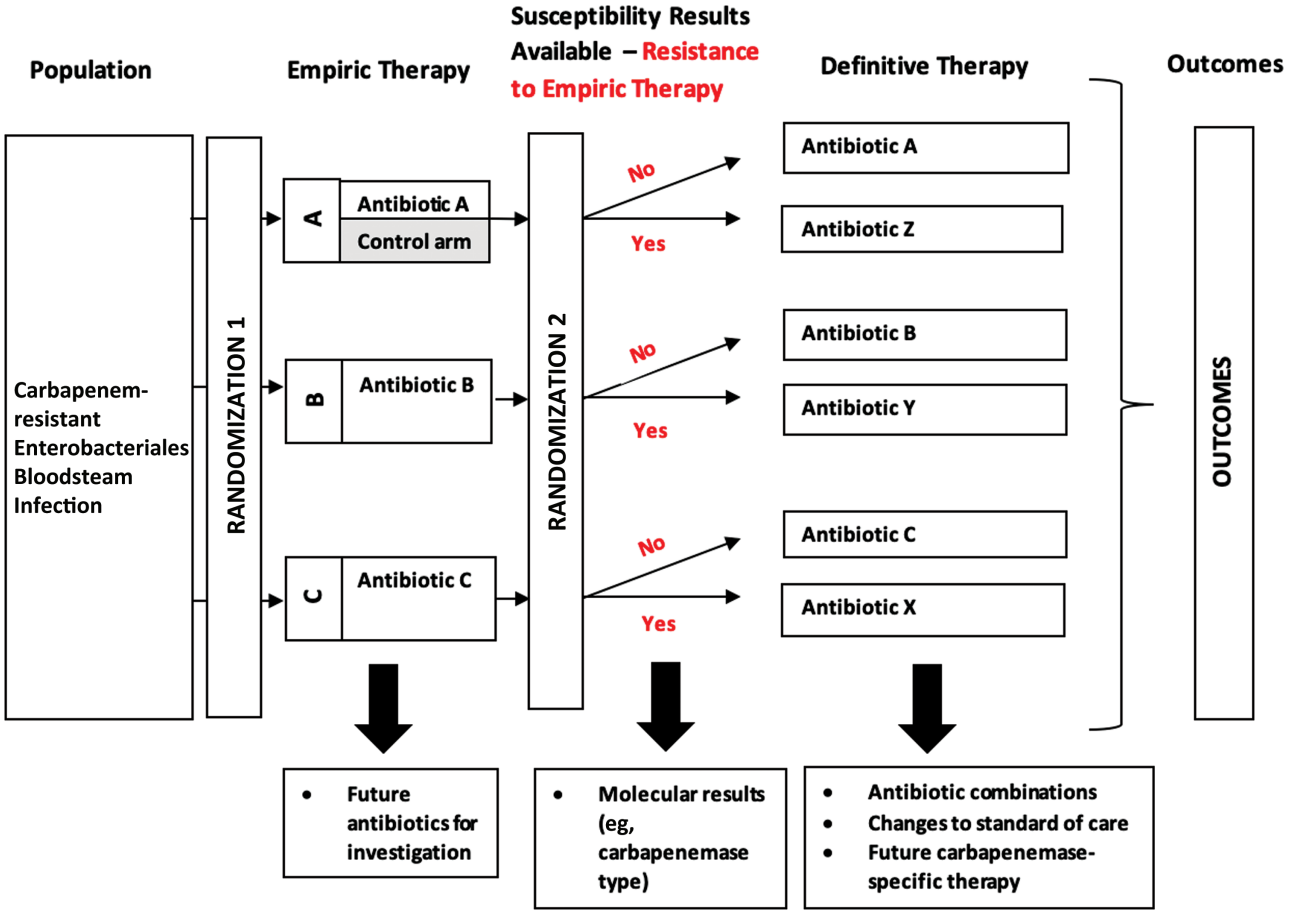

Figure 1. Sequential multiple assignment randomized trial (Comparing Personalised Antibiotic Strategies [SMART-COMPASS]) integrated with multiarm, multistage design to investigate optimal treatment strategy for carbapenem-resistant Enterobacteriaceae bloodstream infection.

Sequential Multiple Assignment Randomized Trial—Comparing Personalized Antibiotic Strategies (SMART-COMPASS)

Evans et al have recently described a trial methodology termed "SMART-COMPASS," which makes an effort to be consistent with decision-making processes in the treatment of patients with serious GNB infections [45]. COMPASS is a trial design that compares strategies consistent with clinical practice, rather than specific therapies. A strategy is a decision rule that guides treatment of serious infections with GNB, comprised of a combination of an empiric therapy decision with a personalized definitive therapy decision, when organism identification and antibiotic susceptibility are known. The goal for COMPASS trials is to identify strategies that produce the best ultimate outcome for the patient.

For infections with GNB, there are likely to be multiple definitive therapy options, given the development of new antibiotics and increased understanding of new anti-infective strategies. For example, for ventilator-associated pneumonia proven to be due to *P. aeruginosa*, there may be an option to use monotherapy given intravenously, combination therapy given intravenously, or one drug given intravenously and a second administered directly to the respiratory tract. In this case, a Sequential Multiple Assignment Randomized Trial (SMART) trial design can be considered. Sequential randomization provides the opportunity to create new strategies that differ with respect to definitive therapy and to compare them in a randomized setting [45]. Trial participants requiring therapy adjustment at the definitive stage can be rerandomized to the definitive therapy options to determine the optimal adjustment and overall strategy. Overall, this allows us to simultaneously (ie, within a single large trial) investigate multiple strategies in both the empiric and definitive therapy populations, with each trial patient being randomized twice during these stages of their treatment period.

Desirability of Outcome Ranking Endpoints

Desirability of Outcome Rankings (DOOR) are ordinal clinical endpoints constructed on the basis of perceived importance (patient and physician centered), including benefits, harms, and quality of life [46]. They assign higher ranks to trial participants who achieve better clinical outcomes overall, and the probability of a randomly selected patient achieving a better

Table 2. Example of Ranked Categorical Composite Outcomes in Trials of Multidrug-resistant Gram-negative Bacteria

1 (best)	Survival; clinical response; microbiological cure; no *Clostridioides difficile* infection; no development of resistance; good functional outcome
2	Survival; clinical response; microbiological cure; no *C. difficile* infection; no development of resistance; poor functional outcome
3	Survival; clinical response; microbiological cure; no *C. difficile* infection; development of resistance
4	Survival; clinical response; microbiological cure; both *C. difficile* infection and development of resistance
5	Survival; clinical response; microbiological relapse/recurrence
6	Survival; delayed/minimal clinical response
7 (worst)	Death

DOOR for the new antibiotic strategy is calculated. It addresses weaknesses of traditional approaches where (1) separate analysis of outcomes fails to capture key associations between outcomes and their accumulative nature; (2) competing risks complicate interpretation; and (3) efficacy and safety analyses, due to being performed in different populations, have impaired generalizability. The partial credit strategy allows patients and clinicians to have their own scoring system; however, outcomes are ordered by the perspective of the rater, running the risk of failing to fully capture all clinically relevant data [47, 48]. Table 2 provides an example of what these ranked composite outcomes might look like in an MDR GNB therapy trial. A recent prospective cohort study incorporated DOOR with a partial credit strategy, using ordinal outcomes for efficacy, safety, and risk-benefit [49]. Many difficulties remain when this approach is used, including arriving at a predetermined consensus regarding ranking of ordinal outcomes for trials. The Antibacterial Resistance Leadership Group has worked on an approach to these issues [50].

What Might Modern Trials Look Like for the Study of ESBL-Producing and Carbapenem-resistant Organisms?

Ultimately, integration of such approaches provides the opportunity to conduct efficient and relevant trials for MDR GNB infection. For example, a MAMS trial combined with SMART-COMPASS, using DOOR to construct meaningful outcomes, is one approach (Figure 1). Here exists a defined, relevant patient population whereby multiple antibiotics (both new and existing) and therapeutic strategies, at different stages in a patient's clinical course, are systematically evaluated in unison. The roll-on nature of this trial structure lends itself well to future changes in standard of care, introduction of new antimicrobials, and potential molecular targeted therapy.

CONCLUSIONS

Significant therapeutic challenges continue to exist in MDR GNB infections. Recent clinical trials other than for registration purposes are few in number and struggle to address relevant issues. Numerous financial and regulatory hurdles exist for independent investigators carrying out meaningful trials. Limitations to recent investigator-led MDR GNB trials have been identified and impede clinical impact and significance. Novel solutions to trial methodology within the infectious diseases sphere can provide clinicians with more relevant outcomes while enhancing overall trial efficiency. Newer approaches are clearly needed as the burden of complications related to gram-negative resistance continues to outgrow the development of new antibiotics and optimal therapeutic strategies to treat them.

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