Title

Sequential, Multiple-Assignment, Randomized Trials for COMparing Personalized Antibiotic StrategieS (SMART-COMPASS).

Journal

Clinical Infectious Diseases, 68(11)

ISSN

1058-4838

Authors

Evans, Scott R
Follmann, Dean
Liu, Ying
et al.

Publication Date

2019-05-17

DOI

10.1093/cid/ciy912

Peer reviewed

Clinical Infectious Diseases

INVITED ARTICLE

Innovations in Design, Education, and Analysis (IDEA): Scott R. Evans and Victor De Gruttola, Section Editors

Sequential, Multiple-Assignment, Randomized Trials for COMparing Personalized Antibiotic StrategieS (SMART-COMPASS)

Scott R. Evans,[1] Dean Follmann,[2] Ying Liu,[3] Thomas Holland,[4] Sarah B. Doernberg,[5] Nadine Rouphael,[6] Toshimitsu Hamasaki,[7] Yunyun Jiang,[1] Judith J. Lok,[8] Thuy Tien T. Tran,[1] Anthony D. Harris,[9] Vance G. Fowler Jr,[4] Helen Boucher,[10] Barry N. Kreiswirth,[11] Robert A. Bonomo,[12] David van Duin,[13] David L. Paterson,[14] and Henry Chambers[5]

[1]The Innovations in Design, Education, and Analysis Committee of the Biostatistics Center, George Washington Milken Institute School of Public Health; [2]National Institute of Allergy and Infectious Diseases, Bethesda, Maryland; [3]Biogen, Inc., Cambridge, Massachusetts; [4]Duke University, Durham, North Carolina; [5]University of California at San Francisco; [6]Emory University, Atlanta, Georgia; [7]National Cerebral and Cardiovascular Center, Japan; [8]Boston University, Massachusetts; [9]University of Maryland School of Medicine, Baltimore; [10]Tufts Medical Center and Tufts University School of Medicine, Boston, Massachusetts; [11]New Jersey Medical School-Rutgers University, Newark; [12]Case Western Reserve University, Cleveland, Ohio; [13]University of North Carolina, Chapel Hill; and [14]University of Queensland Centre for Clinical Research, Royal Brisbane and Women's Hospital Campus, Australia.

(See the Introduction on page 1960.)

Patient management is not based on a single decision. Rather, it is dynamic: based on a sequence of decisions, with therapeutic adjustments made over time. Adjustments are personalized: tailored to individual patients as new information becomes available. However, strategies allowing for such adjustments are infrequently studied. Traditional antibiotic trials are often nonpragmatic, comparing drugs for definitive therapy when drug susceptibilities are known. COMparing Personalized Antibiotic StrategieS (COMPASS) is a trial design that compares strategies consistent with clinical practice. Strategies are decision rules that guide empiric and definitive therapy decisions. Sequential, multiple-assignment, randomized (SMART) COMPASS allows evaluation when there are multiple, definitive therapy options. SMART COMPASS is pragmatic, mirroring clinical, antibiotic-treatment decision-making and addressing the most relevant issue for treating patients: identification of the patient-management strategy that optimizes the ultimate patient outcomes. SMART COMPASS is valuable in the setting of antibiotic resistance, when therapeutic adjustments may be necessary due to resistance.

Keywords. strategy; sequential randomization; pragmatic trial.

Clinical 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. Adjustments are personalized: tailored to individual patients as new information about those patients becomes available.

Consider the treatment of serious bacterial infections. Here, there are 2 major decision-points regarding treatment selection: empiric and definitive therapies. Empiric therapy is selected based on the clinicians' best judgment, given the often-limited information that is immediately available upon recognition of the clinical syndrome. Definitive therapy is selected once the organism identification, antibiotic susceptibility testing (AST) results, tolerability, and clinical course of the patient are known.

In the face of unknown information (eg, AST results, tolerability), clinicians would benefit from understanding which strategy—or sequence of decisions, based on up-to-date information at each step of the way—optimizes the patient outcome and experience. For example, a clinician may be interested in the effectiveness of the following strategy for a patient with blood culture–growing, Gram-positive cocci in clusters: start or continue vancomycin; if it turns out to be coagulase-negative staphylococci, stop antibiotics; if methicillin-susceptible *Staphylococcus aureus*, switch to cefazolin; if methicillin-resistant *S. aureus*, continue with vancomycin, unless there are treatment-limiting side effects, in which case switch to daptomycin; or if blood cultures are persistently positive, for example, switch to ceftaroline or add ceftaroline.

Traditional antibiotic trials are often nonpragmatic (Table 1), comparing drugs or drug combinations for definitive therapy when drug susceptibilities are known. This reflects a focus on licensure rather than providing practical information for helping clinicians make treatment decisions by evaluating which decision-making strategies produce the best outcomes for patients in clinical practice: a distinction that often goes unrecognized. We propose a trial design framework to address these limitations and better inform decision-making in clinical practice.

COMPASS

COMparing Personalized Antibiotic StrategieS (COMPASS) is a trial design that compares strategies consistent with clinical

Received 20 June 2018; editorial decision 9 October 2018; accepted 19 October 2018; published online October 23, 2018.

Correspondence: S. R. Evans, George Washington University, 6110 Executive Blvd, Suite 750, Rockville, MD 20852 (sevans@bsc.gwu.edu).

Clinical Infectious Diseases® 2019;68(11):1961–7

DOI: 10.1093/cid/ciy912

Table 1. Examples Illustrating a Lack of Pragmatism of Traditional Antibiotic Trials

• Drugs are evaluated in subgroups of patients but, in the clinical setting, whether a patient belongs to the subgroup is unknown until after treatment initiation. For example, drugs are often evaluated in patients with infections caused by susceptible organisms, but whether a patient's infection is caused by a susceptible organism is unknown until after treatment initiation.
• There is a focus on evaluating specific drugs rather than the therapeutic strategies that optimize ultimate patient outcomes. For example, a patient's response is characterized as a failure if they change therapy—a subjective determination—though they may not ultimately clinically fail. Interest in patients that change therapy wanes, despite the opportunity to evaluate the next important step in clinical practice: therapeutic adjustments that may effectively treat the patient.
• The overwhelming majority of patients with the infection of interest are not represented in clinical trials, as evidenced by the high screen-to-enrollment rates observed in many trials.
• Drugs are evaluated in 1 population in clinical trials but then used to treat a different population in practice. For example, in noninferiority (NI) trials, patients with recent prior therapy are excluded to ensure assay sensitivity to detect differences if they exist. But drugs approved on the basis of NI trials are used in patients with prior therapy.
• NI trials are not conducted to address the question of which therapy is better to use for treating patients in practice. Furthermore, they often require eligibility restrictions that limit generalizability and the feasibility of enrollment.
• Separate trials are often inefficiently conducted to address different research questions, such as: How should the patient be treated if they have a resistant organism? How should the patient be treated if they do not respond well to empiric therapy? How should the patient be treated if they do respond well to empiric therapy?
• Empiric therapy carries downstream effects, affecting definitive therapy options and effectiveness. The compartmentalized evaluation of empiric therapy suffers from non-ignorable censoring of adverse events after empiric therapy discontinuation. The compartmentalized evaluation of definitive therapy often suffers from poor generalizability, due to eligibility restrictions on empiric therapy.

practice. A strategy is a decision-rule that guides patient treatment, comprised of an empiric therapy decision combined with a personalized, definitive-therapy decision. The most important goal for clinical practice is to identify the strategy that produces the best ultimate outcome.

Consider the treatment of patients for complicated urinary tract infection (cUTI). Levofloxacin is a standard-of-care, empiric, oral therapy for cUTI that is effective in infections caused by levofloxacin-susceptible organisms. Levofloxacin resistance is common [1]; thus, some clinicians are concerned about prescribing levofloxacin for a suspected cUTI. But suppose that when levofloxacin resistance exists, an adjustment of therapy can ultimately rescue the patient and elicit a positive outcome. In clinical practice, the important question is how the strategy of empiric, oral levofloxacin with an adjustment if levofloxacin resistance is discovered compares with an alternative strategy—for example, utilizing an empiric regimen that covers levofloxacin-resistant organisms—with respect to the ultimate patient response.

There is an important distinction between a strategy and the treatments received. Patients on the same strategy can receive different treatments, due to different early responses or AST results. Consider the following strategy for the treatment of cUTI:

- Empiric treatment with oral levofloxacin; for definitive therapy, if AST indicates levofloxacin resistance, then change to an oral agent to which the organism is susceptible; otherwise, continue levofloxacin.

Suppose Simon and Garfunkel are randomized to this strategy. At the definitive stage, Simon's AST indicates levofloxacin resistance; thus, Simon is switched to oral fosfomycin (as there is no other effective, oral alternative). Garfunkel's AST indicates levofloxacin susceptibility; thus, Garfunkel remains on levofloxacin. Simon and Garfunkel receive different treatments, but are part of the same strategy. Either may ultimately fail or succeed at a test-of-cure visit. Here, the AST acts as the tailoring criterion for directing patient treatment at the definitive stage.

The tailoring criterion could also incorporate a short-term clinical response: for example,toxicity, requiring a therapy adjustment. For example, the Antibacterial Resistance Leadership Group [2] is conducting a randomized trial comparing the above, oral, step-down strategy with an alternative strategy for the treatment of cUTI: empiric treatment with a once-daily, 3-gram, oral dose of fosfomycin; for definitive therapy, if fosfomycin induces intolerable diarrhea, then the treatment is changed to levofloxacin; otherwise, fosfomycin is continued. Suppose Hall and Oates are randomized to this strategy. At the definitive stage, Hall has intolerable diarrhea; thus, Hall is switched to levofloxacin. Oates does not experience diarrhea; thus, Oates remains on fosfomycin. Hall and Oates receive different treatments, but are part of this same alternative strategy.

SMART COMPASS

When there are multiple definitive-therapy options, then a sequential, multiple-assignment, randomized (SMART) COMPASS trial can be considered. Sequential randomization [3–5] provides the opportunity to create new strategies, which differ with respect to definitive therapy selection, and compare them in a randomized setting. Trial participants requiring therapy adjustment at the definitive stage can be re-randomized to the definitive therapy options to determine the optimal adjustment path and overall strategy.

For illustration, consider a trial evaluating treatments for infection at a specific infection site, where Gram-stain results are known (Figure 1). Suppose there are 2 empiric treatment options: A1 and A2. Further, suppose that at the definitive stage, a patient remains on the original empiric therapy if the patient is responding well and AST results indicate susceptibility to the empiric therapy selection. However, if the patient is not responding well or the AST results indicate resistance to empiric therapy, then there are 2 definitive treatment options (B1 and B2) for patients on empiric A1 therapy and 2 definitive treatment options (B1 and B3) for patients on empiric A2 therapy. Adjustment options for patients on empiric therapies A1 and A2 may be similar or dissimilar.

Here, patients could be randomized to A1 or A2 for empiric therapy. If a patient is randomized to A1 and is not responding well or the AST results indicate resistance to A1, then

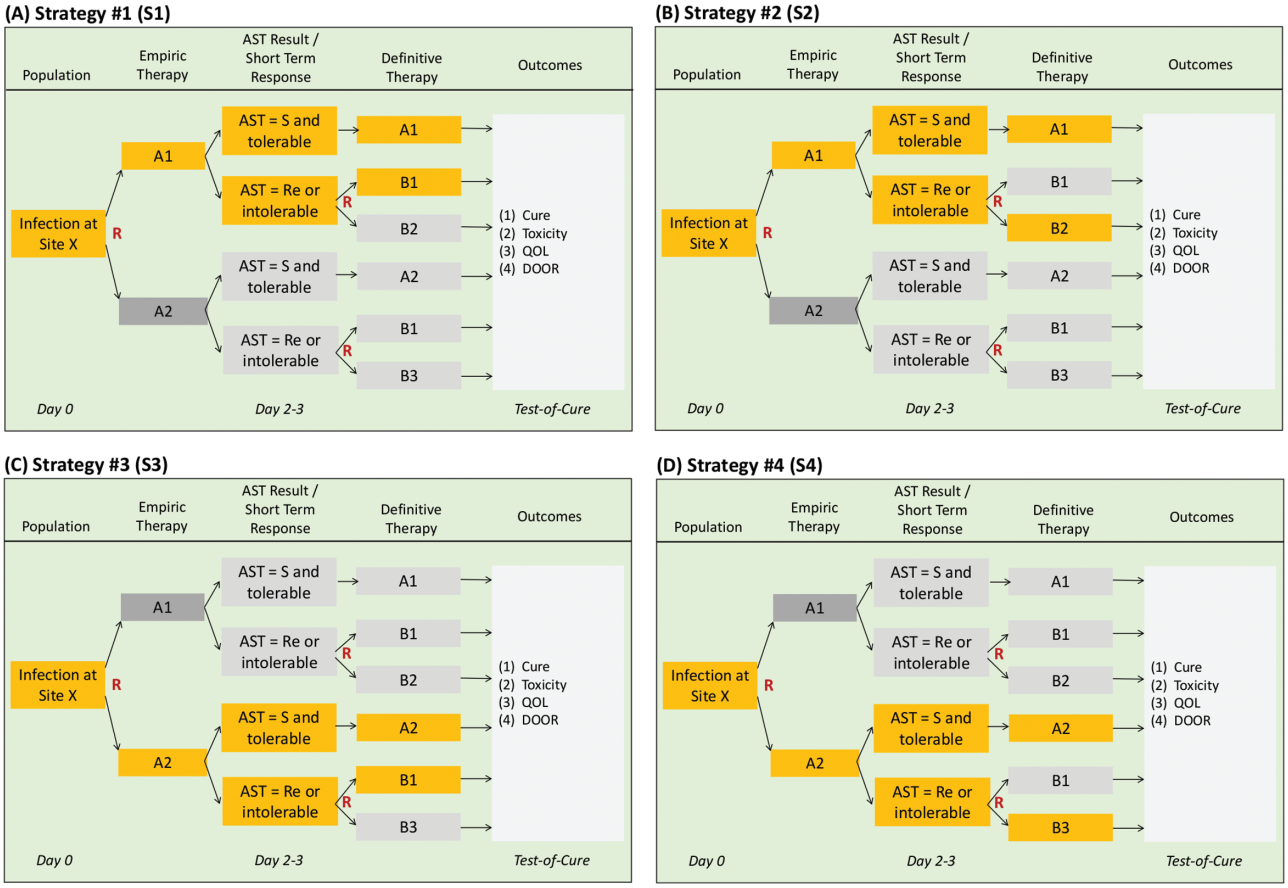

Figure 1. Examples of the SMART COMPASS trial, comparing 4 strategies (S1-S4). Each panel highlights a distinct strategy in yellow. (*A*) In S1, initial randomization to empiric therapy A1. For definitive therapy, if AST indicates R or A1 is not tolerated, then path changes and is re-randomized to B1. Otherwise, path continues with definitive therapy A1. (*B*) In S2, initial randomization to empiric therapy A1. For definitive therapy, if AST indicates R or A1 is not tolerated, then path changes and is re-randomized to B2. Otherwise, path continues with definitive therapy as A1. (*C*) In S3, initial randomization to empiric therapy A2. For definitive therapy, if AST indicates R or A2 is not tolerated, then path changes and is re-randomized to B1. Otherwise, path continues with definitive therapy as A2. (*D*) In S4, initial randomization to empiric therapy A2. For definitive therapy, if AST indicates R or A2 is not tolerated, then path changes and is re-randomized to B3. Otherwise, path continues with definitive therapy A2. Abbreviations: AST, antibiotic susceptibility testing; DOOR, desirability-of-outcome ranking; QOL, quality of life; R, randomization; Re, resistance; S, susceptibility; SMART COMPASS, sequential, multiple-assignment, randomized trials for comparing personalized antibiotic strategies.

the patient will be re-randomized to B1 or B2. Otherwise, the patient will remain on A1. If a patient is randomized to A2 and is not responding well or the AST results indicate resistance to A2, then the patient will be re-randomized to B1 or B3. Otherwise, the patient will remain on A2. With this design, 4 treatment strategies (S1-S4) could be investigated (Figure 1).

Sequential randomization provides efficiencies compared to a traditional, 4-arm, randomized trial, where each trial participant is randomized exactly once to 1 of the 4 strategies at the start of the trial. The efficiency stems from the fact that data from individual patients can contribute to the evaluation of multiple strategies. Suppose a patient is randomized to A1 for empiric therapy and, subsequently, the AST indicates susceptibility and A1 is well tolerated; thus, A1 is continued. The experience of this patient is consistent with each of the first 2 strategies: S1 and S2. Their data can be used to evaluate both strategies.

RESEARCH QUESTIONS ADDRESSED WITH SMART COMPASS

The SMART COMPASS design can be used to evaluate multiple research questions. The primary intent of SMART COMPASS is to compare strategies, consistent with the goal of finding the optimal clinical treatment plan rather than a single best drug. Note that each of the 4 strategies in Figure 1 could be compared in a pairwise manner (6 possible comparisons, in this case: S1 vs S2, S1 vs S3, S1 vs S4, S2 vs S3, S2 vs S4, and S3 vs S4). Research teams can evaluate and prioritize research questions, based upon the specific objectives of the trial, in order to appropriately power the study, given that multiple comparisons [6, 7] between treatment strategies will be made. Note that 2 of the comparisons would involve a smaller number of patients. A comparison of S1 vs S2 represents a comparison of B1 vs B2 for definitive therapy in patients with prior empiric A1 therapy whose AST indicates either resistance or intolerability to A1. A comparison of S3 vs S4 represents a comparison of B1 vs B3

for definitive therapy in patients with prior empiric A2 therapy whose AST indicates either resistance or intolerability to A2. Given that these 2 comparisons are restricted to subgroups of patients, they may be under-powered unless sample size adjustments are made.

Secondary analyses may include comparing empiric therapies (A1 vs A2), adjusting for or averaging over subsequent definitive treatments. Subgroup analyses based on baseline characteristics, such as susceptible diseases, can be conducted, as in other clinical trials. For example, a comparison of A1 vs A2 in a subgroup of patients that is susceptible to both A1 and A2 may be of interest in a regulatory setting.

Exploratory analyses may include evaluating how baseline factors or covariates measured in the empiric stage (eg, adherence) affect definitive-treatment contrasts. This may inform future revisions to the tailoring criterion, subsequently defining new strategies that may enhance personalized treatment.

We illustrate SMART COMPASS designs with 2 examples.

Example 1: Gram-negative Infection

Consider the treatment of patients with sepsis in the intensive care unit or the treatment of cancer patients with neutropenic fever: populations in which antibiotic-resistant, Gram-negative bacteria are common. Plazomicin is a novel, aminoglycoside antibiotic that has extended activity against a wide range of Gram-negative bacterial pathogens, including carbapenem-resistant *Enterobacteriaceae* (CRE) [8]. However, how plazomicin should be used in clinical practice to optimally treat patients with infections remains unclear.

Some theorize that it would be added to a best-available therapy (BAT). However, it is unknown whether plazomicin would provide greater benefits in combination with BAT, compared to BAT alone. Furthermore, if it does provide benefits, it is unknown whether it would be optimal to add plazomicin to BAT at the empiric or the definitive therapy stage. The advantage of treating people with plazomicin at the empiric stage is that patients with CRE and other relevant pathogens for which plazomicin may have beneficial effects will be treated at the soonest possible time, optimizing their chance of a successful outcome. However, patients without CRE and other relevant pathogens would be sub-optimally exposed to plazomicin, but would be unlikely to benefit. Alternatively, unnecessary exposure to plazomicin could be avoided by delaying treatment to the definitive stage. However, the treatment of patients with infections due to CRE and other relevant pathogens that may benefit from plazomicin would be delayed a few days, potentially critically limiting its effectiveness.

A SMART COMPASS trial can be conducted to determine the optimal use of plazomicin (Figure 2). In the empirical stage, patients would be randomized to BAT alone vs BAT + plazomicin. For patients randomized to BAT alone, if laboratory testing indicates CRE or another relevant pathogen, then these patients would be re-randomized to BAT vs BAT + plazomicin. Here, BAT is not a specific drug, but a strategy of using the best, known therapy at a particular moment in time. For the patients randomized to BAT + plazomicin in the empirical stage, if laboratory testing indicates that they do not have CRE or a relevant pathogen, then plazomicin can be withdrawn. This would result in a trial with 3 strategies (Figure 2) that could then be compared with respect to the ultimate patient outcomes.

Example 2: Gram-positive Infection

Staphylococcus aureus bloodstream infection is a serious, common infection without a defined, optimal treatment strategy [9]. Current standard-of-care treatment involves extended durations of potentially-toxic antibiotics, long-term intravenous access, and blood draws for drug monitoring.

When treating patients with complicated *S. aureus* bloodstream infections, an important clinical question is identification of the best management strategy for the completion of therapy. Options may include continuing, switching, or intensifying initial therapy, depending on the clinical response. A SMART COMPASS design (Figure 3) could be used to evaluate options. Trial participants with methicillin-resistant *Staphylococcus aureus* bacteremia would be randomized to vancomycin or daptomycin for initial therapy. Follow-up cultures would be obtained, per the standard of care. If the follow-up cultures were negative, then the initial, randomized agent would be continued. If the follow-up cultures were persistently positive, then trial participants initially on vancomycin would be re-randomized to: (1) add ceftaroline, or (2) switch to ceftaroline. Trial participants initially on daptomycin would be re-randomized to: (1) add ceftaroline, or (2) switch to ceftaroline. This produces a trial evaluating 4 strategies (Figure 3).

Statistical Considerations

When using SMART COMPASS, complex statistical calculations are required for confidence interval estimation, hypothesis testing, and sample size determination. The complexity arises from the fact that different strategies can "share" patients, in contrast to standard trials, where distinct patients are used for each arm. In Example 1, CRE-negative patients receive the same treatment; thus, they contribute to both strategies 2 and 3. This is statistically more efficient than traditional trials, where a single patient's data only contributes to a single strategy. However, sharing patients adds complexity. To obtain an unbiased estimate of the overall response for strategy 2 (or 3), CRE-negative patients must be down-weighted relative to the CRE-positive patients in strategy 2 (or 3). Technical details are provided in the Supplementary Material, with a catalogue (Supplementary Table 1) of sample sizes, estimators, and parameters for the design described in Example 1.

As for any trial, the feasibility of a SMART COMPASS trial depends on the type of patients that can be enrolled. Consider the design from Example 1. If resistant pathogens are very rare,

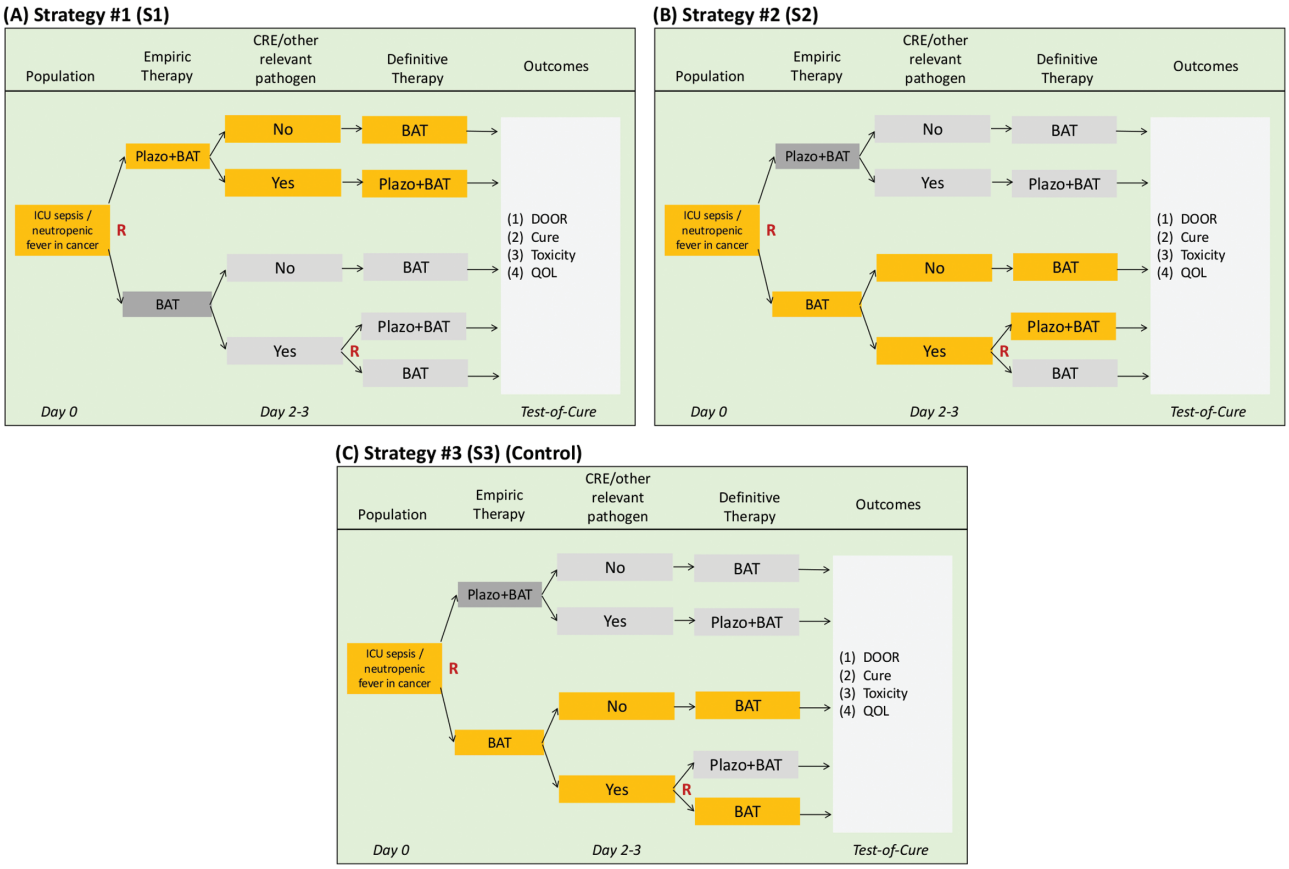

Figure 2. Example of Gram-negative SMART COMPASS trial, comparing 3 strategies (S1-S3). Each panel highlights a distinct strategy in yellow. (*A*) In S1, empiric therapy is BAT + plazomicin. For definitive therapy, if a case has CRE or another specific pathogen, then continue BAT + plazomicin; if not, then switch to only BAT. (*B*) In S2, empiric therapy is BAT. For definitive therapy, if a case has CRE or another specific pathogen, then add plazomicin to BAT; if not, then continue with only BAT. (*C*) In S3, empiric therapy is BAT and definitive therapy is BAT. Abbreviations: BAT, best-available therapy; CRE, carbapenem-resistant *Enterobacteriaceae*; DOOR, desirability-of-outcome ranking; ICU, intensive care unit; QOL, quality of life; R, randomization; SMART COMPASS, sequential, multiple-assignment, randomized trials for comparing personalized antibiotic strategies.

then strategies 2 and 3 are virtually identical, and the trial is effectively a comparison of early plazomicin vs early BAT. In the planning stage, the feasibility of different designs should be thoroughly explored.

DISCUSSION

COMPASS may have an ethical attractiveness as a form of personalized medicine, tailoring adjustments to therapy based upon new, patient-specific information as it is obtained. Clinicians and patients may find this attractive, potentially increasing trial participation and retention.

COMPASS is pragmatic approach, mirroring antibiotic treatment decision-making processes as they unfold in clinical practice and addressing the most relevant question for treating patients: identification of the patient-management strategy that optimizes the ultimate patient outcomes. COMPASS is particularly valuable in the setting of antibiotic resistance, where adjustments to therapy may be necessary. Patients in the same strategy can receive different treatments. Consider a phage treatment where the phage is tailored based upon the specific infection. Though different patients will received distinct, tailored phages, interest lies in evaluating the strategy of phage application. The intervention is defined by the strategy, not solely by the biological makeup. The evaluation of strategies represents the fundamental intention-to-treat principle, which states to analyze as randomized, regardless of the treatment received.

The pragmatic nature of COMPASS lends itself to pragmatic benefit:risk assessments and global outcomes, such as the desirability-of-outcome ranking [10], where rank-based or partial credit analyses could be performed [11]. Simpler, traditional outcomes, such as treatment success, can also be evaluated. If there are costs to making adjustments, then adjustment-free treatment success can be evaluated as an outcome.

Industry sponsors typically prefer an evaluation of a specific drug and consider a change of therapy as a failure. But understanding ultimate patient outcomes in the presence of therapeutic adjustments helps to inform the utility of empiric use. The importance and cost of a necessary therapeutic change depends on whether therapeutic adjustments effectively manage or rescue the patient.

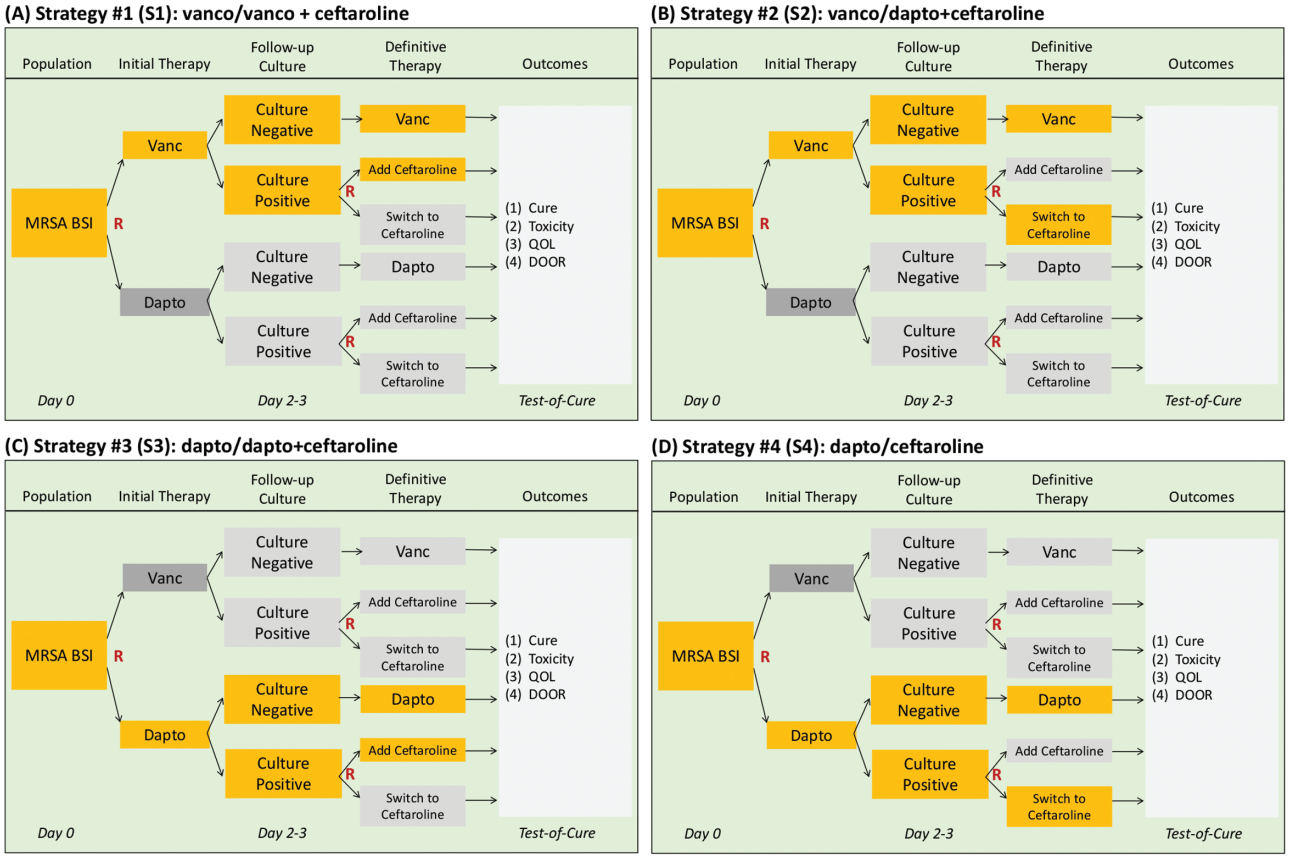

Figure 3. Example of Gram-positive SMART COMPASS trial, comparing 4 strategies (S1-S4). Each panel highlights a distinct strategy in yellow. (*A*) S1 uses vancomycin, with or without ceftaroline. Initial therapy uses only vancomycin; for definitive therapy, if a follow-up blood culture is positive, then ceftaroline should be added. Otherwise, continue only vancomycin. (*B*) S2 uses either vancomycin or ceftaroline. Initial therapy uses only vancomycin; for definitive therapy, if a follow-up blood culture is positive, then ceftaroline should be used instead. Otherwise, continue only vancomycin. (*C*) S3 uses daptomycin, with or without ceftaroline. Initial therapy uses daptomycin; for definitive therapy, if a follow-up blood culture is positive, then ceftaroline should be added. Otherwise, continue only daptomycin. (*D*) S4 uses either daptomycin or ceftaroline. Initial therapy uses daptomycin; for definitive therapy, if a follow-up blood culture is positive, then ceftaroline monotherapy should be used instead. Otherwise, continue only daptomycin. Abbreviations: BSI, bloodstream infection; dapto, daptomycin; DOOR, desirability-of-outcome ranking; MRSA, methicillin-resistant *Staphylococcus aureus*; QOL, quality of life; R, randomization; SMART COMPASS, sequential, multiple-assignment, randomized trials for comparing personalized antibiotic strategies vanco, vancomycin.

SMART COMPASS provides the opportunity to compare adjustment alternatives and evaluate which are optimal when adjustments are needed. It provides efficiencies, since individual patients can contribute to the estimation of outcomes for multiple strategies. SMART COMPASS can be viewed as a type of platform trial, given its multi-strategy focus.

SMART COMPASS trial results depend on, for example, the prevalence of resistance when ASTs are used as the tailoring criterion. Since the goal of SMART COMPASS trials is to obtain answers for real-world questions in clinical practice, pragmatic enrollment strategies that mimic clinical practice, with trials utilizing fewer entry criteria restrictions, may be considered. However, an advantage of SMART COMPASS is that researchers can calibrate response rates and resulting treatment contrasts to resistance rates unobserved in the trial. The treatment contrast can be plotted as a function of the resistance prevalence and the resistance rate, representing a turning point at which a particular therapy can be identified as superior to another. This is particularly appealing given the dynamic nature of the pathogen population over time, due to resistance evolution and the geographic heterogeneity of resistance.

Disadvantages of SMART COMPASS include complicated logistics and analyses. Therapeutic adjustments create challenges for blinding. Sequential randomization creates operational complexities, with an additional stage of randomization. During sample size calculations and analyses, weighting of patients is required to obtain appropriate estimates of effects and associated standard errors. Estimates of the proportions of patients that will be re-randomized at the definitive treatment stage are required for sample size calculations.

When implementing SMART COMPASS, consenting trial participants should focus on the strategy, rather than individual treatments (although these will also be discussed) or stages of treatments, given the efficiency of consenting once rather than at each therapeutic stage. Although a goal of consenting to the strategy is to prevent loss to follow-up, a second stage of

randomization is a time at which trial participants may be more likely to drop out, as they may be most focused on the initial therapy. Investigators must carefully explain the therapeutic strategy foci, rather than specific interventions, and the importance of completing the complete strategy, regardless of therapeutic adjustments. Separate randomization at each stage, rather than a single, up-front randomization, has the advantage of allowing for stratified randomization at the definitive stage. During trial monitoring of COMPASS and SMART COMPASS trials, medical monitors and data-monitoring committees must transition the focus from evaluating the benefits and harms of specific drugs or drug combinations to evaluating the equipoise of the strategies.

Traditional randomized, controlled trials are designed to compare the safety and efficacy of specific drugs in a carefully-controlled, circumscribed, clinical setting. This often does not reflect how the drugs are actually used in clinical practice. Clinical decision-making is not a single event: rather, it is a strategy; a series of decisions occurring over time as new information becomes available and as clinical events evolve. COMPASS and SMART COMPASS are pragmatic trial designs that address the practical questions in clinical practice by comparing therapeutic strategies.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Disclaimer. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health (NIH).

Financial support. This work was supported by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health (award number UM1AI104681).

Potential conflicts of interest. H. B. receives personal fees from Merck, outside the submitted work. N. R. has received grants from the National Institutes of Health (NIH) Division of Microbiology and Infectious Diseases (Vaccine and Treatment Evaluation Units) during the conduct of the study; grants from the NIH Division of Allergy, Immunology, and Transplantation (Human Immunology Project Consortium) and the NIH Division of AIDS, outside the submitted work; and funding from Sanofi, outside the submitted work. D. vD. reports grants from the Antibacterial Resistance Leadership Group, during the conduct of the study; and personal fees from Astellas, Achaogen, T2 Biosystems, Shionogi, Allergan, Merck, NeuMedicine, and Roche, outside the submitted work. S. B. D. reports personal fees from Genentech and Actelion, outside the submitted work. V. G. F. served as Chair of V710 Scientific Advisory Committee (Merck); has received grant support from Basilea, Cerexa/Actavis, Pfizer, Advanced Liquid Logics, NIH, MedImmune, Cubist/Merck, Karius, Contrafect, Regeneron, and Genentech; has the NIH Small Business Technology Transfer/Small Business Innovation Research grants pending with Affinergy, Locus, and Medical Surface, Inc; has been a paid consultant for Achaogen, Astellas, Arsanis, Affinergy, Basilea, Bayer, Cerexa, Contrafect, Cubist, Debiopharm, Durata, Grifols, Genentech, MedImmune, Merck, Medicines Co., Pfizer, Novartis, Novadigm, Theravance, xBiotech, Regeneron, and Destiny; has received honoraria from Theravance and Green Cross; and has a patent pending in sepsis diagnostics. T. Holland reports personal fees from the Medicines Company (oritavancin), Basilea Pharmaceutica (ceftobiprole), Duke University Medical Center, Motif Bio (iclaprim), and Genentech (immunotherapeutic), outside the submitted work. S. R. E. reports personal fees from Takeda/Millennium; Pfizer; Roche; Novartis; Achaogen; the Huntington Study Group; Auspex; Alcon; Merck; Chelsea; Mannkind; QRx Pharma; Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks; Genentech; Affymax; FzioMed; Amgen; GlaxoSmithKline; Boehringer-Ingelheim; the American Statistical Association; the Food and Drug Administration; Osaka University; City of Hope; the National Cerebral and Cardiovascular Center of Japan; the NIH; Muscle Study Group; Society for Clinical Trials; Drug Information Association; University of Rhode Island; New Jersey Medical School/Rutgers; Preclinical Pain Research Consortium for Investigating Safety and Efficacy; Statistical Communications in Infectious Diseases; Cubist; AstraZeneca; Teva; Repros; Austrian Breast & Colorectal Cancer Study Group/Breast International Group and the Alliance Foundation Trials; Zeiss; Dexcom; the American Society for Microbiology; Taylor and Francis; Claret Medical; Vir; Arrevus; Five Prime; Shire; Alexion; Gilead; Spark; the Clinical Trials Transformation Initiative; Nuvelution; and Tracon; outside the submitted work. D. L. P. reports personal fees from Merck, Shionogi, Pfizer, and GSK, outside the submitted work. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Qiao LD, Chen S, Yang Y, et al. Characteristics of urinary tract infection pathogens and their in vitro susceptibility to antimicrobial agents in China: data from a multicenter study. BMJ Open **2013**; 3:e004152.
2. Chambers HF, Cross HR, Evans SR, Kreiswirth BN, Fowler VG Jr; Antibacterial Resistance Leadership Group (ARLG). The Antibacterial Resistance Leadership Group: Progress Report and Work in Progress. Clin Infect Dis **2017**; 64:3–7.
3. Lavori PW, Dawson R. Dynamic treatment regimes: practical design considerations. Clin Trials **2004**; 1:9–20.
4. Lavori PW, Dawson R. Introduction to dynamic treatment strategies and sequential multiple assignment randomization. Clin Trials **2014**; 11:393–9.
5. Almirall D, Compton SN, Gunlicks-Stoessel M, Duan N, Murphy SA. Designing a pilot sequential multiple assignment randomized trial for developing an adaptive treatment strategy. Stat Med **2012**; 31:1887–902.
6. Dmitrienko A, D'Agostino R Sr. Traditional multiplicity adjustment methods in clinical trials. Stat Med **2013**; 32:5172–218.
7. Alosh M, Bretz F, Huque M. Advanced multiplicity adjustment methods in clinical trials. Stat Med **2014**; 33:693–713.
8. Connolly LE, Jubb AM, O'Keeffe B, et al. Plazomicin (PLZ) associated with improved survival and safety compared to colistin (CST) in serious carbapenem-resistant enterobacteriaceae (CRE) infections: Results of the CARE study. In: Program and abstracts of the 27th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) (Vienna, Austria); Session OS042 Late-breaker: Recent clinical trials; Category: (Other; Abstract OS0250F). **2017**.
9. Holland TL, Arnold C, Fowler VG Jr. Clinical management of Staphylococcus aureus bacteremia: a review. JAMA **2014**; 312:1330–41.
10. Evans SR, Rubin D, Follmann D, et al. Desirability of outcome ranking (DOOR) and response adjusted for duration of antibiotic risk (RADAR). Clin Infect Dis **2015**; 61:800–6.
11. Evans SR, Follmann D. Using outcomes to analyze patients rather than patients to analyze outcomes: A step toward pragmatism in benefit:risk evaluation. Stat Biopharm Res **2016**; 8:386–93.