Written responses to remaining audience questions of the webinar 'Post-licensing clinical trials for advancing the use of antimicrobials' by Steven Tong & Patrick Harris, moderated by Holly Jackson.
Originally broadcast on 22 May 2025. See webinar recording here: https://revive.gardp.org/post-licensing-clinical-trials-for-advancing-the-use-of-antimicrobials/

Question asked	Response from the speakers
If daptomycin performs worse than standard-of-care (vancomycin) for MRSA bacteraemia—even if the difference is not statistically significant—should we consider switching to it in cases of persistent MRSA bacteraemia on vancomycin (either as monotherapy or in combination)? This is especially relevant given that the CAMERA-2 trial did not demonstrate a clear benefit from combination therapy (vancomycin + β-lactam), and was terminated early due to increased toxicity associated with cloxacillin.	The short answer is that we don't know. There are many 'reasonable' options in the absence of good evidence. In our recent JAMA review, we wrote: 'For patients with persistent bacteremia, clinicians may consider switching antibiotics or adding antibiotics, although there are no randomized clinical trial data to provide guidance in such situations. Options include adding agents such as ertapenem to cefazolin[83] or fosfomycin to antistaphylococcal β-lactams for MSSA[60] and adding cefazolin,[57] fosfomycin,[59] ceftaroline,[58] or ceftobiprole[7] to vancomycin or daptomycin for MRSA.'
Given that cefiderocol is more costly and less readily available compared to the standard-of-care agents used in the GAME CHANGER trial, what are your thoughts on the chosen non-inferiority margin and the interpretation of the results? Do you think a more conservative reporting approach would be appropriate, considering these real-world limitations?	Setting the NI margin for these kind of trials is a major challenge. A very tight margin can have an enormous effect on your required sample size (to the extent that it becomes impractical for an investigator-initiated trial), yet a very large margin becomes somewhat meaningless and does not persuade the clinical end-users, even if NI is demonstrated. It could be argued that a 10% NI margin for mortality is perhaps too wide, but this has been used in other recent RCTs of new antibiotics, which used mortality based primary outcomes, e.g. RESTORE-IMI (Titov et al., CID 2020), ASPECT-NP (Kollef et al., Lancet ID 2019), REPROVE (Torres et al., Lancet ID 2017). But would generally agree that a tighter margin is often desirable if practicalities allow.
As you mentioned, trials in appropriate populations to address key clinical questions are difficult to recruit. What compromises in statistical rigor, if any, are acceptable to allow these trials to be done?	I think we should be maintaining statistical rigor. Strategies to consider are improved recruitment processes, large scale pragmatic trials, and use of novel but clinically meaningful endpoints (e.g., hierarchical composite endpoints like DOOR) that may improve the power of a study.

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To both speakers: Steven showed a graph depicting the highest deaths by Staphylococcus while Patrick showed otherwise, E. coli, can this be clarified?	ST: The references I used are listed below. In the first, S. aureus highest estimated mortality burden of 33 bacterial pathogens. In the second, E. coli most common cause of bacteraemia and S. aureus 2nd most common. Because S. aureus is associated with about 2x the case fatality rate as E. coli, the absolute number of deaths due to *S. aureus* is higher. GBD 2019 Antimicrobial Resistance Collaborators. Global mortality associated with 33 bacterial pathogens in 2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2022 Dec 17;400(10369):2221-2248. doi: 10.1016/S0140-6736(22)02185-7. Epub 2022 Nov 21. PMID: 36423648; PMCID: PMC9763654. Verway M, Brown KA, Marchand-Austin A, Diong C, Lee S, Langford B, Schwartz KL, MacFadden DR, Patel SN, Sander B, Johnstone J, Garber G, Daneman N. Prevalence and Mortality Associated with Bloodstream Organisms: a Population-Wide Retrospective Cohort Study. J Clin Microbiol. 2022 Apr 20;60(4):e0242921. doi: 10.1128/jcm.02429-21. Epub 2022 Mar 7. PMID: 35254101; PMCID: PMC9020345.
For Dr. Harris: Would it be possible to address the impact of the types of carbapenemase or non-carbapenemase carbapenem-resistance in the upcoming/ongoing GNB trials?	The wide variety of gram-negative species and associated carbapenemase genes or even on-carbapenemase mechanisms that lead to carbapenem-resistance makes designing these kinds of pathogen-directed trials very hard to do. With Gram-positive RCTs like SNAP, you are generally dealing with one species and a handful of resistance mechanisms/ phenotypes. The situation in GNBs is much more complex, dynamic and variable across the world. We generally want to enrol people into these trials as quickly as possible, but gathering detailed information such as a full resistance profile (including perhaps non-first line drugs) and key AMR genes that may determine which "silo" a patient is randomized into as part of a platform trial, requires very close and timely interaction with the laboratory. Increasingly some form of rapid diagnostics will be needed to ensure appropriate randomization occurs with minimal delay – but this can add considerable demands and costs on the trial infrastructure.

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Is obtaining ethical approval challenging when fast-tracking clinical trials across different countries?	Yes. But definitely surmountable. In SNAP, each regional has a sponsor who is responsible for trial conduct (including ethics submissions) and who understands the local regulatory landscape. Yes – would agree that having regional sponsors helps to delegate the administrative burden. In many ways, ethics is often the relatively easy part – while the contracting / legal processes can be the more prolonged and complex and is highly variable across different institutions / countries. Requires a very patient trial management team!
@Steven: Many trials of newer agents don't offer contemporaneous antimicrobial susceptibility testing. Did these trials do AST as, or prior to enrolment?	Answered during the live Q&A
The results from SNAP trial, if it is too early to conclude on anything, what can one actually expect to get out of the platform trial ?	Answered during the live Q&A
Given that most of the countries involved in the SNAP trial are high-income countries , are there any plans or steps being considered to include more low- and middle-income countries — beyond Malaysia — in future phases or related initiatives, to enhance equity and inclusivity in the trial's findings?	Answered during the live Q&A
What policy or strategy should be used to ensure access to new antibiotics in resource-limited countries? This is especially true given that antibiotic use is not well controlled in this context. Is there a risk of resistance emerging to these new antibiotics?	Asked during the live Q&A

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Great presentation Steven, it just stopped when we wanted to hear more: the results from SNAP trial, if it is too early to conclude on anything, what can one actually expect to get out of the platform trial ?	Asked during the live Q&A
@Patrick: the findings for Cefiderocol are ugly indeed and you say it casts a cloud on the drug usability but you are not mentioning the potential of combining it with MBL specific BLi that would compensate completely the effect maybe?	Asked during the live Q&A