Use of co-primary outcomes for trials of antimicrobial stewardship interventions

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Antimicrobial resistance (AMR) is a major public health threat that will cause an estimated 10 million deaths worldwide by 2050. [1] Because antimicrobial use drives selection and transmission of AMR, [2, 3] there is an urgent need to continue to develop, evaluate, and implement effective, evidence-based antimicrobial stewardship (AMS) interventions that safely reduce antimicrobial use in both primary and secondary healthcare. [4, 5]

AMS interventions can benefit individual patients, but are often viewed as trading potential increased short-term individual risk for long-term societal gain, [6] and so some consider them 'bedside rationing'. [7] The need to consider the ethical implications of AMS programmes, and acceptable trade-offs, will increase as antimicrobial prescribing is reduced and programmes are investigated among patients with an increased chance of benefit from antimicrobials.

While there is a clear need to ensure that reductions in antimicrobial use are not at the expense of patient outcomes, most current research considers these outcomes separately. AMS studies are therefore generally powered on only one of these aspects (typically antimicrobial use), and as a result, are frequently underpowered to detect clinically meaningful differences in important clinical secondary outcomes, and do not pre-specify whether between-group differences in clinical outcomes will be investigated under superiority, non-inferiority, or equivalence hypotheses.

This article describes the use of co-primary outcomes as a solution to this problem, presents two examples of co-primary outcomes in AMS intervention trials, and argues for their routine use in AMS intervention evaluations.

Co-primary outcomes involve the use of two or more primary outcomes, and rejecting both null hypotheses is necessary for the intervention to be declared successful. This contrasts with studies that have multiple primary outcomes where rejecting the null hypothesis for at least one (i.e. alternative primary outcomes) determines success. The use of co-primary outcomes in AMS intervention research encourages researchers to pay close attention to both antimicrobial use and patient-relevant measures (e.g. recovery from illness, safety outcomes), ensuring the study is adequately designed to simultaneously answer *both* questions. Thus, any reduction in antibiotic use *must* be judged in conjunction with any negative impact on patient recovery. Additional sample size considerations for

trials with co-primary outcomes include the assumed correlation between outcomes and the overall power of the study. When outcomes are completely independent, the overall power (to detect similar effect sizes in both outcomes) is the product of the power for each individual outcome, and only when they are perfectly correlated is the overall power unaffected. [8]

The PACE determined the effectiveness of C-reactive Protein (CRP) point-of-care testing on safely reducing antibiotic use in patients presenting in primary care with an acute exacerbation of chronic obstructive pulmonary disease (AECOPD). [9] The study used two co-primary outcomes: i.) Antibiotic use for AECOPD within the first four-weeks post-randomisation; ii.) COPD health status, as measured by the COPD Clinical Questionnaire at two-weeks post-randomisation. These co-primary outcomes were investigated for superiority and non-inferiority respectively. The study aimed to recruit 650 participants in order to achieve between 81% and 90% power to detect a 20% absolute difference in antibiotic use, and a COPD health status that is no worse (with a non-inferiority margin of 0.3).

The BATCH study is investigating the effect of procalcitonin-guided management on antibiotic use in children with severe bacterial infection. [10] The co-primary outcomes for the study are i.) Number of days of intravenous (IV) antibiotic therapy, and; ii.) Safety (comprising unscheduled admissions/re-admissions; re-treatment for same condition within 7 days of stopping IV antibiotics; mortality). The study aims to recruit 1942 participants to achieve between 99% power to detect a decrease in antibiotic duration and 90% power to test non-inferiority in safety. Assuming that the antibiotic use and safety primary outcomes are independent, this will give at least 89% power for the combined analysis.

Reducing antimicrobial use is essential to preserving antimicrobial effectiveness, but should not harm patients in the process. AMS intervention evaluations must consider the clinical implications of changed antimicrobial use, and the use of co-primary outcomes ensures that both use and safety outcomes are considered jointly. Researchers in this field may therefore wish to consider the use of co-primary outcomes, and research funders may consider mandating this dual focus when commissioning AMS intervention studies.

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