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Title: The DURATIONS design: a practical randomised trial design to optimise treatment duration

Abstract:
Introduction: Trials to identify the minimal effective treatment duration are needed in different therapeutic areas, including antibiotics, TB and Hepatitis C. However, standard non-inferiority designs have several limitations, including arbitrariness of choice of shorter duration arms and large sample sizes.
Methods: We propose a multi-arm trial design, allocating patients to different treatment durations. We recast the problem of testing for non-inferiority of a single shorter treatment duration in terms of modelling the entire duration-response curve within a pre-specified range. We use fractional polynomials to flexibly model the duration-response curve. We compare different methods to draw inference from the estimated curve, i.e. to choose the "optimal" duration. We explore both different estimands and estimation methods, in terms of newly developed operating characteristics.
Results: Through simulations we show that, in a variety of scenarios, when using fractional polynomials 5-7 equidistant duration arms are generally enough to get a good estimate of the duration response curve. In order to draw inference from this curve, the simplest estimand to target is the shortest duration non-inferior to the control one within a certain non-inferiority margin. The margin can itself be dependent on duration. In terms of estimation method, using bootstrap is preferable, as it accounts for model selection variability, and leads to type-1 error rates within the nominal level in all scenarios considered.
Discussion: Our proposed practical trial design is an alternative to standard non-inferiority designs, avoiding many of their limitations, and yet being fairly robust to different possible duration-response curves.