Reviewer’s report

Title: Optimising trial designs for identifying appropriate antibiotic treatment durations

Version: 1 Date: 26 Feb 2019

Reviewer: Mical Paul

Reviewer's report:

As background, please consider delineating the difficulty in assessing treatment duration in observational studies - what are the difficulties that cannot be well circumvented.

Figure 1: difficult to understand. Would start with defining the graphs (diamonds, solid/ dashed lines). Are the lines hypothesized or actual event rates, given that they show non-compliance? The last sentence of the legend is very unclear. I'm not sure this figure is in its place, because it addresses compliance, which is mentioned only much further on in the manuscript. The statements (a bit repetitive) that "such a trial does not answer the more important question of 'what is the optimal antibiotic treatment duration for prostatitis?' and Such RCTs provide information about the two evaluated durations, but do not provide much information about durations not considered in the trial" do not require a figure; they are clear as presented in text. Furthermore, when you raise the problem of compliance in duration trials (Line 284-292), you do not provide a solution: "The effect of non-compliance, which is likely not completely random, can be taken into account". This is an important issue, can you provide more specific guidance on how to take into account? Can you merge an explanation with the figure, explaining better what the figure shows?

Table 1: under "Obtain information about which durations" you write "considered and non-considered durations" for the trial designs other than the simple 2-arm design. Is this true? This wording might be confusing. All durations allocated in the trial are considered in advance. All trial designs are interventional, meaning the interventions were pre-planned, thus considered.

Power/ sample size calculation is the most significant challenge for the trial designs proposed. There is no free lunch; assessing more durations and patient subgroups requires a larger sample size to avoid type II errors. Can you provide guidance? How would the stopping rules be taken into account when computing the same size? In line 300 you mention that it is preferable to define futility stopping criteria at the planning stage. This is not preferable, but required.

An example of a planned trial would be appreciated, putting the suggested design into practice. You started with the example of prostatitis; it would be helpful if you provide the design of the optimized trial to assess treatment duration of prostatitis (but could be any infection), including the assessment of short term outcome, rarer, long term events and resistance development (not optional, but required in antibiotic duration trials), with the power of the trial to detect the different outcomes. This could be provided in a supplement.
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