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Yang J, Parvizi J, Hansen EN, et al. 2020 Mark Coventry Award: Microorganism-directed oral antibiotics reduce the rate of failure due to further infection after two-stage revision hip or knee arthroplasty for chronic infection: a multicentre randomized controlled trial at a minimum of two years. *Bone Joint J*. 2020;102-B(6 Supple A):3-9.

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Sir,

The authors of this recent publication, which reports the efficacy of a three-month course of antibiotics after two-stage revision arthroplasty for chronic periprosthetic joint infection (PJI) in preventing failure due to further infection, should be congratulated on the completion of a randomized trial on the management of this uncommon and challenging condition.[1] We agree that their results are intriguing and have the potential to inform clinical practice. However, a detailed review of the analytical plan and a statistical re-analysis of the data presented suggest some methodological flaws in the application of the primary outcome, the statistical tests applied, the management of missing outcome data (MOD), potential biases in outcome assessment and sample size determination which challenge the validity of the conclusions. We also note that an unplanned interim analysis of this trial published elsewhere describes a different follow-up protocol and application of 'intention to treat' (ITT) analysis.[2]

The trial was first registered on 3 January 2013 (NCT01760863). In the interim analysis, it is reported that recruitment started in July 2011, before the trial was registered.[2] On the trial registry, the primary outcome and brief summary sections state "infection rate, 24 months" and "re-infection following hospital discharge, defined as deep infection of the joint space/capsule that requires return to the operating room within 24 months of the re-implantation procedure", respectively. In the methods section presented in the interim analysis,[2] it was specified that patients were evaluated at three weeks, six weeks, three months, 12 months, and 24 months. The sample size justification is a "reduction in the risk of further infection from 16% to 4% with a power of 0.8 and α of 0.05". This also indicates that analysis was planned on the basis of a dichotomous primary outcome. Furthermore, we have recalculated the sample size (using different calculators) to be 190 to 226 participants without accounting for loss to follow-up,[3,4] comparable with the original numbers planned on the trial registry (n = 200), but more than in the 'a priori analysis' provided in the Methods (n = 144).

Taken together, the implication is that the trial was designed to have a follow-up period of two years and that the primary outcome would be met if there was any failure due to infection within this time period, a binary outcome. Our interpretation is that these data should be analyzed using either a Chi-squared or Fisher's Exact test, comparing the dichotomous primary outcome of failure due to infection within 24 months according to a dichotomous treatment allocation. However, in the statistical analysis

section provided, the primary outcome was analyzed using survival analysis (log-rank test), with the primary outcome assessment at a 'minimum of two years', rather than ***within*** two years.

It is reported that of those randomized, 23% in the intervention group and 20% in the control group did not have an evaluable primary outcome due to death, screen failure, or loss to follow-up. It is generally recommended that the methods for managing MOD are explicitly reported in the trial publication. Common approaches to this include using the last outcome carried forward (LOCF), sensitivity analyses and imputation.[5] Here, the 'ITT analysis' included only those with evaluable outcome data, rather than all participants randomized.

We have concerns about the inclusion of culture-negative cases as indicative of failure due to infection as the operating surgeons were not blinded to treatment allocation and were also responsible for outcome arbitration. Clinical details on the four culture-negative cases, or non-infection-related revisions, are not provided. We acknowledge that the diagnostic criteria do allow for culture-negative PJI, but in the light of potential ascertainment bias, we believe that culture-confirmed cases, or any revision surgery, should be considered a more robust objective outcome for PJI trials.

Such inconsistencies may have an impact on the analysis and interpretation of the authors' results. In light of these concerns, we have re-analyzed the data available, applying Fisher's exact test (GraphPad Prism version 8.0.1 for Windows, GraphPad Software, San Diego, California USA), presenting the results with relative risks (RR) and their respective 95% confidence intervals. A number of re-analyses have been performed which account for a dichotomous primary outcome. These include the 'ITT' participants presented, but also those restricted to a two-year follow-up (participants with infections after this timepoint were excluded) and those with culture-confirmed cases only. As a sensitivity analysis, we then applied the same approach to all patients who were randomized, assuming that they did not have an infection at the time they died or were lost to follow-up and their LOCF to a two-year timepoint. As above, these were also then restricted to participants with outcome data up to two years only and to those with culture-confirmed infections (Table I).

Using Fisher's exact test, a re-analysis of the 'ITT' and 'per-protocol' data provided in the publication shows a striking reduction in relative risk (0.44 [0.21 to 0.89] and 0.44 [0.21 to 0.94]; $p < 0.05$, respectively; Table I). ***However, when all randomized patients are included with last outcome carried forward and restricting it to culture-confirmed cases occurring within the two-year timeframe, the statistically significant differences observed between the groups are lost (RR 0.47 [0.21 to 1.05], p = 0.079).***

We hope the authors receive this assessment of their work in the spirit of constructive criticism. However, given that the study violated several accepted principles of trial design and reporting, we feel that practice guidelines should not be changed on the basis of these data. Although we urge caution when interpreting these data, we agree that further trials using this treatment approach for PJI managed by two-stage exchange procedures are warranted. Future trials should be explicit about the timing of endpoint assessment, be powered and analyzed appropriately, and have a clear plan for managing MOD. Ideally, participants should be blinded to their allocation with placebo. Outcome arbitration should be undertaken by experienced clinicians blinded to the treatment allocation or, if this is not possible, should limit the assessments to those patients with arthroplasty revision for any cause, or those with culture-confirmed infections only.

Table I. Re-analysis using dichotomous outcomes with data provided in the publication.[1]

Outcome	Oral antibiotics: Failure/not failure	Control: Failure/not failure	Relative risk (95% confidence interval)	Fisher's exact test, *p*-value
"ITT"	9/63	20/50	0.44 (0.21 to 0.89)	0.022
"Per-protocol analysis"	8/55	20/50	0.44 (0.21 to 0.94)	0.033
"ITT" outcomes restricted to 2-year outcomes	8/64	17/53	0.46 (0.21 to 0.99)	0.048
"ITT" outcomes restricted to culture-confirmed cases at 2 years	8/64	16/54	0.49 (0.22 to 1.06)	0.075
All patients randomized, assuming no infection and last observation carried forward restricted to 2-year outcomes and culture-confirmed infection	8/85	16/72	0.47 (0.21 to 1.05)	0.079

ITT, Intention to treat[1]

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Conflict of Interest: None