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BCC:

Subject: BMJ - Decision on Manuscript ID BMJ.2014.022885.R1

Body: 16-Jan-2015

Dear Dr. Paul:

Manuscript ID BMJ.2014.022885.R1 entitled "Trimethoprim-sulfamethoxazole vs. vancomycin for severe infections caused by methicillin-resistant Staphylococcus aureus: randomized controlled trial" which you submitted to BMJ,

Thank you for sending us this paper and giving us the chance to consider your work, which we enjoyed reading.

Decision: We are pleased to say that we would like to publish it in the BMJ as long you are willing and able to revise it as we suggest in the report below from the manuscript meeting: we are provisionally offering acceptance but will make the final decision when we see the revised version.

Deadline: Because we are trying to facilitate timely publication of manuscripts submitted to BMJ, your revised manuscript should be submitted by one month from todays date. If it is not possible for you to submit your revision by this date, we may have to consider your paper as a new submission.

https://mc.manuscriptcentral.com/bmj?URL_MASK=232b5d69b846407990724f19daf34ada

Yours sincerely

Georg Roeggla
groggla@bmj.com,

** THE REPORT FROM THE MANUSCRIPT COMMITTEE MEETING, REVIEWERS' REPORTS, AND THE BMJ'S GENERAL REQUIREMENTS FOR RESEARCH PAPERS ARE AVAILABLE AT THE END OF THIS LETTER.**

First, however, please read these four important points about sending your revised paper back to us:

1. Deadline: Your revised manuscript should be returned within one month.

2. Online and print publication: All original research in The BMJ is published with open access. The full text online version of your article, if accepted after revision, will be the indexed citable version (full details are athttp://resources.bmj.com/bmj/about-bmj/the-bmjs-publishing-model), while the print and iPad BMJ will carry an abridged version of your article, usually a few weeks afterwards. This abridged version of the article is essentially an evidence abstract called BMJ pico, which we would like you to write using a template and then email it to papersadmin@bmj.com (there are

more details below on how to write this using a template). Publication of research on bmj.com is definitive and is not simply interim "epublication ahead of print", so if you do not wish to abridge your article using BMJ pico, you will be able to opt for online only publication. Please let us know if you would prefer this option.
If/when your article is accepted we will invite you to submit a video abstract, lasting no longer than 4 minutes , and based on the information in your paper's BMJ pico evidence abstract. The content and focus of the video must relate directly to the study that has been accepted for publication by The BMJ, and should not stray beyond the data.

3. Open access publication fee: The BMJ is committed to keeping research articles Open Access (with Creative Commons licences and deposit of the full text content in PubMedCentral as well as fully Open Access on bmj.com). To support this we are now asking all authors to pay an Open Access fee of £3000 on acceptance of their paper. If we accept your article we will ask you to pay the Open Access publication fee; we do have a waiver policy for authors who cannot pay. Consideration of your paper is not related to whether you can or cannot pay the fee (the editors will be unaware of this), and you need do nothing now.

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Once the revised manuscript is prepared, you can upload it and submit it through your Author Center. When submitting your revised manuscript, you will be able to respond to the comments made by the reviewer(s) and Committee in the space provided. You can use this space to document any changes you make to the original manuscript and to explain your responses. In order to expedite the processing of the revised manuscript, please be as specific as possible in your response to the reviewer(s).

As well as submitting your revised manuscript, we also require a copy of the manuscript with changes highlighted. Please upload this as a supplemental file with file designation 'Revised Manuscript Marked copy'.

IMPORTANT: Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.

Report from The BMJ's manuscript committee meeting

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Manuscript meeting 15.01.2015

Elizabeth Loder (chair), Tim Cole (stats), Georg Roggla, Wim Weber, Jose

Merino, Anita Jain, Tiago Villanueva, Rebecca Burch, Emma Parish, Rubin Minhas

Decision: Provisional acceptance.

The committee was interested in the topic of your research. The following concerns were mentioned:

• Please provide detailed information why only 252 of evaluated 782 patients were included (additional to the information in figure 1).
• Isn't the non-inferiority margin of 15% quite wide for a composite outcome that includes death?
• What does your paper add to Markowitz N et al. TRIMETHOPRIM-SULFAMETHOXAZOLE COMPARED WITH VANCOMYCIN FOR THE TREATMENT OFSTAPHYLOCOCCUS-AUREUS INFECTION. ANNALS OF INTERNAL MEDICINE 1992; 117:390-398.
• The analysis could be simpler and easier to understand: You report a PP analysis as well as ITT, p-values in Table 1, a table of adverse events which is not cited (Table 3), and a multivariable logistic regression (Table 4) which is superfluous.
• The methods don't list the variables considered in the logistic regression, and there is a list of variables on page 11 that are excluded as they are correlated with others (?).
• Figure 1 indicates that 25+21 patients were excluded from the ITT analyses, yet the results in Table 2 include them. Not clear what Figure 1 means.
• Please discuss the high dose of TMP-SMZ being used.
• Please report primary and secondary outcomes in accordance to the trial registry.

First and foremost, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below. Please also respond to the additional comments by the committee.

IMPORTANT
When you revise and return your manuscript, please take note of all the following points about revising your article. Even if an item, such as a competing interests statement, was present and correct in the original draft of your paper, please check that it has not slipped out during revision.

a. In your response to the reviewers and committee please provide, point by point, your replies to the comments made by the reviewers and the editors, and please explain how you have dealt with them in the paper. It may not be possible to respond in detail to all these points in the paper itself, so please do so in the box provided

b. If your article is accepted it will then be edited, proofed, and - after your approval - published on bmj.com with open access. This open access Online First article will not be a pre-print. It will represent the full, citable, publication of that article. The citation will be year, volume, elocator (a unique identifier for that article): eg BMJ 2008;337:a145 — and this is what will appear immediately in Medline, PubMed, and other bibliographical indexes. We will give this citation in print and online, and you will need to use it when you cite your article.

c. Please write an abridged version of the article for the print and iPad BMJ using the appropriate BMJ pico template for your study's design. Please be reassured that it doesn't take long to complete this. When your BMJ pico is ready please email it to papersadmin@bmjgroup.com.The templates for you to download are at
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d. Please include these items in the revised manuscript to comply with BMJ style:

Title: this should include the study design eg "systematic review and meta-analysis”

Abstract
structured abstract including key summary statistics, as explained below (also see http://resources.bmj.com/bmj/authors/types-of-article/research)
for every clinical trial - and for any other registered study - the study registration number and name of register – in the last line of the structured abstract.

Introduction
this should cover no more than three paragraphs, focusing on the research question and your reasons for asking it now

Methods:
for an intervention study the manuscript should include enough information about the intervention(s) and comparator(s) (even if this was usual care) for reviewers and readers to understand fully what happened in the study. To enable readers to replicate your work or implement the interventions in their own practice please also provide (uploaded as one or more supplemental files, including video and audio files where appropriate) any relevant detailed descriptions and materials. Alternatively, please provide in the manuscript urls to openly accessible websites where these materials can be found
Results
please report statistical aspects of the study in line with the Statistical Analyses and Methods in the Published Literature (SAMPL) guidelines http://www.equator-network.org/reporting-guidelines/sampl/

summary statistics to clarify your message. Please include in the results section of your structured abstract (and, of course, in the article's results section) the following terms, as appropriate:

For a clinical trial:
• Absolute event rates among experimental and control groups
• RRR (relative risk reduction)
• NNT or NNH (number needed to treat or harm) and its 95% confidence interval (or, if the trial is of a public health intervention, number helped per 1000 or 100,000)

For a cohort study:
• Absolute event rates over time (eg 10 years) among exposed and non-exposed groups
• RRR (relative risk reduction)

For a case control study:
• OR (odds ratio) for strength of association between exposure and outcome

For a study of a diagnostic test:
• Sensitivity and specificity
• PPV and NPV (positive and negative predictive values)

For a systematic review and/or meta-analysis:
point estimates and confidence intervals for the main results

one or more references for the statistical package(s) used to analyse the data, eg RevMan for a systematic review. There is no need to provide a formal reference for a very widely used package that will be very familiar to general readers eg STATA, but please say in the text which version you used
for articles that include explicit statements of the quality of evidence and strength of recommendations, we prefer reporting using the GRADE system
Discussion
please write the discussion section of your paper in a structured way, to minimise the risk of careful explanation giving way to polemic.Please follow this structure:

statement of principal findings of the study
strengths and weaknesses of the study
strengths and weaknesses in relation to other studies, discussing important differences in results and what your study adds. Whenever possible please discuss your study in the light of relevant systematic reviews and meta-analyses (eg Cochrane reviews)
meaning of the study: possible explanations and implications for clinicians and policymakers and other researchers; how your study could promote better decisions
unanswered questions and future research

Footnotes and statements

What this paper adds/what is already known box (as described at http://resources.bmj.com/bmj/authors/types-of-article/research)

ID of ethics committee approval and name of the ethics committee/IRB; or a statement that approval was not required (see http://resources.bmj.com/bmj/authors/editorial-policies/guidelines) and a statement that participants gave informed consent before taking part

a statement that any identifiable patients have provided their signed consent to publication. Please submit, as a supplemental file, the signed BMJ patient consent form giving consent to publication in The BMJ of any information about identifiable individual patients. Publication of any personal information about a patient in The BMJ, for example in a case report or clinical photograph, will normally require the signed consent of the patient.

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signed patient consent form(s), if the article gives enough personal information about any patient(s): this sometimes occurs even in research papers - for example in a table giving demographic and clinical information about a small subgroup in a trial or observational study, or in quotes/tables in a qualitative study - (see http://resources.bmj.com/bmj/authors/editorial-policies/copy_of_patient-confidentiality)

a data sharing statement declaring what further information and data you are willing to make available, over and above the results reported in the paper. Suggested wording: "Data sharing: technical appendix, statistical code, and dataset [state whether any patient level data have been anonymised] are available at this repository or website OR from the corresponding author at ". If there are no such further data available, please use this wording: "Data sharing: no additional data available". For papers reporting the main results of trials of drugs or devices we require that the authors state, at a minimum, that the relevant anonymised patient level data are available on reasonable request from the authors
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a statement describing the role of the study sponsor(s), if any, in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication
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Patient centred research
for studies that are relevant to patients we expect authors to report in their articles the extent of their study's patient-centredness, as highlighted by these questions:
did you involve patients/service users/carers/lay people in the design of this study? Please state whether you did, and give details (Methods section)
was the development and/or selection of outcome measures informed by patients' priorities and experiences? Please give details (Methods section)
were patients/service users/carers/lay people involved in developing plans for participant recruitment and study conduct? If so, please specify how (Methods section)
have you planned to disseminate the results of the study to participants? If so how will this be done? (Describe in brief footnote)
are patients thanked in the contributorship statement or acknowledgements?
for articles reporting randomised controlled trials: did you assess the burden of the intervention on patients' quality of life and health? If so, what evaluation method did you use, and what did you find? (Methods and Results sections)

Reviewer: 1

Recommendation:

Comments:
This is an open-label RCT designed to evaluate whether TMP-SMZ is noninferior to vancomycin for severe MRSA infections. Overall, this study is well-done and is a valuable contribution to the literature; there is a clear unmet need for high quality data in treatment of serious MRSA infections.

* Originality - does the work add enough to what is already in the published literature? If so, what does it add? If not, please cite relevant references.

There is a need for additional data on therapeutic options for MRSA infections, especially bacteremia. There is only one prior RCT comparing TMP/SMZ to vancomycin (Markowitz et al, cited in paper). These same authors have published a small retrospective matched study to examine the role of TMP/SMX in MRSA bacteremia (Goldberg et al, J Antimicrob Chemother 2010), the promising results of which provide justification for this RCT.

* Importance of work to general readers - does this work matter to clinicians, patients, teachers, or policymakers? Is a general journal the right place for it?

Yes on both counts. S aureus bacteremia is common and knowledge of its treatment should be of interest to the general audience

* Scientific reliability
Research Question - clearly defined and appropriately answered?
Yes, the question of noninferiority of TMP-SMZ to vancomycin for invasive infections is clearly defined.

Overall design of study - adequate ?
Yes. The number of bacteremia patients is small but this is a notoriously difficult population to enroll, and their sample size of N=91 MRSA bacteremia is the same as the sole high-quality RCT previously reported (Fowler et al, dapto vs standard therapy, MRSA bacteremia N=89)

Participants studied - adequately described and their conditions defined? Yes

Methods - adequately described? Complies with relevant reporting standard - Eg CONSORT for randomised trials ? Ethical ?
Methods adequately described. Would like clarity around whether all bacteremic patients had documentation of clearance of bacteremia (see below) and information on concomitant antibiotic therapy. I see no ethical concerns.

Results - answer the research question? Credible? Well presented?
The research question is answered – TMP-SMZ did not meet noninferiority criteria.

Interpretation and conclusions - warranted by and sufficiently derived from/focused on the data? Message clear? Yes. Would be more circumspect length of stay data as TMP-SMZ did not have a clear advantage in LOS in this study or in the prior studies cited.

References - up to date and relevant? Any glaring omissions?
- Could add their own prior observational study as noted above (Goldberg et al, J Antimicrob Chemother 2010)
- Recent JAMA review examining treatment options, including TMP/SMZ, for MRSA bacteremia (Holland et al, JAMA 2014)

Abstract/summary/key messages/What this paper adds - reflect accurately what the paper says?
yes

Other specific comments:
-the authors are to be commended for the high proportion of screened patients that were enrolled. It does seem likely that sicker patients were more likely to be excluded, since N=165 were excluded as they were unable to provide consent. Could comment on this

Page 4, paragraph 3 – would reword the comment on resistance to vancomycin. Resistance to vanc remains very uncommon; there is healthy debate about whether vancomycin is the optimal agent for infections due to MRSA with vancomycin MIC at the higher end of the susceptible range (e.g. MIC=2), however resistance (MIC>=4) remains rare. The role of TMP/SMZ for vanc MIC=2 has been specifically explored in observational fashion by Campbell et al, Annals Pharmacother 2012

Page 5, paragraph 1 – several inaccuracies here - I don't think that sample size is correct. In Markowitz, there were 38 patients with MRSA bacteremia, of 65 total patients with bacteremia. Also, hospital stay was not significantly different in those with MRSA infection, and the duration results were compared for all patients with MRSA infection, not just bacteremia.

Methods: I am curious why patients with CNS infections were excluded – TMP/SMZ is likely inferior for MSSA meningitis but is a reasonable option for therapy in MRSA infections

Would acknowledge that vancomycin dosing was less aggressive than current guidelines recommend for severe infections (target trough 15-20, higher loading doses for seriously ill patients – Rybak et al 2009), and that the vancomycin dosing regimen in this trial may thus have underestimated the efficacy of vancomycin.

Concomitant antibiotics were allowed – what proportion of patients in each group received other antibiotics that may have been potentially effective?

Please clarify – you state "blood cultures were repeated daily for patients with persistent fever or other signs [of] infection" – were there patients with bacteremia who did not have clearance of bacteremia documented (ie no negative cultures)? If so, how was duration of bacteremia calculated for these patients?

What proportion of patients in the vancomycin arm had trough levels >=15?

Page 12, paragraph 1, line 25 – typo "TMP-TMZ"
Page 13 – paragraph 2 – in reference to Markowitz study – duration of hospital stay was not different overall between TMP/SMZ and vancomycin (24.6 vs 24.7 days) and even in the MRSA subgroup was not statistically different – would not use that study as evidence that TMP-SMZ use is associated with shorter hospital stay
Page 13, paragraph 3 – would update the list of treatment options to include the newer agents approved for ABSSSI – tedizolid, dalbavancin, oritavancin
Page 14, paragraph 1 – in the Fowler daptomycin study, there were 246 patients overall, 235 in mITT population. The comparison was between daptomycin and standard therapy (not just dapto vs vanc), so would be more accurate to say either "daptomycin was non-inferior to standard therapy for SAB" or "among the subgroup with MRSA bacteremia, daptomycin was noninferior to vancomycin"

Table 1 – do you know what proportion of patients with bacteremia had complicated vs uncomplicated bacteremia?

Table 2, footnote 2 – not immediately clear what "C" and "V" refer to here… I did eventually figure out "C" is for "cotrimoxazole", but this is not clear as presented

Table 2, footnote 5 – would not use the word "cotrimoxazole" as the term TMP-SMZ is otherwise used throughout the paper. Also, doubt that the acronym CRE will be familiar to the general reader – would spell out. And would consider doing the same for VISA and VRE. And again, "3C " and "5V" are confusing terms

Additional Questions:
Please enter your name: Thomas Holland

Job Title: Medical Instructor, Dept of Medicine, Division of Infectious Diseases

Institution: Duke University

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: Yes

Funds for a member of staff?: No

Fees for consulting?: Yes

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests (please see BMJ policy) please declare them here: I have NIH funding under UM1-AI104681 and have served as a consultant for The Medicines Company.

Reviewer: 2

Recommendation:

Comments:
MRSA has been declining in many countries but remains important. Cotrimoxazole is used for more specialist indications than formerly in view of adverse effects. This study includes a reasonable number of MRSA infections given the difficulty in recruitment. While risk ratio did not indicate a difference in efficacy of the two regimens the logistic regression showed co-trimoxazole to be associated with treatment failure. This is a useful outcome though not entirely surprising. Vancomycin resistance in MRSA is rare despite the assertion in the introduction.

Criteria for healthcare acquired infections were adapted from surveillance definitions but not defined. Treatment was given for 7 days even though most recommend a 14 day course of staphylococcal bacteremia (Lancet Infectious Diseases 2011; 11: 208–22). Please confirm the CONSORT criteria applied? In Table 1 p values are not useful, the one possible difference was given in text. Table 3 explain RIFLE.

Only 252 of 782 patients were included so that more information is needed on the excluded group to provide reassurance of no bias. The rules regarding informed consent were beyond the investigators' control but a large proportion refused consent – were these patients the more ill? Where differences are not statistically significant it is preferable not to say there was a difference. This applies where the difference was thought 'clinically significant'. This can be misleading as no safe inference can be drawn without statistical significance. Therefore that statement needs to be removed from the discussion and conclusion. The most that can be said is the results show a trend to a difference. The actual finding of not establishing non-inferiority and an Odds Ratio in favour of treatment failure are sufficient to suggest cotrimoxazole should not be used for severe MRSA infections.

Additional Questions:
Please enter your name: Peter Wilson

Job Title: Consultant Microbiologist

Institution: University College London Hospitals

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests (please see BMJ policy) please declare them here:

END

Date Sent: 16-Jan-2015