Review report

BSMMUJ-17.3 – 74383
High dose cotrimoxazole treatment in patients with severe COVID-19: A randomised controlled trial
Jesmin H *et al.* (dr.jesmin.humayra@gmail.com)

REVIEW COMMENTS		AUTHOR RESPONSE [Note: Please write the responses to each point here mentioning line number(s). You must change the manuscript as per your response.]
A. Technical review		
ROUND 1		
Reviewer's name: **Naeem Shahzad**		
ORCID: -		
Date assigned: **9-Jul-24**		
Date submitted: **10-Jul-24**		
Do you have any conflict of interest with the author/s? **No**		
Do you wish to be disclosed to the author? **Yes**		
Comments sent to author (Date: **7-Sep-24**)		Date: **17-Sep-24**
	Score	[Note: Please response if the score is below 6]
How would you rate the originality and depth of the manuscript?	8	-
Is the manuscript written in a scholarly manner?	8	-
Does the manuscript have the potential to make a valuable contribution to the world of knowledge?	9	-
Does the manuscript meet ethical standards?	8	-
1. The article is thoroughly researched, providing in-depth information on the topic.		
Reviewer's recommendation: **Accept Submission**		
Reviewer's name: **F**		
ORCID: -		
Date assigned: **20-Aug-24**		
Date submitted: **26-Aug-24**		
Do you have any conflict of interest with the author/s? **No**		
Do you wish to be disclosed to the author? **No**		
	Score	[Note: Please response if the score is below 6]
How would you rate the originality and depth of the manuscript?	10	-
Is the manuscript written in a scholarly manner?	8	-
Does the manuscript have the potential to make a valuable contribution to the world of knowledge?	7	-
Does the manuscript meet ethical standards?	9	-
a. Overview of the manuscripts This manuscript details a randomized controlled trial conducted in Bangladesh from May to September 2021, evaluating the efficacy of Cotrimoxazole added to standard therapy for hospitalized COVID-19 patients requiring oxygen. The study included 166 adults who were randomly assigned to receive either standard treatment alone or standard treatment with Cotrimoxazole for seven days. Key outcomes included duration of hospitalization, ICU admission, ventilation needs,		-

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changes in C-Reactive Protein levels, and in-hospital mortality. Notably, the Cotrimoxazole group had a significantly lower in-hospital mortality rate (11%) compared to the standard therapy group (29%). However, there were no significant differences in recovery time or other secondary outcomes. The authors acknowledge the discrepancy between their findings and previous studies that have supported Cotrimoxazole's use in other settings. Scholarly writing seems original. These types of studies are present in other country settings; however, the results are not similar. This opens the need to further research to validate these results and understand the observed differences. Additionally, the potential for antimicrobial resistance in Bangladeshi patients could be influencing these outcomes. Testing for resistance before administering Cotrimoxazole might provide insights into these differences. Overall, while initial findings were promising, this study suggests that Cotrimoxazole may not offer substantial benefits over standard treatment for COVID-19 patients, demanding further investigation.	
b. Major points: 1. The Study does not mention whether any blinding was implemented. It seems important to clarify whether participants, caregivers, or outcome assessors were blinded to the treatment allocation. If blinding wasn't feasible, please acknowledge this limitation.	Blinding was implemented. It was a double blind placebo controlled trial. A new paragraph under the heading masking has been added in the methodology section to clarify the blinding process further. (lines 132 to 138)
2. The study lists components of standard therapy but it lacks specifics. Such as, what specific antibiotics were used, and providing more details about the standard therapy protocol or proper referencing of the protocol is crucial for result interpretation.	Standard therapy includes antibiotics and other supportive measures as per institution protocol. It has been mentioned in the methodology section. (lines 124 to 131)
3. The discussion initially states no statistically significant decrease in mortality, but later mentions the Cotrimoxazole group having a lower mortality rate (11% vs. 29%, P=0.020). This needs clarification. Was this difference statistically significant or not?	These findings are not from our study. It is the study finding of another researcher. (Reference 10). (lines 205-206) However, the sentence has revised.
4. The study mentions ethical approval and informed consent. However, it would be helpful to specify if any provisions were made for patients who were unable to provide informed consent due to their condition.	It was not needed as no patient in our study was unable to consent at the time of enrolment. (line 113)
5. There are conflicts between the findings of this study and previous research, which has generally supported the use of Cotrimoxazole alongside standard treatment in other countries. These conflicting results suggest a need for further investigation to better understand and justify the observed outcomes. Additionally, the possibility of antimicrobial resistance in Bangladeshi patients could be a contributing factor. Testing for resistance before administering Cotrimoxazole might provide clarity and help explain the differences in effectiveness observed in this study. If possible, please include this data or discussion.	The plausible explanation could be high dose cotrimoxazole does not influence the outcome of severe COVID which has been included in the discussion. (lines 212 -215)
6. Please recheck the referencing. The errors in the references include incorrect formatting of journal names,	Rechecked and revised as advised. (line 254 onwards)

REVIEW COMMENTS	AUTHOR RESPONSE [Note: Please write the responses to each point here mentioning line number(s). You must change the manuscript as per your response.]
inconsistent DOI presentation, and discrepancies in author lists and article titles.	
c. Minor points: 1. Minor grammatical and inconsistencies throughout the manuscript could be improved. For example, "Co-trimoxazole" is sometimes written as "Cotrim" without clear introduction or consistent use.	Cotrim has been replaced throughout the manuscript with co-trimoxazole. (Throughout the text as applicable)
2. While the study found no significant benefits for Cotrimoxazole, stating it "may establish fundamental evidence of the lack of efficacy" seems too strong. Hence, consider softening the language.	We have revised our conclusive remark. (lines 226-229)
Reviewer's recommendation: **Revisions Required**	
Reviewer's name: **G**	
ORCID: -	
Date assigned: **27-Aug-24**	
Date submitted: **9-Sep-24**	
Do you have any conflict of interest with the author/s? **No**	
Do you wish to be disclosed to the author? **No**	
1. Please provide an Overview of the manuscripts within 100 words. This should be a distilled summary of the work and your overall impression. The study was done on Covid 19 patients to see the efficacy of high-dose cotrimoxazole brand name Cotrim (perhaps it was Cotrim DS) in terms of reduced hospitalisation and mortality reduction. The study did not reveal any benefit. It was a randomised controlled trial. However, the process of randomisation is not clear. The idea of including only one private medical college (AKMC) and nominating the study as a multi-centre study is not clear.	High dose co-trimoxazole therapy may improve prognosis in severe COVID-19 patients due to its antibacterial, immunomodulatory, and anti-inflammatory properties. But we conducted a two-centre randomised placebo-controlled trial with two parallel groups, where 166 participants were enrolled, with 93 receiving standard therapy and 96 receiving co-trimoxazole. The results showed that high dose cotrimoxazole did not significantly shorten in-hospital stay or reduce in-hospital mortality or mortality at day 28 in adult severe COVID-19 patients.
To claim the study as "meticulous" in the last paragraph of the discussion does not sound good.	Revised accordingly.
The study was done on a calculated sample size. So, claiming the small sample size as a Limitation is not also correct.	Removed the word. Revised accordingly.
Is it a preliminary report? (Please see 3rd paragraph in the discussion section). If so, publish as such.	Removed as advised. (line 208)
2. Is the title appropriate? No *It is better to add "High-dose" before Co-trimoxazole	High dose Co-trimoxazole has been mentioned and title has been revised.
3. Does the abstract provide a complete and accurate description of the content of the article?* No It is better to write either High-dose cotrimoxazole or Cotrim DS throughout the text including the abstract	High dose Co-trimoxazole has been mentioned throughout the text.
4. Are the study objective(s) clearly stated and logical?* **No** Objective(s) should have been clearly stated in a separate paragraph	It has been stated in the last line of introduction. (Lines 100 & 101)
5. Is the rationale/justification for conducting the study clear?* **No**	The rationale is mentioned in the introduction. We intended to see the effect of high dose Cotrimoxazole in severe COVID-19 infections (lines 96 to 101).

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Rationality has not been clearly stated. No knowledge gap in the issue of research has been identified	
6. Are the methods described in sufficient detail so that the study could be reproduced?* **No** It is not a multi-centre study in the true sense. What is the idea behind including only Anwarkhan Medical College with BSMMU? The Process of randomisation is not clear. It is to clear whether the intervention group received antibiotics other than Cotrim as a part of standard therapy. Did all the patients receive the same brand of cotrimoxazole and what was the source of the drug?	We have changed that it is a two-centre study. We included AKMMCH because of the researchers' convenience and accessibility to COVID units. The process of randomisation has been further detailed in the revised manuscript as well as a paragraph on how blinding was implemented has been added in the methodology section. The intervention group received other antibiotics in addition to high dose cotrimoxazole. Yes, the Patient received the same brand and active drug, and the placebo was procured from same pharmaceutical company. (Lines 132- 138).
7. Is the study design robust and appropriate to the stated objective(s)? **No** Stated in 6a	Given the response to 6a.
8. Are statistics used appropriately and described fully? **Yes**	NA
9. Are the table(s) and figure(s) clear and appropriate to address the objective(s) or research question(s)? **No** SpO2, requirement of oxygen support, duration of hospital and ICU stay in Table 1 should not be included in Table 1 as baseline characteristics. Rather chest findings and image findings in both groups should have been included. Plasma sulfa methoxazole concentration (as described in the Study population) should be in the result section.	Table 1 and Table 2 have been revised.
10. Is the discussion section critical and comprehensive about the main message of the manuscript? **No** The discussion should have been in more detail. Why high dose of cotrimoxazole was used? The message in 3rd paragraph should be in clear language. Moreover, the discussion should have been objective-oriented.	Revised the discussion section.
11. Are the conclusions drawn supported by the results/ data? **Yes** .	NA
12. Are the references appropriate in number and up-to-date?* **Yes** All the references should follow the Journal's instructions	References have been edited according to the journals instructions.
Reviewer's recommendation: **Revisions Required**	
ROUND 1	
Executive Editor's name: **M Mostafa Zaman**	
ORCID: **0000-0002-1736-1342**	
Comments sent to author (Date: **9-Jul-24**)	Date: **17-Sep-24**
1. Abstract: Do not use a separate heading for the objective. Why is a two-centre study labelled as multicentre study?	It has been edited as two centers study**.** (line 105)
2. Highlights: The first bullet has appeared suddenly without contextualization. Kindly change or drop it.	Dropped the first bullet.
3. Introduction: Objective should be a part of the last paragraph.	Objective is mentioned in the last line of introduction. (line 101)

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4. Methods: The randomization procedure is not clear. Have you pooled all subjects (in two hospitals) to randomize, or randomization was done separately for two hospitals? Your standard of care included antibiotics; did you use that antibiotic and cotrimoxazole (two antibiotics) for the intervention group? Ethical concern: should be described here. There might be some ethical issues in-built due to the pandemic and study design itself. Sample size: Make it clear if 94 subjects in each group was required. Funding: Provide Memo number and date. Ethics approval: provide date of the Memo.	Randomisation and blinding have been further clarified in the methodology section. Yes, 94 participants in each group were required according to sample size calculation. Memo no. and date are not available. Date of Ethics approval has been added. (line 247)
5. Tables: Table 1: provide results up to one decimal points. There is a mixture of number (%) and mean (SD). Group them or indicate them in the table. Our style is to use parenthesis, not +/-.	We have revised as advised.
Table 2: Acronyms should be avoided or clarified in the footnote. Provide percentages after the numbers.	We have revised accordingly.
Table 3: It is not well organized. Data presented look like two different tables. Moreover, this table should be presented for two groups (intervention and standard) throughout the table. Addition of the three grades have made the readability difficult.	We have revised it.
Executive Editor's decision: **Revisions Required**	

B. Editorial decision	Date: **19-Sep-24**
Final decision: **Accepted subject to editorial clarifications**	

Editorial Clarification	
Executive Editor's name: **M Mostafa Zaman**	
ORCID: **0000-0002-1736-1342**	
Comments sent to author (Date: **21-Sep-24**)	Date: **23-Sep-24**
1. You submitted the revised Table 3 as per the Executive Editor's suggestions. However, you have not revised the texts in the Methods, Results and Discussion sections. This is essential because the decline in CRO at 28 days is statistically significant in the Intervention group. I have revised it on your behalf, but I am not sure whether these are appropriately tuned. Kindly double-check it.	Following lines can be added in from line 9 in page 4, in result, secondary outcome. In both groups, CRP level reduced significantly at 48 hours compared to baseline (P<0.001). There was no significant difference between groups at baseline and at 48 hours. However, there was a statistically significant mean decline (95% confidence interval) in the intervention group 23.6 (0.5 to 46.7) (P=0.007), while the decline in the standard group was not statistically significant, 7.2 (-21.8 to 7.4) (Table 3).

2. I have added a figure for the symptoms, which you have not provided despite the editor's suggestion. Please check if it is appropriately framed.	We appreciate your help. We also apologize for missing that.
3. You have not addressed another point of the Editor on the use of antibiotics (other than cotrimoxazole) as a part of the "Standard" treatment in the two groups. This might have attenuated the effect of cotrimoxazole. Please one or two lines on this in the Discussion section.	Following lines can be added in result section in at the end of baseline characteristics: Patients of both groups received different antibiotics. 20.4% of intervention group received Meropenem along with high dose Co-trimoxazole while it was 18% in standard group. In both groups, 17 patients received Moxifloxacin. 32.3% patient of intervention arm were given Ceftriaxone whereas 28.8% in the standard arm received the same antibiotic. The use of different antibiotics among groups was not significantly different (P=0.712).
4. The department of the lead author is missing.	The lead author is from the Department of Medicine.
5. Please ensure references 5 and 6 are correct and appropriate.	Reference 5: Correction to citation: Siddiqui KN, Das MK, Alapan B. Cotrimoxazole in the domiciliary management of patients with severe COVID-19: A case series. J. Indian Med. Assoc. 2020 Oct; 118:34-8. URL:https://www.researchgate.net/publication/345360686_Cotrimoxazole_in_the_domiciliary_management_of_patients_with_severe_COVID-19_A_case_series. Reference 6 is correct.
Comments sent to author **(**Date: **24-Sep-24)**	Date: **24-Sep-24**
1. Please provide the full meaning of ARDS.	Full meaning of ARDS is 'Acute respiratory distress syndrome (ARDS)'.
2. Between two groups Kruskall-Wallis test has been used to compare qualitative and quantitative data! This is incorrect. You should use the Mann-Whitney U test for quantitative and the Chi-square test for categorical variables. This has an issue with the Statistical Analysis section and Table 2. I took care of the statistical analysis sub-section. Please provide me with the corrected P values for Table 2 for all rows without touching the texts.	Table 02 Row 1: requirement of intensive care support, Pvalue: 0.52 Row 2: duration of hospital stays, Pvalue: 0.86 Row 3: duration of intensive care unit, Pvalue: 0.47 Row 4: discharge, Pvalue: 0.74 Row 5: hospitalised requiring no oxygen, Pvalue: 0.51 Row 6: Hospitalised with oxygen, Pvalue: 0.62 Row 7: Deaths, Pvalue: 0.56
3. You forgot to add a sentence to the Discussion section about the possible effect of antibiotics as part of the Standard Treatment in both groups. I have added it. Please check whether it is correct.	Thanks for your contribution. We have checked it. It's ok.
4. Reference 5 texts were given from Research Gate, which was incomplete and inappropriate. We obtained it from its primary source, IJMA. Check whether it is correct.	It is correct.