PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Study protocol for ADAPT-TDM: A beta-lactam antibiotic Dose AdaPtation feasibility randomised controlled Trial utilising Therapeutic Drug Monitoring
AUTHORS	Pai Mangalore, Rekha; Chai, Ming; Pope, Jeffrey; Lee, Sue; Padiglione, Alexander; Diehl, Arne; Roberts, Llyod; Sim, Kirsty; Rawson-Harris, Philip; Wicha, Sebastian; Schneider, Hans; Peel, T.; Jenney, Adam; Ayton, Darshini; Peleg, Anton; Udy, Andrew

VERSION 1 – REVIEW

REVIEWER	Sadleir, Paul H M The University of Western Australia
REVIEW RETURNED	03-Feb-2024

GENERAL COMMENTS	Novel and of interest. Hope phase 3 trial includes clinically important outcomes and cost-analysis.

REVIEWER	Lim, Audrey Huili Ministry of Health
REVIEW RETURNED	06-Feb-2024

GENERAL COMMENTS	This is a well designed unblinded randomised controlled trial. Please clarify if culture & sensitivity will be carried out beforehand and elaborate the planned statistical analysis. Also, please define if the outcomes related / unrelated to sepsis are taken into consideration.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Paul H M Sadleir, The University of Western Australia

Comments to the Author:
Novel and of interest. Hope phase 3 trial includes clinically important outcomes and cost-analysis.

Author response: Thank you. We will incorporate these recommendations in our future trial.

Reviewer: 2
Dr. Audrey Huili Lim, Ministry of Health

Comments to the Author:

This is a well designed unblinded randomised controlled trial. Please clarify if culture & sensitivity will be carried out beforehand and elaborate the planned statistical analysis. Also, please define if the outcomes related / unrelated to sepsis are taken into consideration.

Author response: Thank you. I will respond to each of your points below

Reviewer 2: Please clarify if culture & sensitivity will be carried out beforehand

Author response: Given this is a study assessing early recruitment and randomisation, we will not have results of culture and sensitivity at first TDM. However, should this become available while the patient is enrolled we will aim to target our concentration threshold to the ECOFF of the infecting pathogen. We have added this under the dose adaptation paragraph. Our laboratory does not routinely release MIC data as these are performed on a semi-automated analyser. Our results are released as susceptible, susceptible increased exposure and resistant (S or IE or R) in line with EUCAST recommendations.

Reviewer 2: elaborate the planned statistical analysis

Author response: The statistical analysis is further elaborated in Table 3 which outlines all outcomes and how they will be measured. The table, in conjunction with the text, provides detail on the planned analysis. In addition, our statistician, Dr SJ Lee, has re-reviewed this section and recommends no further changes at this stage to the statistical analysis plan.

Reviewer 2: please define if the outcomes related / unrelated to sepsis are taken into consideration.

Author response: We acknowledge that the ultimate survival is not dependent on antibiotics alone in patients with sepsis. Given the primary outcomes of this study are to assess the feasibility and fidelity of TDM-guided dosing, we will only be assessing all-cause mortality. The small sample size of this pilot study limits the assessment of clinical outcomes and attributable mortality.