PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	An open-label, single-centre, cluster-randomized, controlled trial to Evaluate the Potential Impact of Computerized antimicrobial stewardship (EPIC) on the antimicrobial use after cardiovascular surgeries: EPIC trial study original protocol
AUTHORS	Yuan, Xin; Chen, Kai; Zhao, Wei; Hu, Shuang; Yu, Fei; Diao, Xiaolin; Chen, Xingwei; Hu, Shengshou

VERSION 1 – REVIEW

REVIEWER	Daniele Roberto Giacobbe Department of Health Sciences, University of Genoa, Italy
REVIEW RETURNED	17-May-2020

GENERAL COMMENTS	The authors present the protocol for a an open-label, single-centre, cluster-randomized, controlled trial (EPIC). The primary efficacy endpoint is days of therapy (DOT)/admission after cardiovascular surgery, with the intention of evaluating the efficacy of a computerized decision support system (CDSS) in reducing postoperative antimicrobial consumption according to the principles of antimicrobial stewardship. Overall, the methods of the study are well detailed. I have a few minor comments. Minor comments 1) In my opinion, an important lack is that of the description of the involved teams and how the authors will address possible explorable/unexplorable differences that may impact results. Indeed, although teams dealing with peripheral vessel surgeries and with structural heart disease interventions are correctly excluded, also among the remaining teams possible differences (or imbalances in their distributions after randomization) may influence results. 2) In my opinion, infections (e.g., SSI, BSI, pneumonia) are not only a secondary endpoint, but should also be viewed as possible confounding factors for the primary endpoint. Indeed, should their incidence be higher in some teams, this may not always represent the consequence of antimicrobial misuse, but also an antibiotic-independent increased risk of developing infection. In turn, a higher incidence of infections may increase antibiotic use (in this case adequate). In addition, this also supports the previous observation that between-team differences (here in terms of type of patients operated on and their likelihood to develop postoperative infection) may confound results. 3) Why DOT/admission as the primary outcome and not DOT/patient-days (reported as a secondary outcome)? The latter should better reflect inappropriate use since it is unaffected by possible differences in length of postoperative stay between teams.

	4) In my opinion, an important aspect would be not only to evaluate the user compliance with the CDSS, but also the performance of the CDSS. For example, according to figure 2 it seems the system detection of presence/persistence of infection is based on few very simple parameters. Diagnosis of infection, including postoperative infections, may be a very complex process, as testified by several studies reporting a favorable effect of infectious diseases specialists (IDs) consultations on relevant patients' outcomes. 5) In this regard, will be IDs consultations provided? Will them be equally distributed across teams? This is another factor that may confound results

REVIEWER	Mayar AL MOHAJER Baylor College of Medicine, Houston, TX
REVIEW RETURNED	27-May-2020

GENERAL COMMENTS	The study aims to provide important information on the role of computerized electronic alerts and decision supports on AS. The protocol is very well-written and the objectives are clear. Well-defined methods.

REVIEWER	Michael Yarrington Duke University Health System
REVIEW RETURNED	08-Jun-2020

GENERAL COMMENTS	Overall: The intent of the study is clear, and the reasoning is sound. However, I think the message is presented semi-confusingly. There should be more clarification of exactly how the CDSS analyzes EHR information and then communicates the messages to the physicians. In addition, an extensive review for grammar and wording is needed to effectively relay the message. Also, thought should be given to the extra limitations that regular peer-comparison during the study period will have on external validity and sustainability after the trial ends. CONCERNS: Page 6, line 7: 'Global' is misspelled. Page 6, line 11: 'the America' is grammatically incorrect. Page 6, line 50: 'labor intensive nature have' is grammatically incorrect. Multiple further grammatical errors occur that limit readability. This manuscript should be revised specifically for grammar and readability. Page 8, line 53 – Certain surgical teams are excluded because of antimicrobial use habits, yet these are not described. This severely limits interpretability or any external validity, and should consider being included especially because the authors chose cardiovascular surgeries due to the nature of surgical site infections that may be applied to other types of surgeries. Page 9, line 18 – Why were ICU stay > 48 hours excluded? Page 10, line 51-60 – How does the system detect 'signs of infection'? This seems like a remarkably advanced statement without explanation (i.e. how does the system automatically identify infection based on chest x-ray?) Page 12, Line 28 – Teams are compared with other teams and provided feedback with this information. This may also influence antimicrobial use outcomes and behavior patterns that will limit external validity outside of this trial design.

	Table 1: Why DOT/100PD when DOT/1000 PD is typically used? Table 1: Postoperative microbial resistance indicators – in the definition column, there is no definition for incidental cultures with MDROs, only the ICD10 code for C diff colitis is present. Overall table is a bit haphazard and confusing as to what gets definitions and what does not. Figure 2: I enjoyed this figure.

VERSION 1 – AUTHOR RESPONSE

Dear Prof. Giacobbe,

Thank you very much for your valuable comments.

We have revised our manuscript in accordance with your comments. Our responses to each of your comments are given point-by-point below:

The authors present the protocol for an open-label, single-centre, cluster-randomized, controlled trial (EPIC). The primary efficacy endpoint is days of therapy (DOT)/admission after cardiovascular surgery, with the intention of evaluating the efficacy of a computerized decision support system (CDSS) in reducing postoperative antimicrobial consumption according to the principles of antimicrobial stewardship. Overall, the methods of the study are well detailed. I have a few minor comments.

Minor comments
1) In my opinion, an important lack is that of the description of the involved teams and how the authors will address possible explorable/unexplorable differences that may impact results. Indeed, although teams dealing with peripheral vessel surgeries and with structural heart disease interventions are correctly excluded, also among the remaining teams possible differences (or imbalances in their distributions after randomization) may influence results.
Response: Thanks for your suggestion. In Fuwai hospital, certain types of cardiovascular surgeries are restricted to a certain department. For instance, congenital heart disease surgeries are only performed in the Department of Pediatric Cardiac Surgery Centre. In this trial, all teams involved belonged to the Department of Adult Cardiac Surgery Centre and Department of Vascular Surgery Centre. Patients in the teams of the two centers are all at the age≥18 years and received open-chest cardiovascular surgeries. As the surgeries performed by the team are similar, patients recruited in this trial will have similar baseline characteristics. Besides, the team leaders in Fuwai hospital are all trained for more than 10 years, and all surgeons are trained with a similar standard training program. The seniority of the surgeons in the surgical team of Fuwai hospital is similar. Therefore, the characteristics of the patients and the surgeons would be similar in the 18 teams. Even so, as you mentioned, there will be possible explorable/unexplorable differences that may impact results. We agreed with your opinion. We will use the inverse probability of treatment weighting (IPTW) method to balance the possible imbalances in patients' baseline characteristics. We added the description of IPTW into the revised manuscript (Page 14, line 355-357).

2) In my opinion, infections (e.g., SSI, BSI, pneumonia) are not only a secondary endpoint, but should also be viewed as possible confounding factors for the primary endpoint. Indeed, should their incidence be higher in some teams, this may not always represent the consequence of antimicrobial misuse, but also an antibiotic-independent increased risk of developing infection. In turn, a higher incidence of infections may increase antibiotic use (in this case adequate). In addition, this also

supports the previous observation that between-team differences (here in terms of type of patients operated on and their likelihood to develop postoperative infection) may confound results.
Response: Thanks for your comments. We agreed that infections were not only a secondary endpoint but also confounding factors for the primary endpoint. The primary objective of our study is to evaluate the impact of CDSS on antibiotic use. We assumed that the CDSS intervention will reduce antimicrobial use and not increase the rate of infection. As previously mentioned, the characteristics of the patients and the surgeons will be similar in both arms because the trial was randomized designed. Theoretically, the rate of infection ought to be similar in the two arms. If the difference of the infection rate exists, an adjustment will be performed with postoperative infection taking as a confounding factor.

3) Why DOT/admission as the primary outcome and not DOT/patient-days (reported as a secondary outcome)? The latter should better reflect inappropriate use since it is unaffected by possible differences in length of postoperative stay between teams.
Response: Thanks for your suggestion. In the revised version, we took DOT/patient-days as a primary outcome as well.

4) In my opinion, an important aspect would be not only to evaluate the user compliance with the CDSS, but also the performance of the CDSS. For example, according to figure 2 it seems the system detection of presence/persistence of infection is based on few very simple parameters. Diagnosis of infection, including postoperative infections, may be a very complex process, as testified by several studies reporting a favorable effect of infectious diseases specialists (IDs) consultations on relevant patients' outcomes.
Response: Thanks for your comments. The CDSS was designed primarily for increasing surgeon compliance to the guidelines and the regulations for antimicrobial stewardship (AMS), instead of designed for automatic diagnosis of infection. Thus, the basic function of the CDSS system is detection, warning alarm, and recording when AMS rules are violated. As you mentioned, the diagnosis of infection may be a very complex process, and the current CDSS could not fulfill this function. But this system does have functions to detect signs of infection automatically, such as routine blood tests, chest X-rays, and bacterial culture. The issue of IDs will be replied in next.

5) In this regard, will be IDs consultations provided? Will them be equally distributed across teams? This is another factor that may confound results
Response: Thank you very much for your questions. The favorable effect of infectious disease specialists (IDs) should be considered carefully. In this trial, infectious disease and emergency operations were excluded as we stated on Page 9, line 200-201. The IDs consultation would be provided when needed. As the baseline characteristics of the patients and the surgeons are supposed to be similar, and each surgical team has equal access to IDs consultation, the IDs consultations would be similar between arms. We will collect the data of IDs consultations of each team during the trial. Certain statistical methods to balance the confounding factors will be performed if there is an unbalance in the IDs consultations between the two arms.

Best,

Shengshou.

Dear Prof. MOHAJER,

Thank you very much for your kind comments.

Best,

Shengshou.

Dear Prof. Yarrington,

Thank you very much for your valuable comments.

We have revised our manuscript in accordance with your comments. Our responses to each of your comments are given point-by-point below:

Overall:
The intent of the study is clear, and the reasoning is sound. However, I think the message is presented semi-confusingly. There should be more clarification of exactly how the CDSS analyzes EHR information and then communicates the messages to the physicians. In addition, an extensive review for grammar and wording is needed to effectively relay the message. Also, thought should be given to the extra limitations that regular peer-comparison during the study period will have on external validity and sustainability after the trial ends.

CONCERNS:
Page 6, line 7: 'Global' is misspelled.
Page 6, line 11: 'the America' is grammatically incorrect.
Page 6, line 50: 'labor intensive nature have' is grammatically incorrect.
Multiple further grammatical errors occur that limit readability. This manuscript should be revised specifically for grammar and readability.
Response: Thanks for your reminder. We are so sorry for the spelling and grammar mistakes. We invited our colleague with high language proficiency for revision.

Page 8, line 53 – Certain surgical teams are excluded because of antimicrobial use habits, yet these are not described. This severely limits interpretability or any external validity and should consider being included especially because the authors chose cardiovascular surgeries due to the nature of surgical site infections that may be applied to other types of surgeries.
Response: We appreciated your comments. We excluded four surgical teams which perform operations on peripheral vessels (mainly stenting) or structural heart disease. These teams performed operations without opening the chest, so prophylaxis antimicrobial is not routinely applied. The protocols of antimicrobial stewardship for these surgeries are largely different from traditional open-chest operations. Therefore, we suppose that our exclusion criteria might not ruin the generalization of the current study.

Page 9, line 18 – Why were ICU stay > 48 hours excluded?
Response: Thanks for your question. In usual clinical practice, most antimicrobial use is for prophylaxis purpose. According to the guideline, the prophylaxis antimicrobial use is restricted within 48 hours. The patients in the ICU are particularly at risk of acquiring antimicrobial resistance infections due to the intensity of the treatment, use of invasive devices, increased risk of transmission and exposure to antibiotics. Thus, the protocol of antimicrobial stewardship in ICU is different. (Jan etc. Intensive Care Med (2018) 44:189–196 and Jean-François etc. Intensive Care Med (2019) 45:172–189) Therefore, we excluded ICU stay ＞48 hours in this trial.

Page 10, line 51-60 – How does the system detect 'signs of infection'? This seems like a remarkably advanced statement without explanation (i.e. how does the system automatically identify infection based on chest x-ray?)
Response: Fuwai has deployed an in-house electronic medical record (EMR) system and a computerized physician order entry (CPOE) system since 2009. This part is in the original version of the manuscript (Page 8, line 171-174). All information was collected into the server of the Information

Centre of Fuwai hospital. The CDSS was set up based on the EMR and CPOE system on the server of the Information Centre. The EMR system collected not only the digital medical records written by the surgeons, but also the report of laboratory tests and image diagnosis. The EMR system record all the detailed information on medications. The CDSS was able to access all the information from the EMR and CPOE system in real-time, and extract all the data from the server of the Information Centre, including the antimicrobial use from the CPOE system, and the body temperature, white blood cell count, the report of chest x-ray from the EMR system. Our team wrote a set of logic rules that collects and estimate the data in the CDSS. If the available data does not indicate infection or violations of the antimicrobial stewardship (AMS) rules of antimicrobial use are detected, a reminder will be triggered and appear on the computer screen of the CPOE system. In the revised manuscript, more detailed descriptions about the system have been added in the method section (Page 10, line 233-235).

Page 12, Line 28 – Teams are compared with other teams and provided feedback with this information. This may also influence antimicrobial use outcomes and behavior patterns that will limit external validity outside of this trial design.
Response: Thank you very much for your comments. The feedback is a part of the fundamental functions of this computerized AMS program. Feedback will be available in the intervention arm, but not in the control arm. As you mentioned, the influence of the feedback system and the behavior patterns might still be ambiguous. We stated the limitation in the revised version (Page 18, line 452-455). We are going to analyze the influence of the feedback system and the behavior patterns of the surgeons in further studies.

Table 1: Why DOT/100PD when DOT/1000 PD is typically used?
Response: Thanks for your reminder. We felt sorry for this typo error. We corrected the information in the revised manuscript.

Table 1: Postoperative microbial resistance indicators – in the definition column, there is no definition for incidental cultures with MDROs, only the ICD10 code for C diff colitis is present
Overall table is a bit haphazard and confusing as to what gets definitions and what does not.
Response: Thank you very much for your suggestion. The definition of incidental cultures with MDROs was controversial, so we take the most accepted definition as "resistant to three or more antimicrobial classes". We added it to Table S1. As there were excessive contents in original Table 1, we refined Table 1 by moving the "definitions" to supplement material.

Figure 2: I enjoyed this figure.
Response: Thank you.

VERSION 2 – REVIEW

REVIEWER	Daniele Roberto Giacobbe Ospedale Policlinico San Martino - IRCCS, Genoa, Italy
REVIEW RETURNED	28-Aug-2020

GENERAL COMMENTS	Thank you for your kind responses to comments.