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Open-label, single-centre, cluster-randomised controlled trial to Evaluate the Potential Impact of Computerisedantimicrobial stewardship (EPIC) on the antimicrobial use after cardiovascular surgeries: EPIC trial study original protocol

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ABSTRACT

Introduction Inappropriate antimicrobial use increases the prevalence of antimicrobial-resistant bacteria. Surgeons are reluctant to implement recommendations of guidelines in clinical practice. Antimicrobial stewardship (AMS) is effective in antimicrobial management, but it remains labour intensive. The computerised decision support system (CDSS) has been identified as an effective way to enable key elements of AMS in clinical settings. However, insufficient evidence is available to evaluate the efficacy of computerised AMS in surgical settings.

Methods and analysis The Evaluate of the Potential Impact of Computerised AMS trial is an open-label, single-centre, two-arm, cluster-randomised, controlled trial, which aims to determine whether a multicomponent CDSS intervention reduces overall antimicrobial use after cardiovascular surgeries compared with usual clinical care in a specialty hospital with a big volume of cardiovascular surgeries. Eighteen cardiovascular surgical teams will be randomised 1:1 to either the intervention or the control arm. The intervention will consist of (1) re-evaluation alerts and decision support for the duration of antimicrobial treatment decision, (2) re-evaluation alerts and decision support for the choice of antimicrobial, (3) quality control audit and feedback. The primary outcome will be the overall systemic antimicrobial use measured in days of therapy (DOT) per admission and DOT per 1000 patient-days over the whole intervention period (6 months). Secondary outcomes include a series of indices to evaluate antimicrobial use, microbial resistance, perioperative infection outcomes, patient safety, resource consumption, and user compliance and satisfaction.

Ethics and dissemination The Ethics Committee in Fuwai Hospital approved this study (2020-1329). The results of the trial will be submitted for publication in a peer-reviewed journal.

Trial registration number NCT04328090.

Strengths and limitations of this study

► This adequately powered, cluster-randomised controlled trial addresses many inadequacies in designs of the previous studies.
► Different from previous studies in terms of the scope, setting and timing, the Evaluate of the Potential Impact of Computerised antimicrobial trial is among the first to assess the impact of computerised decision support system tools on antimicrobial use in hospital settings.
► To the best of our knowledge, this trial will be one of the first trials carried out in surgery settings.
► This trial is a single centre study which may increase type II error.

INTRODUCTION

Antimicrobial drug resistance among common bacterial pathogens has become a global health crisis.[1–3] It is reported that more than two million illnesses and 23 000 deaths are caused by antimicrobial-resistant bacteria in the USA in 2017.[4] This crisis is even more serious in low-income to middle-income countries.[5]

Inappropriate antimicrobial use after surgeries increases the prevalence of antimicrobial-resistant bacteria and subsequently unnecessary risk of adverse drug events to patients as well as loads heavy economic burden on the healthcare system.[6 7] Despite many published guidelines of antimicrobial use and decades of efforts to change prescribing patterns, a survey revealed that the practice of antimicrobial use varies substantially among surgeons.[8] Furthermore,

studies have shown that surgeons are reluctant to implement recommendations of guidelines in their regular clinical practice.[9][10] Therefore, interventions to standardise surgeons' practice of antimicrobial use are highly important.

Antimicrobial stewardship (AMS), the primary goal of which is to optimise antimicrobial use, has been proven to be effective to improve surgical outcomes with increasing evidence.[11–13] However, as the idea becomes more widespread, implementing AMS remains a big challenge. Most of the AMS interventions require manual assessment and are best served by the expertise of infectious disease physicians or clinical pharmacists. The labour-intensive nature has impeded AMS implementation on a large and sustainable scale.[14][15] Under circumstances where the important personnel are not adequate, computerised decision support system (CDSS) has been identified as one way to enable key elements of AMS in clinical settings.

However, little evidence supports the application of CDSS in the AMS system in surgical settings. The controlled before–after and non-randomised study design in the related studies may lead to bias and reduce the validity of causal inference.[16] In addition, previous studies mainly focused on the primary care and little high-quality studies assessed the computer-based intervention for the in-hospital antimicrobial use in both surgical and non-surgical settings.[17–19] Therefore, based on the moderate-quality evidence in the literature, the 2016 AMS guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America gave 'weak recommendation' on the integration of CDSS into AMS programmes.[20]

To address this evidence gap, we planned to start a cluster-randomised trial in the largest cardiovascular surgery specialty hospital in China. We chose cardiovascular surgery rather than other surgical procedures because surgical site infections (SSIs) associated with cardiovascular surgeries are particularly severe; moreover, cardiovascular surgery-related SSIs are typically associated with skin flora, and thus, the evidence from this population may have significance for other surgical procedures.[21–26]

The Evaluate the Potential Impact of Computer AMS (EPIC) trial aims to assess if a multicomponent computer-based system incorporated into the workflow will reduce days of therapy (DOT) per admission and DOT per 1000 patient-day after cardiovascular surgeries in the intervention surgical teams compared with the controlled surgical teams, over a 6-month period.

METHODS/DESIGN

This trial is an open-label, two-arm, cluster-randomised controlled trial with cardiovascular surgical teams as the unit of randomisation (figure 1, flow chart).[27] Eligible teams (as defined in the Inclusion/exclusion criteria section) with written consent are randomised to the intervention or control arm by using an interactive web response system. The computer-based, multicomponent intervention targeting the reduction of perioperative antimicrobial use will be delivered to the intervention teams and the control teams will keep the usual clinical care.

A trial steering committee has been set up to monitor the conduct of the trial and the management of the data. Members of the trial steering committee will meet throughout the study period. The committee will include research staff, a clinical pharmacist and two surgeons who are not directly involved in the trial.

Study setting

The study will be launched in Fuwai Hospital, a 1500-bed tertiary care medical centre with an annual cardiovascular surgery volume of approximately 15 000 cases. Twenty-two surgical teams led by paid specialists in Fuwai perform approximately 10 000 various cardiovascular surgeries independently for adult patients (over 18 years old).

Fuwai has deployed an in-house electronic medical record (EMR) system and a computerised physician order entry (CPOE) system since 2009. All surgical teams fulfil the function of medical record management and physician order entry by using the in-house EMR and CPOE systems.

Inclusion/exclusion criteria

At the cluster level, 18 adult cardiovascular surgical teams in Fuwai Hospital will be invited to participate in this trial. Two surgical teams dedicated to peripheral vessel surgeries (mainly stenting) and two dedicated to structural heart disease interventions, which performed operations without opening the chest, are excluded because of their different AMS protocols.

At the physician level, the participants are the surgeons who prescribe antimicrobial to patients in the surgical teams.

At the patient level, the inclusion criteria are: (1) over 18 years of age and (2) receiving at least one open-chest cardiovascular surgery during the same admission. The exclusion criteria are: (1) intravenous or oral antimicrobial use within 2 weeks before surgery; (2) emergent/urgent surgery; (3) admitted for isolated stenting, heart transplantation or implantation of ventricular assist device, or implantation of extracorporeal membrane oxygenation; (4) admitted for subacute bacterial endocarditis and (5) length of ICU stay over 48 hours.

AMS intervention
AMS protocol in Fuwai Hospital

The development of AMS programme in Fuwai Hospital is based on previous guidelines as well as local policies.[20][28–31] The programme is multifunctional with the review of all positive blood cultures, regular teaching sessions for physicians and internal/external audit of antimicrobial use and resistance. The programme is regularly updated according to antimicrobial prescribing guidelines.
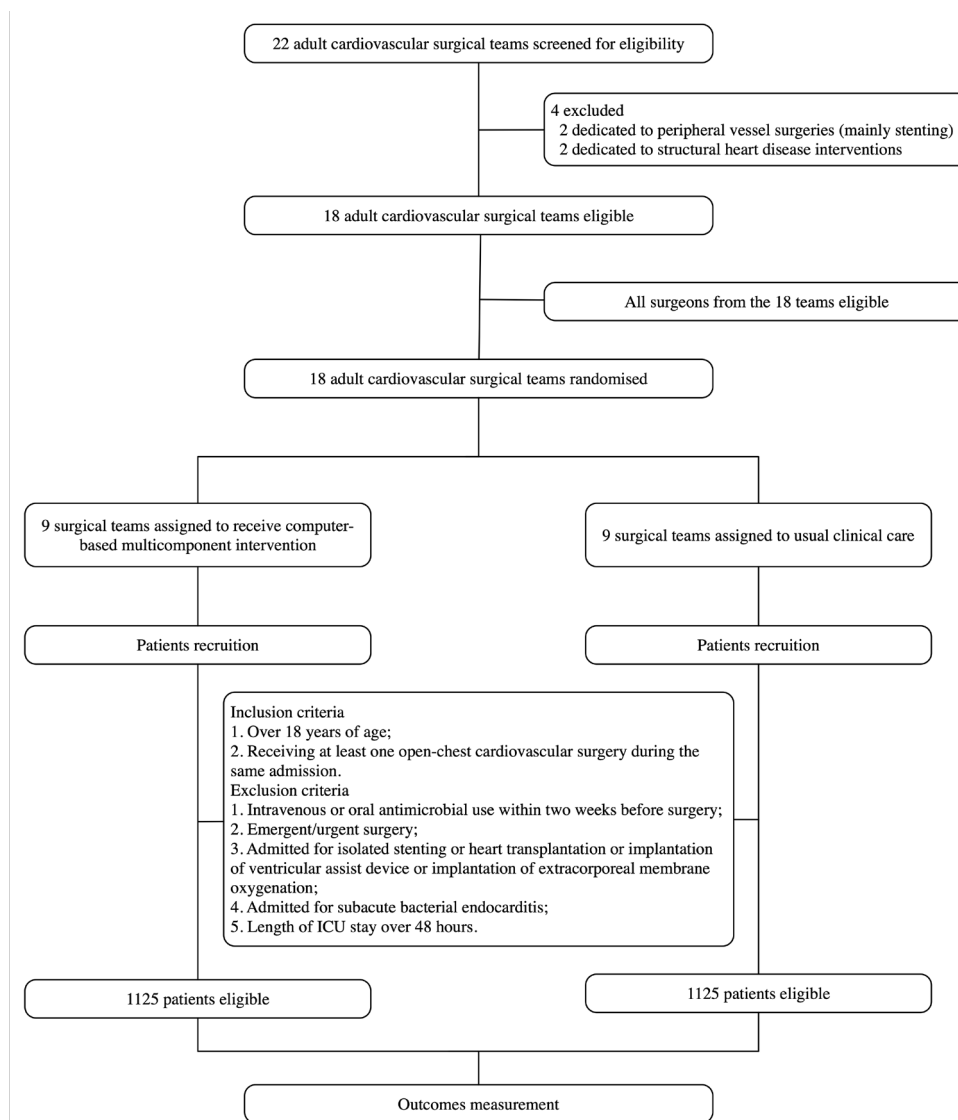
Figure 1 Flow chart of the study design.

Briefly, a bundled intervention is implemented in regular workflow and comprises: (1) preoperative screening and decolonisation; (2) an infusion of antimicrobial 30–60 min before incision; (3) intraoperative redosing if the duration of the procedure exceeds 3 hours or two half-lives of the antimicrobial or there is excessive blood loss (mainly aortic surgeries); (4) a duration of antimicrobial prophylaxis less than 48 hours at the postoperative stage and (5) evaluation of microbiological findings, appropriateness of antimicrobial therapy and de-escalation strategies at the postoperative stage.

Computer-based AMS intervention system

The intervention in the EPIC trial targets the control of postoperative antimicrobial use. The development of the computer-based multicomponent intervention is informed by existing medical records, behavioural intervention theory, systematic review evidence, qualitative research with trial and non-trial practices, clinical guidelines and national policies.[18–20 28–33]

The computer-based AMS intervention system was set up based on the EMR and CPOE systems on the server of Information Centre, which could access all the information from the EMR and CPOE systems in real time. The computer-based evaluation will be activated at the time of the entry of antimicrobial order in the CPOE system. Popup banners, in a man-machine interactive manner, will appear in the centre of the screen to inform the physicians if violation against AMS rules is detected. General information about AMS rules will be provided as information buttons on the lower right corner of the screen. The interventions function in three domains (figure 2):

► Re-evaluation alerts and decision support for the duration of antimicrobial treatment:
For prophylaxis use:
On postoperative calendar day 3, a visual alert will routinely appear on the CPOE screen to remind the physicians to stop antimicrobial prophylaxis.
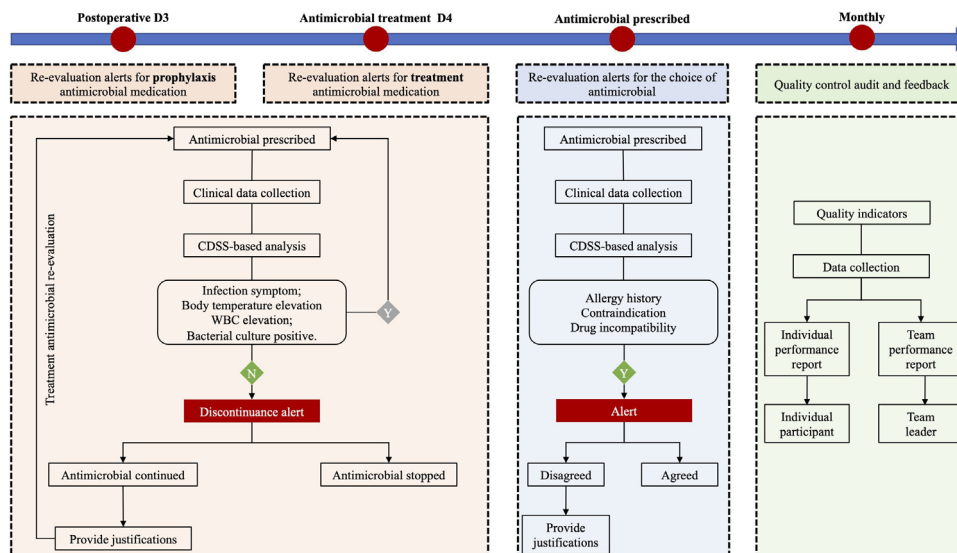
Figure 2 The multicomponent, computer-based interventions in the Evaluate the Potential Impact of Computer trial. CDSS, computerised decision support system. WBC, white blood cell.

To be noted, the system will assess patient-specific data such as clinical manifestations, routine blood tests, chest X-ray, microbiological results and use of other medications within the first two postoperative days. If there are no signs of infection, discontinuance reminder will appear even if the duration of the antimicrobial prophylaxis treatment doesn't reach in 2 days.

For treatment use:

The same method for postoperative antimicrobial treatment (with signs of postoperative infection) will be applied. Alert will appear on the calendar day 6 of the treatment. Discontinuance alert, on the basis of clinical data, will appear on any day before calendar day 6 if there are no signs of infection.

If the antimicrobial treatment is modified before calendar day 6, the system will assume to set up a re-evaluation and no alert will be displayed on day 6.

If the alerts mentioned above are ignored and the antimicrobial treatment is continued, physicians will be asked to provide accountable justifications. The options for justifications include prophylaxis, empirical and targeted treatment; as for targeted treatment, a predefined list of potential reasons will be provided with the availability to also enter free text, making it possible to assess prescribing quality and to provide specific decision supports.

► Re-evaluation alerts and decision support for the choice of antimicrobial:

Physicians will be asked to select the treatment type at the time of prescribing (prophylaxis, empirical or targeted treatment). At the same time, the system will evaluate the justifications of the prescription on clinical data and according to the basic AMS rules (history of drug allergy, serum creatinine, drug incompatibility, etc).

If the existing treatment strategy violates the basic AMS rules, the prescriber will be offered the choice to switch to the guideline-recommended treatment. Otherwise, prescribers will be asked to provide a justification for the deviation from the guidelines.

Moreover, treatment with regard to intravenous oral switch, de-escalation or stopping therapy will be recommended by the system if it is appropriate.

► Quality control audit and feedback:

Quality indicators of antimicrobial prescribing such as concordance with local guidelines (in terms of duration of therapy and antimicrobial selected) will be automatically assessed based on the information collected during the prescribing process.

Team leaders in a given participant team in the intervention arm will receive monthly graphical reports outlining the performance of the team compared with the other participating teams and compared with the guideline recommendation (if applicable). The individual participant surgeons will receive the monthly audit report of their own performance.

Outcomes measures

Table 1 gives detailed information about primary and secondary outcomes, including full names, abbreviations and evaluation purposes. The definitions of the terms were listed in online supplemental table S1.

The primary outcome will be the overall systemic antimicrobial use measured in DOT of systemic antimicrobial use per admission and per 1000 patient-day based on CPOE-derived data.

Secondary outcomes include a series of indices to evaluate antimicrobial use, microbial resistance, perioperative infection outcomes, patient safety, resource consumption and user compliance/satisfaction.

Table 1	Outline of primary and secondary outcomes
Outcomes	Evaluation purposes
Primary outcomes	
1. Days of antimicrobial therapy (DOT) per admission 2. DOT per 1000 patient-days (PD)	To evaluate the difference in overall systemic antimicrobial use in terms of duration of treatment and combination therapies between the intervention arm and control arm.
Secondary outcomes	
Antimicrobial use indicators	
1. Drug usage per 100 PD and per admission	The same as the evaluation purposes for 'DOT per admission'.
2. Length of therapy per 100 PD and per admission	
3. Days per treatment period overall and for specific indications	
Postoperative microbial resistance indicators	
1. *Clostridium difficile* colitis	To evaluate the efficacies of the computer-based multicomponent intervention to reduce the incidence of antimicrobial resistance.
2. Incident clinical cultures with multidrug-resistant organisms (MRSA, ESBL-E, CRE, VRE or *Pseudomonas aeruginosa*) per 1000 PD and admission.	
Postoperative infection indicators	
1. In-hospital or 30-day surgical site infections	To evaluate the potential side effects of the computer-based multicomponent intervention to elevate the incidence of antimicrobial resistance.
2. In-hospital bloodstream infections	
3. In-hospital pneumonia	
Patient safety indicators	
1. In-hospital or 30-day mortality, postoperative	We do not anticipate any potential serious adverse events that could be directly attributable to the intervention but we could not rule out the indirect association between these outcomes and the intervention.
2. In-hospital or 30-day myocardial infarction, postoperative and newly onset	Therefore, in consideration of patient safety issues, we will compare the surgical-related complications between the two arms.
3. In-hospital or 30-day stroke, postoperative and newly onset	
4. In-hospital or 30-day acute kidney injury, postoperative and newly onset	
Resource-consuming indicators	

Continued

Table 1	Continued
Outcomes	Evaluation purposes
1. Length of hospital stay	One of the main interest to various parts of the healthcare system.[44] These indicators are set to evaluate the efficacies of the computer-based AMS system to reduce the overall resource consumption.
2. Costs of administered antimicrobials (overall and by class) per admission	
3. Total costs of hospitalisation.	
User compliance and satisfaction indicators	
1. User satisfaction with the system	These two indices are to evaluate the barriers and facilitators to implementation and the use of the computer-based intervention.
2. User compliance with the system	

AMS, antimicrobial stewardship; DDD, defined daily dose; ESBL-E, extended spectrum beta-lactamase producing Enterobacteriaceae; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant enterococci.

Sample size

The sample size calculation is based on the primary outcome (DOT per admission and DOT per 1000 patient-day) and has been performed taking into account the clustered design of the study according to the approach proposed in the literature.[34]

The mean annual surgery volume of a team is about 450 cases in Fuwai Hospital, then one team will include 225 patients who are undergoing adult cardiac surgeries over the research period (6 months). Assuming one team will recruit 125 eligible patients and assuming nine teams per arm will have an average size of 1125 admissions, antimicrobial use of 5.0 DOT/admission in the control group with an SD of 2.0 (based on antimicrobial use data of 2019 in Fuwai Hospital) and a two-sided type I error of 0.05, we would have a power of 80% to detect an absolute difference of at least 0.5 in average DOT/admission between the intervention and control arm.

Blinding and randomisation

The trial steering committee is responsible for recruiting surgical teams to the trial and supervising the research process but had no access to the randomisation procedure. The extraction of the outcome measures will be performed primarily by research staff not directly involved in the study. The data analysts will be blinded to the randomisation.

Neither the research staff directly involved in the intervention, nor the participant surgeons, nor the participant patients are blinded to the randomisation due to the nature of the intervention.

Surgical teams will be randomised 1:1 to the intervention or control arm using an interactive web response

system. The randomisation plan will be established by research staff not directly involved in the study.

Scheme for statistical analysis

The efficacy of the intervention will be evaluated by analysing EMR and CPOE data that are routinely collected into the Fuwai database. Patients' data will be collected by their anonymised electronic case report form, including preoperative information (demographics, diagnosis and comorbidities), surgical information and details of prescriptions; anonymised surgeon information will be retrieved from the database of the personnel division of Fuwai. Written consents will be obtained from the participant patients.

Outcome variables will first be summarised across treatment and intervention groups and then explored using descriptive statistics. The DOT/admission at the individual level and DOT/1000 patient-day will be compared between two arms using a random-effects Poisson model. The following confounders will be considered: (1) patient: sex, age, type of comorbidities and type of cardiovascular surgeries and (2) surgeon: age, annual volume, professional title and academic title. All variables that result in a change of >5% in the coefficient for the intervention effect in bivariate regression will be added to the multivariate model, and the most parsimonious model will be selected through the conditional Akaike information criterion (AIC). Collinearity will be checked through a correlation matrix, whereby the most relevant, clinical variable will be selected in case of R^2 >0.8. The inverse probability of treatment weighting will be applied, if imbalances exist after randomisation.

The logistic regression analysis for clinical outcomes (indicators of patient safety, infection and antimicrobial resistance) will estimate the difference (95% CI) in the outcome between intervention and control arms, adjusting for variables at patient level as well as surgeon level.

Data for healthcare usage and costs will be analysed at the individual level as reported previously.[35] Total cost and antimicrobial cost will be compared between trial arms. A general linear model will be used to estimate the mean costs for the patients.

As a part of process evaluation, users' compliance and satisfaction with the computer-based intervention protocol will be assessed. As for user compliance, the evaluation will be done by documenting the total number of times the intervention tools fail to change the physicians' decision on antimicrobial prescription over the intervention period. The number representing compliance will be divided into quartiles and a trend test will be implemented by introducing these into analyses as continuous variables.

As for user satisfaction, a series of questionnaires will be developed to explore participants' experiences of using the intervention tools and experiences of the study implementation. Inductive thematic analysis will be used to analyse qualitative data.

Data collection and process

The in-hospital information will be retrieved from the hospital's database which is stored in the form of electronic case report form. Surgically associated adverse events and SSIs events within 30 days will be followed up. The detailed protocol about the follow-up was described elsewhere.[36] Briefly, patients discharged alive were followed at regular time intervals including the time point of postoperative 30 days. If the patients reported adverse events, the medical records of the patients in the outpatient clinic of Fuwai Hospital are double-checked. If the patients visit another hospital, they will be required to send paper copies of medical records by mail or photocopies through the internet. De-identified data for research use will be stored in password-protected Microsoft Excel files on secured hospital servers.

For analysis, data will be imported into SAS V.9.4 (SAS Institute). Only investigators directly involved in the trial will have access to the data. The data will be stored on secure servers with backup systems for 5 years after the end of the trial.

Duration of the trial

The intervention period, lasting 9 months, is composed of two parts: an internal pilot period (3 months) and the research period (6 months).

Before the launch of the research, an internal pilot will be conducted to demonstrate the feasibility and acceptability of the intervention. Also, the pilot will allow a period for the participant surgical teams to get familiar with the new computer-based tools for AMS.

In the pilot phase, intermediate outcome measures will include (1) the compatibility of the new operation module with our EMR and EPOE systems; (2) evidence that the intervention tools are accessed and used by prescribing members of staff in surgical teams and (3) successful delivery of regular feedback reports to surgical teams.

Ethics approval

The Ethics Committee in Fuwai Hospital approved this study. Participant surgeons in Fuwai Hospital gave informed consent to the study. Although the intervention is at the surgical team level, patients' informed consent will be obtained. In addition, an information leaflet will be provided to patients in the participating surgical teams.

Patient and public involvement

Patients and public will not get involved in the development of the research question, study design or any other part of this protocol.

Dissemination and reporting

Several publications in peer-reviewed journals are expected from this trial, and these will include description of the intervention development of the intervention content and main findings of the trial. Also, the findings are planned to be presented at national and international conferences.

DISCUSSION

Enlightened by the evidence in the literature, the EPIC trial is designed to evaluate the efficacy of CDSS support tools to reduce postoperative antimicrobial use. This study has several strengths and limitations.

Strengths: (1) the adequately powered, cluster-randomised controlled trial addresses many inadequacies in designs of the previous studies[33 37–39]; (2) different from previous studies in terms of the scope, setting and timing[17–19 40] the EPIC trial is among the first to assess the impact of CDSS tools on antimicrobial use in hospital settings and (3) also, to the best of our knowledge, this trial will be one of the first trials carried out in surgery settings. On the basis of the increasing incidence of antimicrobial resistance, we are trying to figure out a method to achieve the goal of a more reasonable use of antimicrobial agents.[41 42]

Limitations: this trial is a single centre study which may increase type II error. However, heterogeneous organisations of AMS programmes are noted among healthcare providers, possibly due to patient-specific considerations, institution-specific factors and local antimicrobial use policies.[43] It is a challenge to carry out multicentre trials because the factors above may be hard to be balanced or a huge sample size will be required which is beyond the sample size of the programme recruitment. Therefore, to carry out a single centre trial in a large volume, hospital with adequate surgical teams under the same AMS system is required. The feedback is a part of the computerised tools in management of antimicrobial, which may also influence antimicrobial use outcomes and behaviour patterns that will limit external validity outside of this trial design. Further study will be conducted to investigate the influence of the feedback.

An important output of this research will figure out a way of delivering a set of computer-based multicomponent interventions to reduce antimicrobial use in surgical settings. As a part of the study, rigorous audit mechanisms will examine facilitators and barriers to implementation of the intervention and assess user compliance/satisfaction with the intervention protocol. The process above will expose whether surgeons' behaviours will be changed by the CDSS during the intervention period. As a result, a similar, low-cost system could be applied for the regular surgical workflow in other hospitals.

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