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Protocol

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

Short title: Study protocol for EPIC

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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. Computerized decision support system (CDSS) has been identified as effective way to enable key elements of AMS in clinical settings. However, insufficient evidence is available to evaluate the efficacy of computerized AMS in surgical settings.

Methods and analysis

The Evaluate of the Potential Impact of Computerized antimicrobial stewardship (EPIC) trial is an open-label, single-centre, two-arm, cluster-randomized, 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 randomized 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 per admission over the whole intervention period (six 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.

Key words

Antimicrobial stewardship; computerized decision support system; cardiovascular surgery; randomized controlled trial.

Strengths and limitations of this study

1. This adequately powered, cluster-randomized, controlled trial addresses many inadequacies in designs of the previous studies.

2. Different from previous studies in terms of the scope, setting and timing, the EPIC trial is among the first to assess the impact of CDSS tools on antimicrobial use in hospital settings.

3. To the best of our knowledge, this trial will be one of the first trials carried out in surgery settings.

4. This trial is a single centre study which may increase type II error.

INTRODUCTION

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

Inappropriate antimicrobial use after surgeries increases the prevalence of antimicrobial resistant bacteria and subsequently subjects patients to unnecessary risk of adverse drug events and loads heavy economic burden on healthcare system.[6 7] However, despite many published guidelines and decades of efforts to change prescribing patterns, a survey revealed that the practice of antimicrobial use varies substantially among surgeons.[8] What's more, studies have shown that surgeons are reluctant to implement recommendations of guidelines in their routine clinical practice.[9 10] Therefore, interventions to standardize and audit surgeons' practice of antimicrobial use are quite important.

Antimicrobial stewardship (AMS), the primary goal of which is to optimize 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 have impeded AMS implementation on a large and sustainable scale.[14 15] Under circumstances where the important personnel are not adequate, computerized decision support system (CDSS) has been identified as one way to enable key elements of AMS in clinical settings.

However, little evidence is available to support the uptake of CDSS into AMS system

in surgical settings. There exist several studies,[16] but the controlled before-after and non-randomized feature in design may lead to bias and endanger the validity of causal inference.[17] Actually, related studies mainly focused on primary care and there is an obvious lack of high-quality studies assessing the impact of computer-based interventions on the in-hospital antimicrobial use in both surgical and non-surgical settings.[18-20] Therefore, on the basis of 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 programs.[21]

To address this evidence gap, we planned to organize a cluster randomized 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 can be particularly severe; what's more, cardiovascular surgery-related SSIs are typically associated with skin flora and thus the evidence from this population may have significance for other surgical procedures.[22-27]

The aim of the EPIC trial is to assess if a multicomponent computer-based system incorporated into the workflow can reduce days of therapy (DOT) per admission after cardiovascular surgeries in the intervention surgical teams compared with controlled surgical teams, over a one-year period.

METHODS/DESIGN

This trial is an open-label, two-arm, cluster-randomized, controlled trial with cardiovascular surgical teams as the unit of randomization (Figure 1, flow chart).[28] Eligible teams (as defined in "Inclusion/exclusion criteria" section) with written consent are randomized to the intervention or control arm by using an interactive web

response system. Computer-based, multicomponent intervention targeting on reduction of perioperative antimicrobial use will be delivered to teams in the intervention arm. Teams in the control arm will continue with usual clinical care.

A trial steering committee have 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 is 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 salaried specialists in Fuwai perform approximately 10,000 various cardiovascular surgeries independently for adult patients (over the 18 years old).

Fuwai has deployed an in-house electronic medical record (EMR) system and a computerized physician order entry (CPOE) system since 2009. All the 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 cluster level, eighteen 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 are excluded because of their obviously different AMS protocols.

At physician level, the immediate participants in the research are all those who may

issue prescriptions for antimicrobial in the participant surgical teams.

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

AMS intervention

AMS protocol in Fuwai Hospital

The development of AMS program in Fuwai Hospital is based on previous guidelines as well as local policies.[21 29-32] The program is multifunctional with review of all positive blood cultures, regular teaching sessions for physicians, and internal/external audit of antimicrobial use and resistance. The program is regularly updated according to antimicrobial prescribing guidelines.

Briefly, a bundled intervention is implemented in routine workflow and comprises: 1. preoperative screening and decolonization; 2. an infusion of antimicrobial 30-60 minutes before incision; 3. intraoperative redosing if the duration of the procedure exceeds three hours or two half-lives of the antimicrobial or there is excessive blood loss (mainly aortic surgeries); 4. A duration of antimicrobial prophylaxis no more than 48 hours at postoperative stage; 5. Evaluation of microbiological findings, appropriateness of antimicrobial therapy, and de-escalation strategies at postoperative stage.

Computer based AMS intervention system

The intervention in the EPIC trial is targeted at 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.[19-21 29-34]

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 three, a visual alert will routinely appear on the CPOE screen to remind the physicians to discontinue antimicrobial prophylaxis.

  To be noted, the system will continuously assess patient-specific data such as clinical manifestations, routine blood test, x-ray, microbiological results or 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 two days.

For treatment use:

The same mechanism functions for postoperative antimicrobial treatment (with signs of postoperative infection). Alert will appear on the calendar day six of the treatment; discontinuance alert, on the basis of clinical data, will appear on any day before calendar day six if there are no signs of infection.

If the antimicrobial treatment is modified before calendar day six, re-evaluation will be assumed to have taken place and no alert will be displayed on day six.

If the alerts mentioned above is ignored and the antimicrobial treatment is continued, physicians will be asked to provide accountable justifications. The options for justifications include prophylaxis, empiric, 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 support.

- 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, empiric 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 (a history of drug allergy, serum creatinine, drug incompatibility, et al.).

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.

What's more, treatment with regard to intravenous-oral switch, de-escalation or stopping therapy will be recommended by the system when 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 a detailed information about primary and secondary outcomes, including full names, abbreviations, definitions, and evaluation purposes.

Primary outcome will be the overall systemic antimicrobial use measured in DOT of systemic antimicrobial use per admission 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.

Sample size

The sample size calculation is based on the primary outcome (DOT per admission) and has been performed taking into account the clustered design of the study according to the approach proposed in the literature.[35]

The mean annual surgery volume of a team is about 450 cases in Fuwai Hospital, then one team will include some 225 patients undergoing adult cardiac surgeries over the research period (six months). Assuming one team will recruit 125 eligible patients and assuming nine teams per arm with an average size of 1,125 admissions, antimicrobial use of 5.0 DOT/admission in the control group with a standard deviation 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 randomization

Trial steering committee is responsible for recruiting surgical teams to the trial and supervising the research process but had no access to the randomization procedure. 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 randomization.

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

Surgical teams will be randomized 1:1 to the intervention or control arm using an interactive web response system. The randomization plan will be established by research staff not directly involved in the study.

Scheme for statistical analysis

The efficacies of the intervention will be evaluated by analysing EMR and CPOE data that are routinely collected into the Fuwai database. Data available for each patient will consist of his/her entire anonymized electronic case report form, including preoperative information (demographics, diagnosis, and comorbidities), surgical information, and details of all the drugs prescribed; anonymized surgeon information can be retrieved from the database of the personnel division of Fuwai. Written consents are obtained from both participant surgeons and participant patients.

Outcome variables will first be summarized across treatment and intervention groups and then explored using descriptive statistics. The DOT/admission at the individual level will be compared between the 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; 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 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 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.[36] 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 document 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 questionnaire 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. Surgical associated adverse events and SSIs events within 30 days will be followed up. The detailed protocol about the follow up were described elsewhere.[37] Briefly, patients discharged alive were followed at regular time intervals including the time point of postoperative 30 day. If the patients reported adverse events, the medical records of the patients in outpatient clinic of Fuwai Hospital are double-checked. If the patients visit another hospital, patients are required to send the 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 version 9.4 (SAS Institute Inc, Cary, North Carolina). 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 five years after the end of the trial.

Duration of the trial

The intervention period, lasting nine months, is composed of two parts: an internal pilot period (three months) and the research period (six 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.

Ethnics 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 surgical team level, patients' informed consents 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. The current study has several strengths and limitations.

Strengths: 1. This adequately powered, cluster-randomized, controlled trial addresses many inadequacies in designs of the previous studies;[34 38-40] 2. Different from previous studies in terms of the scope, setting and timing,[16 18-20] the EPIC trial is among the first to assess the impact of CDSS tools on antimicrobial use in hospital settings; 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 antibiotic resistance, our efforts to find a way to achieve a more rational use of antimicrobial agents is justifiable.[41 42]

Limitations: this trial is a single centre study which may increase type II error. However, obvious heterogeneous organizations of AMS programs are noted among healthcare providers, possibly due to patient-specific considerations, institution-specific factors, and local antimicrobial use policies.[43] This multifactorial heterogeneity make it quite challenging to carry out multicentre trials because the various factors may be hard to be balanced or the huge sample size will be required which exceeds recruitment

capacity of the research program. Therefore, to carry out single centre trial in a large-volume hospital with adequate surgical teams under the same AMS system is warranted.

An important output of this research will be establishing a way of delivering a set of computer-based multicomponent interventions to reduce antimicrobial use in surgical settings. As a part of the current study, rigorous audit mechanisms will be conducted to examine facilitators and barriers to implementation of this intervention and assess user compliance/satisfaction with the intervention protocol. This will help to establish whether the surgeon behaviour will be changed as a result of being exposed to the intervention. If effective, the similar system could be easily translated into routine surgical workflow in other hospitals at low cost.

Conflicts of Interests

None

Author Statement

SSH conceived the original idea for this study which was further developed with all authors, and secured funding for the study. XY and KC wrote the first draft of this manuscript, and designed the CDSS. SH provided input regarding the sample size calculations and statistical analysis. WZ, FY and XLD programmed CDSS. XWC reviewed the regulations of CDSS according to the guidelines and policy. The manuscript was reviewed and edited by all authors.

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Table 1
Outline of primary and secondary outcomes

Outcomes	Definition	Evaluation purposes
Primary outcomes		
Days of antimicrobial therapy (DOT) per admission	DOT: One DOT represents a specific antibiotic administered to an individual patient on a calendar day independent of dose and route.	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. DOT per 100 patient-days (PD) 2. Drug usage (DDDs) per 100 PD and per admission 3. Length of therapy (LOT) per 100 PD and per admission 4. Days per treatment period overall and for specific indications	1. DDDs: Items issued×Amount of drug per item÷DDD* 2. LOT: Number of days during which antimicrobial is used; 3. Treatment period: Antibiotic treatment not interrupted by more than one calendar day or discharge.	The same as the evaluation purposes for "DOT per admission".
postoperative microbial resistance indicators 1. Clostridium difficile colitis 2. Incident clinical cultures with multidrug resistant organisms (MRSA, ESBL-E,	1. Clostridium difficile colitis: Colitis associated with Clostridium difficile infection (ICD 10: A04.7)	To evaluate the efficacies of the computer-based multicomponent intervention to reduce the incidence of antimicrobial resistance.

CRE, VRE, or Pseudomonas aeruginosa) per 1000 PD and admission.		
Postoperative infection indicators 1. In-hospital or 30-day surgical site infections (SSIs) 2. In-hospital bloodstream infections 3. In-hospital pneumonia	1. SSIs:[30] Occurs within 30 days postoperatively and involves skin or subcutaneous tissue of the incision and at least one of the following: (1) purulent drainage from the incision, (2) organisms isolated from an aseptically obtained culture of fluid or tissue from the incision, (3) at least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat, and incision is deliberately opened by surgeon and is culture-positive or not cultured (a culture-negative finding does not meet this criterion), and (4) diagnosis of SSI by the surgeon or attending physician. 2. Blood stream infections: Blood stream infection after surgery (ICD 10: A41.9) 3. Pneumonia: Pulmonary infection after surgery (ICD 10 : J98.402)	To evaluate the potential side-effects of the computer-based multicomponent intervention to elevate the incidence of antimicrobial resistance.
Patient safety indicators		

1. In-hospital or 30-day mortality, postoperative 2. In-hospital or 30-day myocardial infarction (MI), postoperative and newly onset 3. In-hospital or 30-day stroke, postoperative and newly onset 4. In-hospital or 30-day acute kidney injury (AKI), postoperative and newly onset	1. MI (in accordance with the fourth edition of MI definition):[44] Termed type 5 MI, procedure related MI. Briefly, the criteria are as follows: • Elevation of cTn>10 times of the 9th percentile URL with patients with normal baseline; • For patients with elevated preprocedural cTn values, elevation of cTn>10-fold increase and manifest a change from the baseline value of over 20%; • With as least one of the following: • Development of new pathological Q waves; • Imaging evidence of loss of viable myocardium that is presumed to be new and in a pattern consistent with an ischemic aetiology; • Angiographic findings consistent with a procedural flow-limiting complication. 2. Stroke: Refers to newly onset stroke after surgery (ICD 10: I60.0-I60.9; I61.0-I61.9; I62.0; I62.1; I62.9; I63.0-I63.9; I64)	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. Therefore, in consideration of patient safety issues, we will compare the surgical-related complications between the two arms.

	3. AKI: Refers to newly onset AKI after surgery • Acute renal dysfunction within 48 hours (ICD 10: N17); • AKI stage I: creatinine≥26.5μmol/L; creatinine over 1.5-1.9 times of baseline value; urine output<0.5ml/kg/hour for 6-12 hours; • AKI stage II: creatinine over 2.0 to 2.9 times of baseline value; urine output<0.5ml/kg/hour for over 12 hours; • AKI stage III: creatinine≥353.6μmol/L; creatinine over 3 times of baseline value; initiation of renal replacement therapy; urine output<0.3ml/kg/hour for ≥24 hours; anuria for ≥24 hours.	
Resource consuming indicators 1. Length of hospital stay (LOS) 2. Costs of administered antimicrobials (overall and by class) per admission 3. Total costs of hospitalization.	None	One of the main interest to various parts of the healthcare system.[45] These indicators are set to evaluate the efficacies of the computer-based AMS system to reduce the overall resource consumption.
User compliance and satisfaction indicators 1. User satisfaction with the system	1. Satisfaction:	These two indices are to evaluate the barriers

2. User compliance with the system	Users will primarily include surgeons in the intervention arm, but nurses involved with intervention implementation will also be included, aiming for the maximum achievable sample. We will explore their unique and important perspective using questionnaire and an interview guide for the process evaluation of public health interventions and researches.[28] Also, we will explore participants' experiences of using the intervention resources and experiences of the study implementation. As a part of process evaluation, contextual information on initiatives to prescribe antimicrobial will be collected through a popup window at the time when a new antimicrobial order is input in the CPOE system. 2. compliance: As a part of process evaluation, compliance with the multicomponent intervention protocols will be assessed. This will be done by evaluating the total number of times the intervention tools fail to change the physicians' decision on antimicrobial prescription over the	and facilitators to implementation and the use of the computer-based intervention.

	intervention period.	

DDD=defined daily dose, defined as the assumed average maintenance dose per day for a drug used for its main indication in adults.
ICD=international classification of diseases.
CRE=Carbapenem resistant Enterobacteriaceae.
ESBL-E=extended spectrum beta-lactamase producing Enterobacteriaceae.
MRSA=methicillin-resistant Staphylococcus aureus.
VRE=vancomycin-resistant enterococci.
ICU=intensive care unit.
URL=upper range limit.
CPOE= computerized physician order entry.

FIGURE LEGEND

Figure 1. Flow chart of the study design.

Figure 2. The multicomponent, computer-based interventions in the EPIC trial.

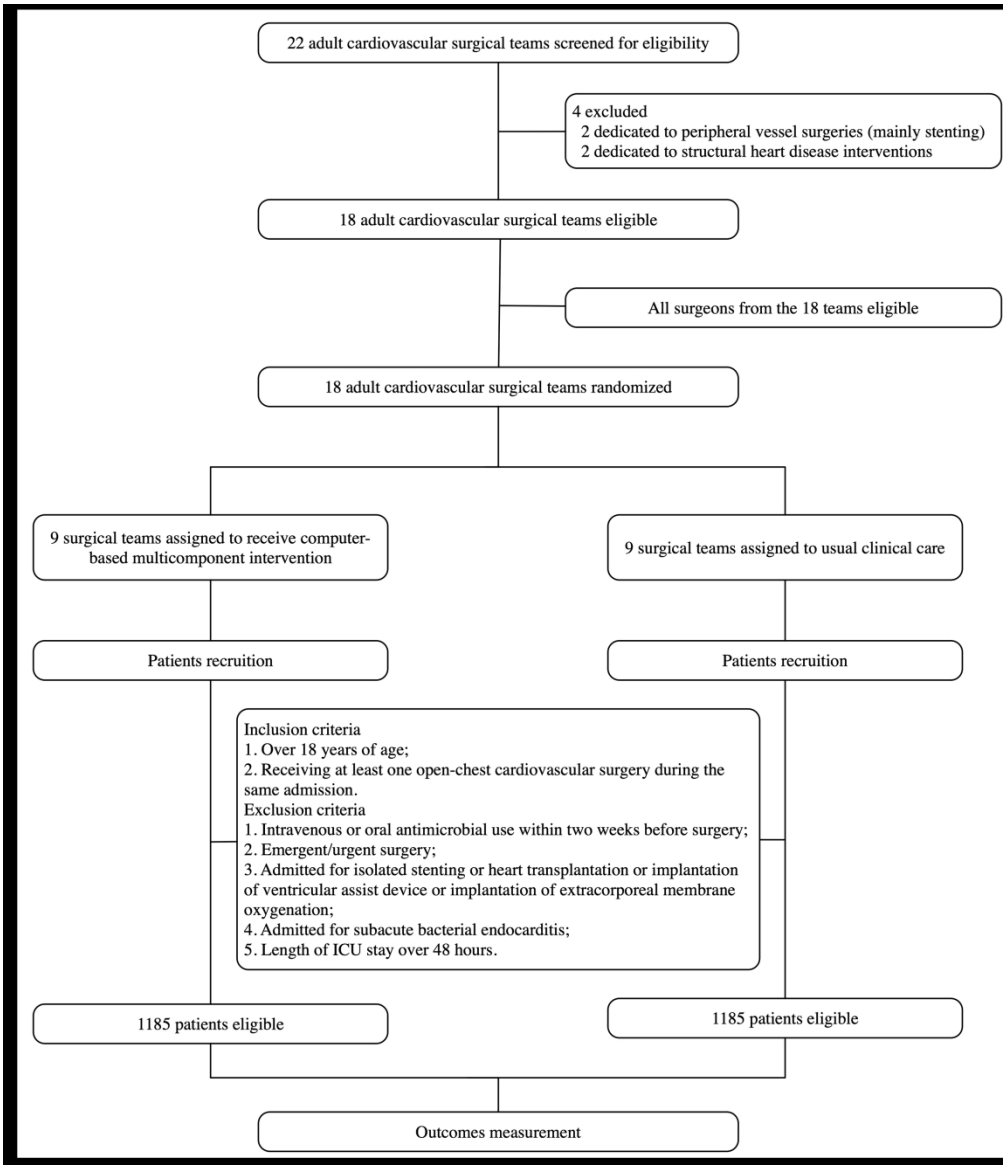

Figure 1. Flow chart of the study design.

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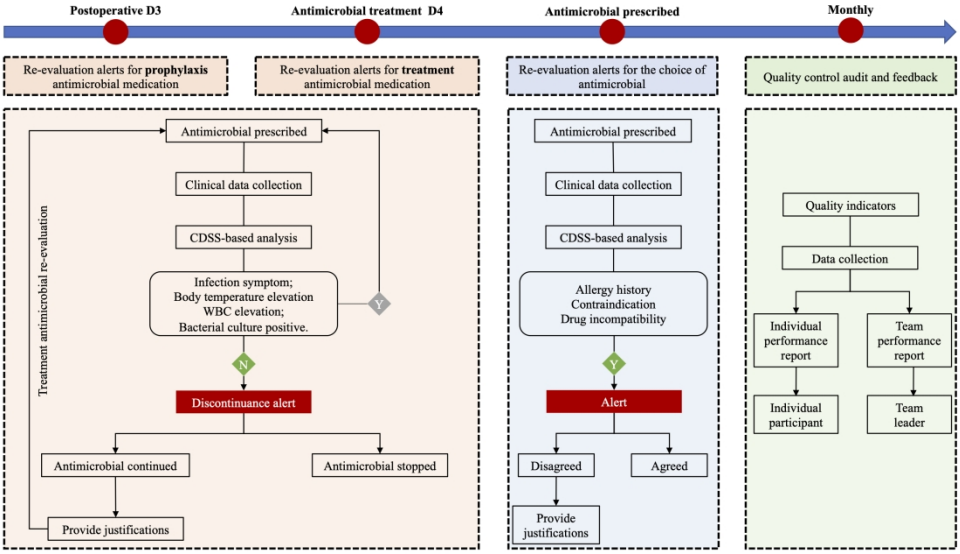

Figure 2. The multicomponent, computer-based interventions in the EPIC trial.

338x190mm (200 x 200 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1-2
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	2
Roles and responsibilities:	#5a	Names, affiliations, and roles of protocol contributors	3-4

contributorship			
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	4
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	4
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	4-5
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-7
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	7
Objectives	#7	Specific objectives or hypotheses	7
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic,	8

		academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8-9
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-11
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	11
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	11-12
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	12
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12-14
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	14-15
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	15

Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	15
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	16
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	16
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	16
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	16-17
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	17
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements,	17

		training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	17-18
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	18
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	18-19
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	19-20
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	20
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	20-21
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	21

Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	21
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	22
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	22
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	22-23
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	23
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	23
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	23
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	24
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	24
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial	24

		participation	
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	24-25
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	25
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	25
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	25
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	25-26

BMJ Open

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

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Primary Subject Heading:	Medical management
Secondary Subject Heading:	Cardiovascular medicine, Medical management, Surgery
Keywords:	Cardiac surgery < SURGERY, Adult cardiology < CARDIOLOGY, Clinical trials < THERAPEUTICS

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Aug 18, 2020

Revised

Protocol

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

Short title: Study protocol for EPIC

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Word count: 3250

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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 computerized 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 computerized AMS in surgical settings.

Methods and analysis

The Evaluate of the Potential Impact of Computerized antimicrobial stewardship (EPIC) trial is an open-label, single-centre, two-arm, cluster-randomized, 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 randomized 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 (six 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.

Key words

Antimicrobial stewardship; computerized decision support system; cardiovascular surgery; randomized controlled trial.

Strengths and limitations of this study

1. This adequately powered, cluster-randomized, controlled trial addresses many inadequacies in designs of the previous studies.

2. Different from previous studies in terms of the scope, setting and timing, the EPIC trial is among the first to assess the impact of CDSS tools on antimicrobial use in hospital settings.

3. To the best of our knowledge, this trial will be one of the first trials carried out in surgery settings.

4. 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 United States in 2017.[4] This crisis is even more serious in low 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 standardize surgeons' practice of antimicrobial use is highly important.

Antimicrobial stewardship (AMS), the primary goal of which is to optimize 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, computerized decision support system (CDSS) has been identified as one way to enable key elements of AMS in clinical settings.

However, little evidence support the application of CDSS in the AMS system in

surgical settings. The controlled before-after and non-randomized 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 programs.[20]

To address this evidence gap, we planned to start a cluster-randomized 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 is 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 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 to the controlled surgical teams, over a six-month period.

METHODS/DESIGN

This trial is an open-label, two-arm, cluster-randomized, controlled trial with cardiovascular surgical teams as the unit of randomization (Figure 1, flow chart).[27] Eligible teams (as defined in "Inclusion/exclusion criteria" section) with written consent are randomized 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 computerized 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, eighteen 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; 2. Receiving at least one open-chest cardiovascular surgery during the same admission. The exclusion criteria are: 1. Intravenous or oral antimicrobial use within two 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; 5. Length of ICU stay over 48 hours.

AMS intervention

AMS protocol in Fuwai Hospital

The development of AMS program in Fuwai Hospital is based on previous guidelines as well as local policies.[20 28-31] The program 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 program is regularly updated according to antimicrobial prescribing guidelines.

Briefly, a bundled intervention is implemented in regular workflow and comprises: 1. preoperative screening and decolonization; 2. an infusion of antimicrobial 30-60 minutes before incision; 3. intraoperative redosing if the duration of the procedure exceeds three 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; 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 system on the server of Information Centre, which could access all the information from the EMR and CPOE system 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 three, a visual alert will routinely appear on the CPOE screen to remind the physicians to stop antimicrobial prophylaxis.

  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 two 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 six of the treatment. Discontinuance alert, on the basis of clinical data, will appear on any day before calendar day six if there are no signs of infection.

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

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, empiric, 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, empiric 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, et al.).

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 Supplementary 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.

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 undergoing adult cardiac surgeries over the research period (six months). Assuming one team will recruit 125 eligible patients and assuming nine teams per arm with will have an average size of 1,125 admissions, antimicrobial use of 5.0 DOT/admission in the control group with a standard deviation 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 randomization

The trial steering committee is responsible for recruiting surgical teams to the trial and supervising the research process but had no access to the randomization 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 randomization.

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

Surgical teams will be randomized 1:1 to the intervention or control arm using an interactive web response system. The randomization 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 anonymized electronic case report form, including preoperative information (demographics, diagnosis, and comorbidities), surgical information, and details of prescriptions; anonymized 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 summarized 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; 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 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 (IPTW) will be applied, if imbalances exist after randomization.

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 document 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. Surgical 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 day. 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 version 9.4 (SAS Institute Inc, Cary, North Carolina). 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 five years after the end of the trial.

Duration of the trial

The intervention period, lasting nine months, is composed of two parts: an internal pilot period (three months) and the research period (six 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.

Ethnics 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-randomized, 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 41] the EPIC trial is among the first to assess the impact of CDSS tools on antimicrobial use in hospital settings; 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 organizations of AMS programs 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 beyond the sample size of the program 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 feed-back is a part of the computerized-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 feed-back.

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.

Conflicts of Interests

None

Author Statement

SSH conceived the original idea for this study which was further developed with all authors, and secured funding for the study. XY and KC wrote the first draft of this

manuscript, and designed the CDSS tools. SH provided input regarding the sample size calculations and statistical analysis. WZ, FY and XLD programmed CDSS tools. XWC reviewed the regulations of CDSS tools according to the guidelines and policy. The manuscript was reviewed and edited by all authors.

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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 (DDDs) per 100 PD and per admission 2. Length of therapy (LOT) per 100 PD and per admission 3. Days per treatment period overall and for specific indications	The same as the evaluation purposes for "DOT per admission".
postoperative microbial resistance indicators 1. Clostridium difficile colitis 2. Incident clinical cultures with multidrug resistant organisms (MRSA, ESBL-E, CRE, VRE, or Pseudomonas aeruginosa) per 1000 PD and admission.	To evaluate the efficacies of the computer-based multicomponent intervention to reduce the incidence of antimicrobial resistance.
Postoperative infection indicators 1. In-hospital or 30-day surgical site infections (SSIs) 2. In-hospital bloodstream infections 3. In-hospital pneumonia	To evaluate the potential side-effects of the computer-based multicomponent intervention to elevate the incidence of antimicrobial resistance.
Patient safety indicators 1. In-hospital or 30-day mortality, postoperative 2. In-hospital or 30-day myocardial infarction (MI), postoperative and newly onset 3. In-hospital or 30-day stroke, postoperative and newly onset 4. In-hospital or 30-day acute kidney injury (AKI), postoperative and newly onset	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. Therefore, in consideration of patient safety issues, we will compare the surgical-related complications between the two arms.
Resource consuming indicators 1. Length of hospital stay (LOS)	One of the main interest to various parts

2. Costs of administered antimicrobials (overall and by class) per admission 3. Total costs of hospitalization.	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.
User compliance and satisfaction indicators 1. User satisfaction with the system **2.** User compliance with the system	These two indices are to evaluate the barriers and facilitators to implementation and the use of the computer-based intervention.

DDD=defined daily dose.
ESBL-E=extended spectrum beta-lactamase producing Enterobacteriaceae.
MRSA=methicillin-resistant Staphylococcus aureus.
VRE=vancomycin-resistant enterococci.

FIGURE LEGEND

Figure 1. Flow chart of the study design.

Figure 2. The multicomponent, computer-based interventions in the EPIC trial.

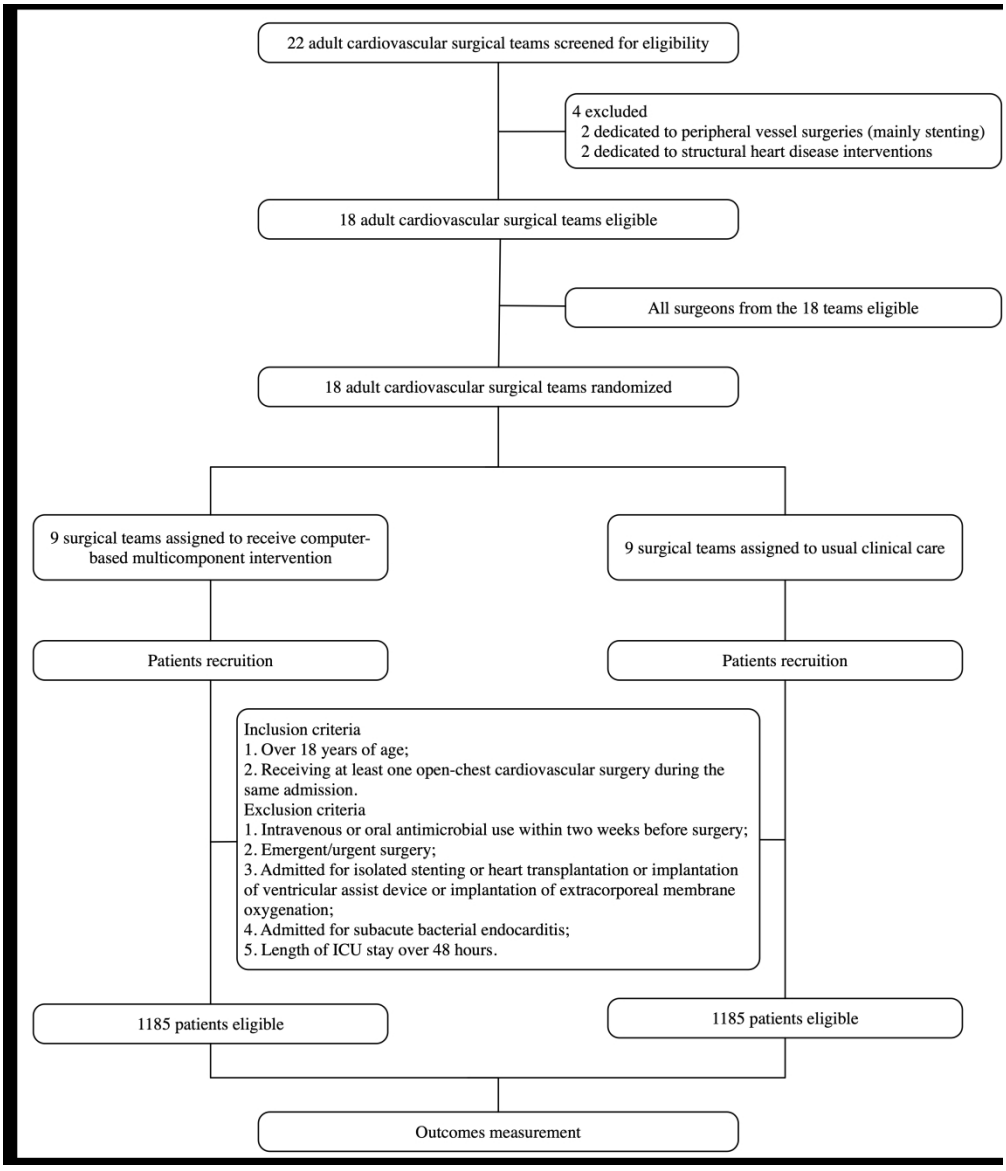

Figure 1. Flow chart of the study design.

246x286mm (400 x 400 DPI)

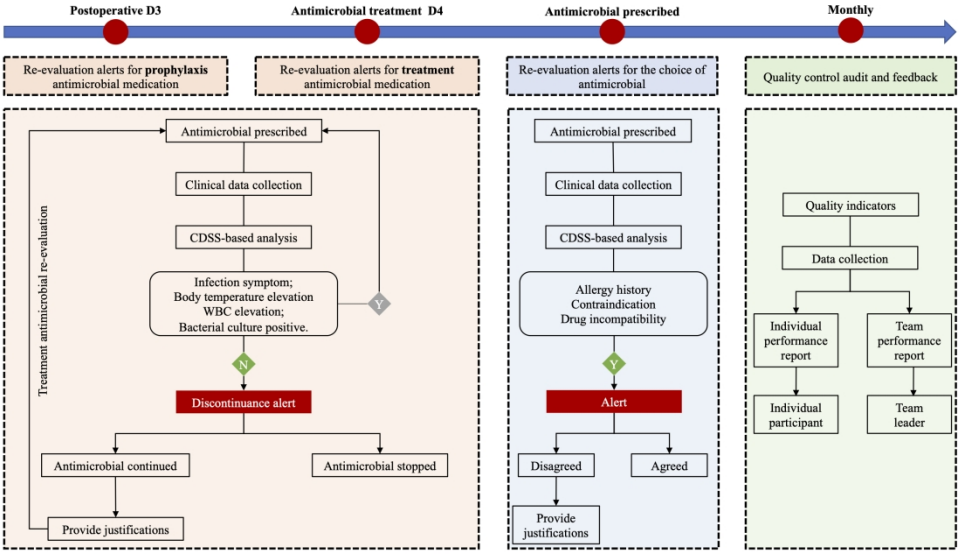

Figure 2. The multicomponent, computer-based interventions in the EPIC trial.

338x190mm (200 x 200 DPI)

Supplementary material

Table S1

Terms and definitions

Term	Definition
Days of therapy (DOT)	One DOT represents a specific antimicrobial administered to an individual patient on a calendar day independent of dose and route.
Defined daily dose (DDD)	The assumed average maintenance dose per day for a drug used for its main indication in adults. Items issued×Amount of drug per item=DDD
Length of therapy (LOT)	Number of days during which antimicrobial is used.
Treatment period	Antimicrobial treatment not interrupted by more than one calendar day or discharge.
Clostridium difficile colitis	Colitis associated with Clostridium difficile infection (ICD 10: A04.7)
Multidrug resistant organisms	Resistant to three or more antimicrobial classes, including methicillin-resistant Staphylococcus aureus (MRSA), extended spectrum beta-lactamase producing Enterobacteriaceae (ESBL-E), carbapenem resistant Enterobacteriaceae (CRE), vancomycin-resistant enterococci (VRE), and Pseudomonas aeruginosa.
In-hospital or 30-day surgical site infections (SSIs)	Occurs within 30 days postoperatively and involves skin or subcutaneous tissue of the incision and at least one of the following: (1) purulent drainage from the incision, (2) organisms isolated from an aseptically obtained culture of fluid or tissue from the incision, (3) at least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat, and incision is deliberately opened by surgeon and is culture-positive or not cultured (a culture-negative finding does not meet this criterion), and (4) diagnosis of SSI by the surgeon or attending physician.[1]
Bloodstream infections	Blood stream infection after surgery (ICD 10: A41.9)
Pneumonia	Pulmonary infection after surgery (ICD 10: J98.402)
Myocardial infarction (MI)	In accordance with the fourth edition of MI definition Termed type 5 MI, procedure related MI.[2] Briefly, the criteria are as follows: • Elevation of cTn>10 times of the 9th percentile URL with patients with normal baseline; • For patients with elevated preprocedural cTn values, elevation of cTn>10-fold increase and manifest a change from the baseline value of over 20%;

	• With as least one of the following: • Development of new pathological Q waves; • Imaging evidence of loss of viable myocardium that is presumed to be new and in a pattern consistent with an ischemic aetiology; • Angiographic findings consistent with a procedural flow-limiting complication.
Stroke	Refers to newly onset stroke after surgery (ICD 10: I60.0-I60.9; I61.0-I61.9; I62.0; I62.1; I62.9; I63.0-I63.9; I64)
Acute kidney injury (AKI)	Refers to newly onset AKI after surgery • Acute renal dysfunction within 48 hours (ICD 10: N17); • AKI stage I: creatinine≥26.5μmol/L; creatinine over 1.5-1.9 times of baseline value; urine output<0.5ml/kg/hour for 6-12 hours; • AKI stage II: creatinine over 2.0 to 2.9 times of baseline value; urine output<0.5ml/kg/hour for over 12 hours; • AKI stage III: creatinine≥353.6μmol/L; creatinine over 3 times of baseline value; initiation of renal replacement therapy; urine output<0.3ml/kg/hour for ≥24 hours; anuria for ≥24 hours.
User satisfaction	Users will primarily include surgeons in the intervention arm, but nurses involved with intervention implementation will also be included, aiming for the maximum achievable sample. We will explore their unique and important perspective using questionnaire and an interview guide for the process evaluation of public health interventions and researches.[3] Also, we will explore participants' experiences of using the intervention resources and experiences of the study implementation. As a part of process evaluation, contextual information on initiatives to prescribe antimicrobial will be collected through a popup window at the time when a new antimicrobial order is input in the CPOE system.
User compliance	As a part of process evaluation, compliance with the multicomponent intervention protocols will be assessed. This will be done by evaluating the total number of times the intervention tools fail to change the physicians' decision on antimicrobial prescription over the intervention period.

ICD=international classification of diseases.

URL=upper range limit.
CPOE= computerized physician order entry.

Reference

1. Bratzler DW, Dellinger EP, Olsen KM, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. Am J Health Syst Pharm 2013;70(3):195-283. doi: 10.2146/ajhp120568 [published Online First: 2013/01/19]
2. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth Universal Definition of Myocardial Infarction (2018). J Am Coll Cardiol 2018;72(18):2231-64. doi: 10.1016/j.jacc.2018.08.1038 [published Online First: 2018/08/30]
3. Linnan L, Steckler A. Process evaluation for public healthinterventions and research. California:Jossey-Bass San Francisco, 2002.

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1-2
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	2
Roles and responsibilities:	#5a	Names, affiliations, and roles of protocol contributors	3-4

contributorship			
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	4
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	4
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	4-5
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-7
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	7
Objectives	#7	Specific objectives or hypotheses	7
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic,	8

		academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8-9
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-11
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	11
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	11-12
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	12
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12-14
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	14-15
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	15

Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	15
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	16
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	16
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	16
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	16-17
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	17
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements,	17

		training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	17-18
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	18
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	18-19
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	19-20
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	20
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	20-21
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	21

Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	21
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	22
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	22
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	22-23
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	23
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	23
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	23
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	24
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	24
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial	24

		participation	
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	24-25
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	25
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	25
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	25
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	25-26