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Multicentre, open label, randomised, controlled clinical trial comparing 2% chlorhexidine – 70% isopropanol and 5% povidone iodine – 69% ethanol for skin antisepsis in reducing surgical-site infection after cardiac surgery: the CLEAN 2 study protocol

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3 **Multicentre, open label, randomised, controlled clinical trial comparing 2%**
4 **chlorhexidine – 70% isopropanol and 5% povidone iodine – 69% ethanol for skin**
5 **antiseptis in reducing surgical-site infection after cardiac surgery: the CLEAN 2 study**
6 **protocol**
7

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ABSTRACT

Introduction: Surgical site infection (SSI) is the second most frequent cause of healthcare-associated infection worldwide and is associated with increased morbidity, mortality and healthcare costs. Cardiac surgery is clean surgery with low incidence of SSI, ranging from 2 to 5%, but with potentially severe consequences.

Perioperative skin antisepsis with an alcohol-based antiseptic solution is recommended to prevent SSI, but the superiority of chlorhexidine (CHG)-alcohol over povidone iodine (PVI)-alcohol, the two most common alcohol-based antiseptic solutions used worldwide, is controversial. We aim to evaluate whether 2% CHG-70% isopropanol is more effective than 5% PVI-69% ethanol in reducing the incidence of reoperation after cardiac surgery.

Methods and analysis: The CLEAN 2 study is a multicentre, open label, randomised, controlled clinical trial of 4100 patients undergoing cardiac surgery. Patients will be randomized in 1:1 ratio to receive either 2% CHG – 70% isopropanol or 5% PVI – 69% ethanol for perioperative skin preparation. The primary endpoint is the proportion of patients undergoing any re-sternotomy between Day 0 and Day 90 after initial surgery and/or any reoperation on saphen venous surgical site between Day 0 and Day 30 after initial surgery. Data will be analysed on the intention-to-treat principle.

Ethics and dissemination: This protocol has been approved by an independent ethics committee and will be carried out according to the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines. The results of this study will be disseminated through presentation at scientific conferences and publication in peer-reviewed journals.

Trial registration: EudraCT 2017-005169-33 & NCT03560193.

STRENGTHS AND LIMITATIONS OF THIS STUDY

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3 • This randomised study is aimed being the largest one performed comparing the
4 efficacy of perioperative skin preparation with either alcohol-based CHG or alcohol-based
5 PVI in reducing severe postoperative complications.
6
7 • Cardiac surgery is a clean surgery where most of the pathogens involved in SSI
8 originate from the skin.
9
10 • The primary endpoint, the incidence of any reoperation at both surgical sites, is a
11 predefined strong unquestionable criterion, overlooking the need – and the risk of bias - for
12 assessing the reality of SSI.
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14 • In addition, limitations due to the lack of masking related to the nature of the
15 intervention will be reduced by assessment of all SSI by an adjudication committee masked to
16 antiseptic group.
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INTRODUCTION

Surgical site infection (SSI) is the second most frequent cause of healthcare-associated infections with an incidence up to 19% depending of the type of surgery, and range from simple wound discharge to life-threatening condition.[1–3] They are associated with increased hospital stay, prolonged antibiotics use and occasional need for reoperation, and are responsible for rising mortality and healthcare costs estimated at € 10 billion per year in the USA.[4]

Cardiac surgery is considered as clean surgery. Incidence of SSI is lower than with other types of surgery, ranging from 2 to 5% depending on the definitions used, but consequences may be greater in terms of both frequency and severity.[5,6] Because pathogens involved in SSI after clean surgery come mostly from skin, perioperative skin antisepsis plays a major role in SSI prevention.

The most common antiseptic agents used for skin disinfection before surgery are aqueous or alcoholic formulations of chlorhexidine (CHG) or povidone iodine (PVI) both of which are available at various concentrations. Several studies have compared their respective efficacy and safety in reducing SSI. Nevertheless, results were contradictory, probably due to different comparators (concentrations, combination with alcohol or water...), different SSI definitions, and different length of follow up.[7–11] In 2010, a meta-analysis of seven randomised-controlled trials (including 3437 patients) compared CHG (at a concentration of 0.5 to 4%) with PVI or other iodophors (at a concentration of 7 to 10%) for preoperative skin antisepsis in clean and clean-contaminated surgery.[12] The use of CHG was associated with fewer SSIs (adjusted RR 0.64; 95%CI 0.51-0.80) compared with iodine. Another meta-analysis of six randomised-controlled trials comparing CHG (at a concentration of 0.5 to 4%) to PVI (at a concentration of 7.5 to 10%) for preoperative skin antisepsis yielded similar findings [OR of 0.68 (0.50-0.94; p=0.019)].[13] However, in most studies CHG was combined with alcohol and PVI was not, which meant that two antiseptics were being compared to only one. A review conducted in 2012 was unable to draw any conclusion about which surgical site antiseptic effectively reduces SSI.[14] Recently, Tuuli and colleagues were the first to conduct a large trial comparing CHG and PVI in alcoholic formulations for skin disinfection before caesarean section.[9] Interestingly, both antiseptic formulations used the same alcohol at the same concentration and both were applied similarly using an applicator. Although this was the first study demonstrating benefit of 2% CHG-70% isopropanol over 8.3% PVI-70% isopropanol, it was monocentre, and did not address all potential methodological limits. Especially, the choice of superficial or deep surgical-site infection as primary endpoint assessed by the surgeon (the diagnosis was made by the treating physician and verified by means of chart review by the principal investigator, who was unaware of the study-group assignments) may generate interpretation biases in an open study. Moreover, the one dual microbial source of pathogens from both skin and vaginal origins in SSI after caesarean delivery and immune modulation in pregnancy raise questions about whether results of trials of preoperative skin antisepsis for caesarean delivery can be extrapolated to others surgical procedures.

Furthermore, the possible superiority of CHG over PVI was not confirmed in a second monocentre trial involving 1404 women requiring caesarean section.[8] Lastly, in a third assessor-blinded, monocentre, randomised trial involving 802 patients scheduled for elective clean-contaminated colorectal surgery, the use of PVI-alcohol failed to meet criterion for non-inferiority for SSI occurrence compared with CHG-alcohol.[11] These contradictory results may explain the lack of universal use of CHG-alcohol for skin antisepsis in surgery despite the recommendations of the World Health Organization (WHO).[15]

The prevalence and potential serious consequences of SSI in cardiac surgery, especially mediastinitis, support a large randomised controlled trial in this setting. We hypothesize that perioperative skin preparation with 2% CHG-70% isopropanol is more effective than 5% PVI-69% ethanol as a means of preventing any reoperation after cardiac surgery.

METHODS AND ANALYSIS

Trial design and setting

The CLEAN 2 trial is an investigator-initiated, publicly-funded multicentre, randomised, controlled, open-label clinical trial with concealed allocation of patients scheduled to undergo cardiac surgery and to receive 1:1 either 2% CHG – 70% isopropanol or 5% PVI– 69% ethanol for perioperative skin preparation. Randomisation will be carried out through a secure web-based randomisation system and stratified by centre (Fig. 1).

The trial will take place at 7 university and non-university hospitals. All participating centres perform more than 500 cardiac surgical procedures per year.

Participant eligibility and consent

During surgery or preoperative anaesthesia consultation, all consecutive patients will be considered candidates for inclusion in the study if they meet all of the inclusion criteria and none of the exclusion criteria. Eligible patients will receive oral and written information and will be enrolled after having given written consent.

Inclusion criteria

- Adult patients (age \geq 18 years) admitted in one of the participating centres
- Scheduled to undergo surgery of the heart (valve, coronary or combined surgery) or of the aorta via median sternotomy
- Having signed informed consent form

Exclusion criteria

- Patients with known allergies to CHG, PVI, isopropanol or ethanol
- Surgery for heart transplantation
- Any signs of inflammation or sternal instability at the site of sternotomy or operation for infection (sternal wound infection or endocarditis)
- History of cardiac surgery within 3 months preceding enrolment
- Participation in another clinical trial aimed at reducing SSI
- Patients already enrolled in this study
- Pregnant or breastfeeding women and potentially childbearing women without effective contraception
- Patients not benefiting from a Social Security scheme or not benefiting from it through a third party
- Persons benefiting from enhanced protection, namely minors, persons deprived of their liberty by a judicial or administrative decision and adults under legal protection.

Assignment of interventions

A computer-generated block-randomisation sequence will be performed by the statistician not involved in either screening the patients or assessing outcomes. Randomisation will be carried out using a secure web-based randomisation system with stratification by centre. The randomisation will be accessible to investigators through user identification and a personal password and will become effective following confirmation of inclusion and exclusion

criteria. Patients will be randomly assigned (1:1) to one of two study groups according to the antiseptic solution used to disinfect the skin before surgery and during all dressing changes (Fig. 1).

Interventions

- 1- *CHG group*: The surgical site will be largely disinfected using applicators of 2% CHG-70% isopropanol (ChloroPrep™, CareFusion). According to local practices, antiseptic application will be preceded (two-step procedure) or not (one-step procedure) by skin scrubbing with 4% CHG (Hibiscrub™, Molnlycke Health Care).
- 2- *PVI group*: The surgical site will be largely disinfected using sterile gauzes soaked with 5% PVI-69% ethanol (Bétadine alcoolique™, MEDA Pharma SAS). According to local practices, antiseptic application will be preceded (two-step procedure) or not (one-step procedure) by skin scrubbing with 4% PVI (Bétadine Scrub™, MEDA Pharma SAS).

In order to ensure respect of treatment group and to achieve traceability, individual boxes containing all disinfecting products required for disinfecting the skin before surgery and during patients' care will be supplied. According to randomisation, each patient will have his own box, which will follow him from the operating room to hospital discharge.

The following care will be applied to all patients and controlled throughout the duration of the study:

- At least one total body shower during the 24 h preceding surgery, using either plain soap or antiseptic soap
- Hair removal if required with clipper (no shaving) before surgery
- Antibiotic prophylaxis according to local protocol applied 30 min prior to incision, and with appropriate reinjection if required for prolonged surgery
- Antiseptic application by moving back and forth for at least 30 s, starting at the incision site and then extending to the entire work area. According to local practices, the antiseptic solution will be applied once or twice, preceded or not by skin scrubbing with an antiseptic soap.
- Application of large sterile drapes once the work area will be dry.

Study outcomes

Primary endpoint

The primary outcome will be the proportion of patients undergoing either any re-sternotomy occurring between Day 0 and Day 90 after surgery or any reoperation on saphen venous site occurring between Day 0 and Day 30 after surgery or both.

Secondary endpoints

- Proportion of patients with mediastinitis according to the Center for Disease Control and Prevention (CDC) criteria [16] occurring by Day 90 after surgery and pathogens involved.
- Proportion of patients with deep incisional SSI at saphen venous site, superficial incisional SSI at sternal or saphen venous sites according to the CDC criteria [16] occurring by Day 30 after surgery and pathogens involved.
- Proportion of patients with sternal wound infection (SWI) requiring reoperation, occurring by Day 90.
- Proportion of patients with SSI at saphen venous site requiring reoperation, occurring by Day 30.

- Proportion of patients with unexpected need for readmission to intensive care unit (ICU) or re-hospitalisation.
- Duration of ICU stay.
- Duration of stay under mechanical ventilation.
- Duration of hospital stay.
- Duration of rehabilitation unit stay.
- All-cause mortality at Day 90 of surgery.
- Proportion of patients with local and systemic side effects possibly linked to antiseptic use.

Two independent assessors masked to the antiseptic group and to the event will review all post-operative reports of patients needing re-sternotomy during the 90 days following surgery and/or reoperation on saphen venous site during the 30 days following surgery. They will classify the case-report as:

- SWI (mediastinitis or superficial sternal SSI)
- And/or deep or superficial saphen venous SSI
- Or no SSI according to CDC criteria

Disagreements between the two assessors will be resolved by consensus conference among all outcome assessors.

Data collection

Independent clinical research assistants will be available at each participating hospital to help with running the study and data collection. Study documents will be de-identified and stored for 15 years, as per the protocol for non-clinical trial notification (CTN) interventional studies. Data will be entered into the web-based eCRF (CSOnline, Clinsight) and electronically stored on double password-protected computers. Hard copies of data (clinical research files) will be stored in a secure locked office. All personnel involved in data analysis will be masked to study groups. Only the principal investigators and the statisticians will have access to the final data set. The following data will be recorded:

Baseline characteristics and preoperative data

Demographic data (age, gender, height, weight and body mass index); American Society of Anaesthesiologists physical status; EuroSCORE II; comorbidities (active smoking; insulin-dependent diabetes; non-insulin-dependent diabetes; hypertension; hypercholesterolaemia; chronic renal failure; COPD; history of cardiac surgery; atrial fibrillation; key laboratory findings; use of preoperative *Staphylococcus aureus* decontamination; hair removal and modality; number and type (soap with or without antiseptic) of preoperative shower.

Intraoperative data

Type of surgery of the heart (valve, coronary, combined surgery, other) or of the aorta; type of scheduling (elective, semi-elective or emergency); skin scrubbing before skin antisepsis; number of antiseptic applications; number of antiseptic products used; antibiotic prophylaxis: molecule, dose, timing and possible redosing; use of iodophor-impregnated incise drapes; number of internal thoracic arteries sampled; sampling of saphen vein and site; length of surgery (incision to closure); duration of cardiopulmonary bypass; minimal and maximal body temperature during surgery; volume infused during surgery and type; number and types of blood transfusion during surgery; type of vasopressor administered during surgery; use of mechanical cardiac support (extra-corporeal life support [ECLS] or intra-aortic balloon pump); adverse events (especially local and systemic side effects possibly linked to antiseptic use).

Postoperative data until hospital discharge

Type and number of blood product given during the 48h following surgery; type and length of vasopressor and/or inotropic drugs administered during the 48h following surgery; use of mechanic cardiac support (ECLS, intra-aortic balloon pump); atrial fibrillation episode; number and results of blood cultures; number, type and results of bacteriological sampling at surgical site; wound status at surgical site (until dressing withdrawal): local signs of infection (local incisional pain/tenderness, localized redness, heat or swelling, purulent drainage from the superficial incision, superficial/deep incision spontaneously or deliberately opened by the surgeon), status of dressing, date of dressing changes; physical examination (temperature, chest pain, sternal instability); antibiotics used (molecule, duration and indication); results of blood samples (standard lab values); duration of mechanical ventilation; length of stay in ICU, surgical ward and high dependency unit; date of hospital discharge; reoperation at sternal site or saphen venous site occurring after surgery (date and reason); SSI occurrence: type (superficial, deep, organ-space), site and date and hour of SSI diagnosis; adverse events (especially local and systemic side effects possibly linked to antiseptic use) and survival status (if the patient is deceased, date of death).

Postoperative data monthly after surgery (until 90 days following surgery)

Phone contact: date; SSI occurrence, date of diagnosis, site and type; planned or unplanned surgical consultation; need for hospital readmission: date, total duration of hospital stay; need for reoperation at sternal site (within 90 days following surgery) or at saphen venous site (within 30 days following surgery): date, reason; date of rehabilitation unit discharge and survival status (if the patient is deceased, date of death).

Safety

According to the French Public Health Code, all suspected unexpected serious adverse events will be reported to the Agence Nationale de Sécurité du Médicament (ANSM). Adverse events will be evaluated at each visit during clinical interview and physical examination. In agreement with ANSM, all serious adverse events related to heart disease (except infections) and not related to antiseptic use will not be to declare immediately but will be reported in the eCRF. Each serious adverse event will be described as completely as possible on the report form designed for this purpose. The initial report will be followed by complementary reports of relevant information as soon as possible.

Sample size calculation

Assuming a 6% reoperation rate in the PVI group, 1863 patients in each treatment arm will be required to demonstrate a 33% reduction of reoperation rate with the use of 2% CHG-70% isopropanol, with statistical risks at 5% and 20% for type I and type II errors, respectively. We are planning to enrol 4100 patients to take into account a maximum patient loss of 10%.

Statistical analysis

The data will be analysed blindly on an intention-to-treat basis. No interim analysis is planned. Demographic data will be described as number and percentage or median and IQR and compared with the χ^2 test or Mann-Whitney test, as appropriate. We will assess antiseptic efficacy with a marginal Cox model and adjusted for covariates that will be significantly imbalanced between groups. We will calculate hazard ratios (HR) and 95% CIs, as well as incidence density and Kaplan-Meier estimates. Proportions of each secondary endpoint assessed at day 30 and day 90 will be compared using similar principles. We will use chi-square tests. A multiple logistic regression will be computed in case of covariates imbalance

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3 between groups. All tests will be two-tailed, stratified by centre and unadjusted for multiple
4 comparisons. Analyses will be done with SAS version 9.4 and R softwares.

5 **ETHICS AND DISSEMINATION**

6 **Research ethics approval**

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8 The clinical trial will be carried out in line with the principles of the Declaration of Helsinki,
9 the guideline for Good Clinical Practice of the International Conference on Harmonization, in
10 accordance with the French law No. 2012-300 of 5 March 2012 on research involving the
11 human person and with the Clinical Trials Directives 2001/20/EC and 2005/28/EC of the
12 European Parliament. Ethical aspects of this research project have been approved by the
13 ethics committee of Ambroise Paré Hospital (CPP Ile de France VIII, Boulogne-Billancourt,
14 France). The CLEAN 2 trial is registered at the European Clinical Trials Database (EudraCT
15 #2017-005169-33) and summarised at ClinicalTrials.gov with the trial identification number
16 NCT03560193.
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19 **Consent**

20 Written informed consent will be requested for each patient prior to enrolment. The
21 investigators will provide clear and precise information about the protocol to the patient
22 before requesting him/her for written informed consent.
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24 **Confidentiality**

25 People with direct access to the data will take all necessary precautions to maintain
26 confidentiality. All data collected during the study will be rendered anonymous. Only initials
27 and inclusion number will be registered.
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29 **Dissemination policy**

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31 The results of the study will be released to the participating physicians, referring physicians
32 and medical community no later than one year after completion of the trial through
33 presentation at scientific conferences and publication in peer-reviewed journals.
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35 The main manuscript will mention the name of the sponsor and all trial sites will be
36 acknowledged. All investigators having included or followed participants in the study will
37 appear with their names under “the CLEAN 2 investigators” in an appendix to the final
38 manuscript. Authorship will be done in accordance with the guidelines of the International
39 Committee of Medical Journal.
40

41 **Funding statement**

42 This work is being funded by unrestricted research grants from the French Ministry of Social
43 Affairs and Health (#16-0619) and CareFusion/ Becton Dickinson. Funders will have no role
44 in the trial initiation, study design, choice of antiseptic products, data collection, data analysis,
45 data interpretation or writing of the report.
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49 **DISCUSSION**

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51 This study will provide new knowledge in the field of SSI prevention, addressing questions
52 raised by the Cochrane review on preoperative skin antiseptics aimed at preventing surgical
53 wound infections after clean surgery.[17] In clean surgery, the majority of pathogens
54 responsible for infectious complications come from the skin and skin disinfection has the
55 potential to reduce both the frequency and severity of SSI in proportion to the efficacy of
56 disinfection. The choice of cardiac surgery is based on the severity of SSI with this surgery,
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3 especially mediastinitis, which frequently requires reoperation. We selected centres with
4 experience in SSI prevention studies and already applying all the other SSI prevention
5 measures recommended by our national guidelines. Their number is limited so as to ensure
6 high quality of follow-up by independent clinical research assistants. Stratified randomisation
7 will protect against bias linked to potential variability in surgical practices between centres.
8 Individual boxes containing allocated disinfecting products will follow the patient from the
9 operating room to hospital discharge to ensure respect of treatment group and to facilitate
10 product traceability. The choice of reoperation as the main endpoint is not subject to
11 evaluation bias in an open study.
12

13 Our study will have several limitations. First, masking will not be feasible, because the two
14 antiseptic solutions differ in both colour and formulation. However, the microbiologists who
15 will perform all microbiological cultures will be unaware of treatment allocation. More
16 importantly, all cases of suspected SSI will be reviewed by masked independent assessors
17 based on internationally accepted definitions.[16] Second, the two antiseptic solutions contain
18 different alcoholic components and use different application methods. However, these
19 products will be used in their commercially available formulations in France and as
20 recommended by our national guidelines. Further studies will be necessary to determine the
21 more efficient type and concentration of alcohol to be combined with CHG or PVI as well as
22 the optimal concentration of CHG and PVI and optimal method for antiseptic application.
23 Third, we choose incidence of reoperation as the primary endpoint. They can be due to non-
24 infectious causes such as postoperative bleeding, valve-dysfunction etc., for which the impact
25 of skin disinfection is probably low. However, their main advantage is to be a strong
26 unquestionable endpoint not subject to assessment bias in an open trial. Fourth, adherence
27 to the study protocol will not be regularly checked by formal audits. However, the health-care
28 providers will attend training sessions designed to homogenise skin preparation practices
29 across hospitals before starting the study and independent clinical research assistants will be
30 available at each participating hospital to monitor the conduct of the trial. Moreover, all study
31 centres will be required to follow French recommendations similar to CDC recommendations
32 for prevention of SSI with no modification allowed during the study period.
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34

35 We will conduct the first large scale randomised trial adequately powered to compare the
36 efficacy and safety of CHX-alcohol over PVI-alcohol in reducing SSI after clean surgery.
37 Reducing SSI after surgery is associated with decreased length of hospital stay, mortality and
38 overall costs and increased patient satisfaction,[4] which should benefit both the patient and
39 the community. The trial is multicentre and almost all eligible patients will be included and
40 will benefit from all the measures recommended by our national guidelines (similar to CDC
41 guidelines) to prevent SSI. As a result, our finding will be reasonably extended to other
42 cardiac surgery centres, to other clean surgeries and, more generally, to all surgical
43 procedures performed worldwide, even if the proportion of skin pathogens involved in SSI is
44 lower than in clean surgery.
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47 **Trial status**

48 The current protocol is version 3.0. The trial is currently in the phase of trial tool development
49 and the opening of centres.
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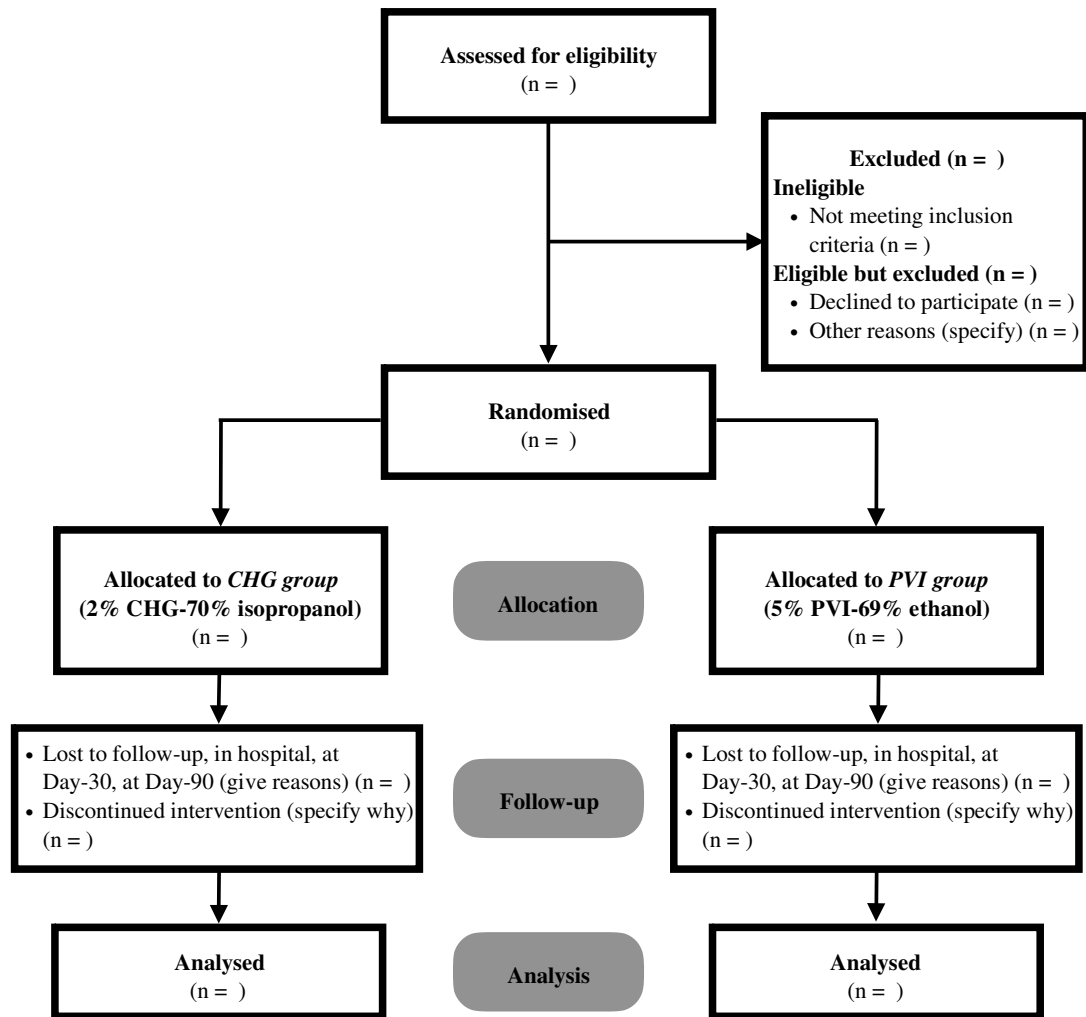
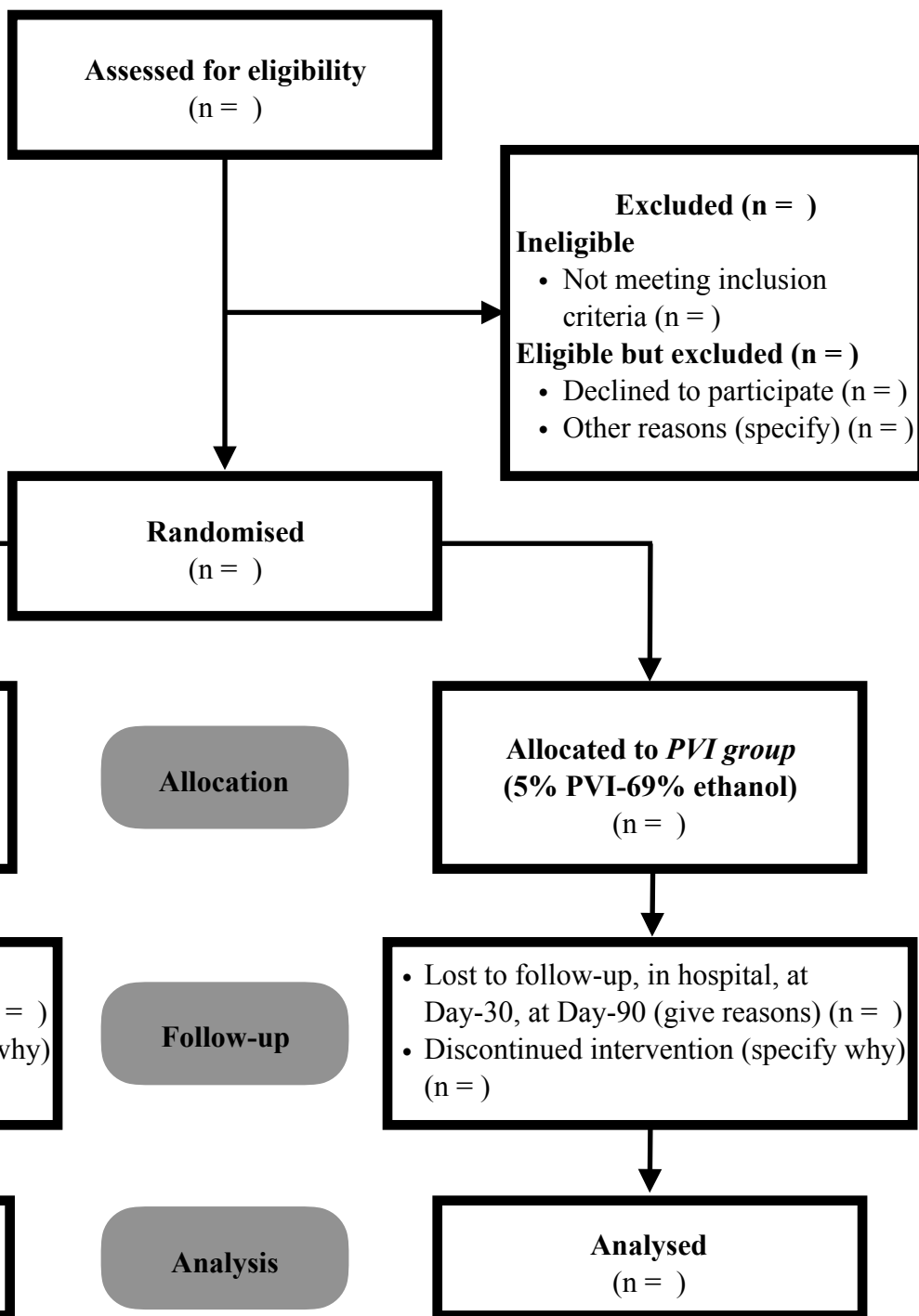


Figure 1. CONSORT diagram (CHG: chlorhexidine, PVI: povidone iodine)

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BMJ Open

Multicentre, open label, randomised, controlled clinical trial comparing 2% chlorhexidine – 70% isopropanol and 5% povidone iodine – 69% ethanol for skin antisepsis in reducing surgical-site infection after cardiac surgery: the CLEAN 2 study protocol

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SCHOLARONE™
Manuscripts

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3 **1 Multicentre, open label, randomised, controlled clinical trial comparing 2%**
4 **2 chlorhexidine – 70% isopropanol and 5% povidone iodine – 69% ethanol for skin**
5 **3 antiseptics in reducing surgical-site infection after cardiac surgery: the CLEAN 2 study**
6 **4 protocol**

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96 ABSTRACT

97 **Introduction:** Surgical site infection (SSI) is the second most frequent cause of healthcare-
98 associated infection worldwide and is associated with increased morbidity, mortality and
99 healthcare costs. Cardiac surgery is clean surgery with low incidence of SSI, ranging from 2
100 to 5%, but with potentially severe consequences.

101 Perioperative skin antisepsis with an alcohol-based antiseptic solution is recommended to
102 prevent SSI, but the superiority of chlorhexidine (CHG)-alcohol over povidone iodine (PVI)-
103 alcohol, the two most common alcohol-based antiseptic solutions used worldwide, is
104 controversial. We aim to evaluate whether 2% CHG-70% isopropanol is more effective than
105 5% PVI-69% ethanol in reducing the incidence of reoperation after cardiac surgery.

106 **Methods and analysis:** The CLEAN 2 study is a multicentre, open label, randomised,
107 controlled clinical trial of 4100 patients undergoing cardiac surgery. Patients will be
108 randomised in 1:1 ratio to receive either 2% CHG – 70% isopropanol or 5% PVI – 69%
109 ethanol for perioperative skin preparation. The primary endpoint is the proportion of patients
110 undergoing any re-sternotomy between Day 0 and Day 90 after initial surgery and/or any
111 reoperation on saphen venous/radial artery surgical site between Day 0 and Day 30 after
112 initial surgery. Data will be analysed on the intention-to-treat principle.

113 **Ethics and dissemination:** This protocol has been approved by an independent ethics
114 committee and will be carried out according to the principles of the Declaration of Helsinki
115 and the Good Clinical Practice guidelines. The results of this study will be disseminated
116 through presentation at scientific conferences and publication in peer-reviewed journals.

117 **Trial registration:** EudraCT 2017-005169-33 & NCT03560193.

118

119 STRENGTHS AND LIMITATIONS OF THIS STUDY

120 • This randomised study is aimed at being the largest one performed comparing the
121 efficacy of perioperative skin preparation with either alcohol-based CHG or alcohol-based
122 PVI in reducing severe postoperative complications.

123 • The primary endpoint, the incidence of any reoperation at both surgical sites, is a
124 predefined strong and unquestionable criterion, underscoring the need – and the risk of bias –
125 to assess the reality of SSI.

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3 126 • Limitations due to the lack of masking related to the nature of the intervention will be
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5 127 reduced by assessment of all SSIs by an adjudication committee masked to the antiseptic
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7 128 group.
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For peer review only

130 INTRODUCTION

131 Surgical site infection (SSI) is the second most frequent cause of healthcare-associated
132 infections with an incidence up to 19% depending of the type of surgery, and ranges from
133 simple wound discharge to life-threatening condition. [1–3] It is associated with increased
134 hospital stay, prolonged antibiotic use and occasional need for reoperation, and is responsible
135 for rising mortality and healthcare costs estimated at € 10 billion per year in the USA. [4]

136 Cardiac surgery is considered as clean surgery. Incidence of SSI is lower than with other
137 types of surgery, ranging from 2 to 5% depending on the definitions used, but its
138 consequences may be greater in terms of both frequency and severity. [5,6] Because
139 pathogens involved in SSI after clean surgery come mostly from skin, perioperative skin
140 antiseptics plays a major role in SSI prevention.

141 The most common antiseptic agents used for skin disinfection before surgery are aqueous or
142 alcoholic formulations of chlorhexidine (CHG) or povidone iodine (PVI), both of which are
143 available at various concentrations. Several studies have compared their respective efficacy
144 and safety in reducing SSI. Nevertheless, results have been contradictory, probably due to
145 different comparators (concentrations, combination with alcohol or water...), different SSI
146 definitions, and different lengths of follow-up.[7–11] In 2010, a meta-analysis of seven
147 randomised-controlled trials (including 3437 patients) compared CHG (at a concentration of
148 0.5 to 4%) with PVI or other iodophors (at a concentration of 7 to 10%) for preoperative skin
149 antiseptics in clean and clean-contaminated surgery.[12] The use of CHG was associated with
150 fewer SSIs (adjusted RR 0.64; 95%CI 0.51-0.80) compared with iodine. Another meta-
151 analysis of six randomised-controlled trials comparing CHG (at a concentration of 0.5 to 4%)
152 to PVI (at a concentration of 7.5 to 10%) for preoperative skin antiseptics yielded similar
153 findings [OR of 0.68 (0.50-0.94; p=0.019)].[13] However, in most studies CHG was
154 combined with alcohol and PVI was not, which meant that two antiseptics were being
155 compared to only one. A review conducted in 2012 was unable to draw any conclusion about
156 which surgical site antiseptic more effectively reduces SSI.[14] Recently, Tuuli and
157 colleagues were the first to conduct a large trial comparing CHG and PVI in alcoholic
158 formulations for skin disinfection before caesarean section.[9] Interestingly, both antiseptic
159 formulations used the same alcohol at the same concentration and both were applied similarly,
160 using an applicator. Although this was the first study demonstrating a benefit of 2% CHG-
161 70% isopropanol over 8.3% PVI-70% isopropanol, it was monocentre, and did not address all
162 potential methodological limits. Especially, the choice of superficial or deep surgical-site

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3 163 infection as primary endpoint assessed by the surgeon (the diagnosis was made by the treating
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5 164 physician and verified through chart review by the principal investigator, who was unaware of
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7 165 the study-group assignments) may generate interpretation biases in an open study. Moreover,
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9 166 the one dual microbial source of pathogens of both skin and vaginal origins in SSI after
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11 167 caesarean delivery and immune modulation in pregnancy raises questions about whether the
12
13 168 results of trials of preoperative skin antisepsis for caesarean delivery can be extrapolated to
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15 169 other surgical procedures.

16 170 Furthermore, the possible superiority of CHG over PVI was not confirmed in a second
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18 171 monocentre trial involving 1404 women requiring caesarean section.[8] Lastly, in a third
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20 172 assessor-blinded, monocentre, randomised trial involving 802 patients scheduled for elective
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22 173 clean-contaminated colorectal surgery, the use of PVI-alcohol failed to meet the criterion for
23
24 174 non-inferiority in SSI occurrence compared with CHG-alcohol.[11] These contradictory
25
26 175 results may explain the lack of universal use of CHG-alcohol for skin antisepsis in surgery
27
28 176 despite the recommendations of the World Health Organization (WHO).[15]

29 177 The prevalence and potential serious consequences of SSI in cardiac surgery, especially
30
31 178 mediastinitis, support a large randomised controlled trial in this setting. We hypothesize that
32
33 179 perioperative skin preparation with 2% CHG-70% isopropanol is more effective than 5%
34
35 180 PVI-69% ethanol as a means of preventing any reoperation after cardiac surgery.

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37 182 **METHODS AND ANALYSIS**

38 183 **Trial design and setting**

39
40 184 The CLEAN 2 trial is an investigator-initiated, publicly-funded multicentre, randomised,
41
42 185 controlled, open-label clinical trial with concealed allocation of patients scheduled to undergo
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44 186 cardiac surgery and to receive 1:1 either 2% CHG – 70% isopropanol or 5% PVI– 69%
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46 187 ethanol for perioperative skin preparation. Randomisation will be carried out through a secure
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48 188 web-based randomisation system and stratified by centre (Fig. 1).

49
50 189 The trial will take place at seven university and non-university French hospitals. All
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52 190 participating centres perform more than 500 cardiac surgical procedures per year.

53 191 **Participant eligibility and consent**

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55 192 During surgery or preoperative anaesthesia consultation, all consecutive patients will be
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57 193 considered candidates for inclusion in the study if they meet all of the inclusion criteria and
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3 194 none of the exclusion criteria. Eligible patients will receive oral and written information and
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5 195 will be enrolled after having given written consent.

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7 196 **Inclusion criteria**

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- 10 • Adult patients (age \geq 18 years) admitted in one of the participating centres
 - 11 198 • Scheduled to undergo surgery of the heart (valve, coronary or combined surgery) or of
 - 12 the aorta via median sternotomy
 - 13 199
 - 14 • Having signed informed consent form
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17 201 **Exclusion criteria**

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- 20 • Patients with known allergies to CHG, PVI, isopropanol or ethanol
 - 21 203 • Surgery for heart transplantation
 - 22 • Any signs of inflammation or sternal instability at the site of sternotomy or operation
 - 23 204 for infection (sternal wound infection or endocarditis)
 - 24 205
 - 25 • History of cardiac surgery within 3 months preceding enrolment
 - 26 206
 - 27 • Participation in another clinical trial aimed at reducing SSI
 - 28 207
 - 29 • Patients already enrolled in this study
 - 30 208
 - 31 • Pregnant or breastfeeding women and potentially childbearing women without
 - 32 209 effective contraception
 - 33 210
 - 34 • Patients not benefiting from a Social Security scheme or not benefiting from it through
 - 35 211 a third party
 - 36 212
 - 37 • Persons benefiting from enhanced protection, namely minors, persons deprived of
 - 38 213 their liberty by a judicial or administrative decision and adults under legal protection.
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42
43 215 **Assignment of interventions**

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45 216 A computer-generated block-randomisation sequence will be performed by a statistician not
46 217 involved in either screening the patients or assessing outcomes. Randomisation will be carried
47 218 out using a secure web-based randomisation system with stratification by centre. The
48 219 randomisation will be accessible to investigators through user identification and a personal
49 220 password and will become effective following confirmation of inclusion and exclusion
50 221 criteria. Patients will be randomly assigned (1:1) to one of two study groups according to the
51 222 antiseptic solution used to disinfect the skin before surgery and during all dressing changes
52 223 (Fig. 1). To avoid randomisation of a patient with cancelled surgery, this will be done a few
53 224 days before or on the day of surgery.

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225 **Interventions**

- 226 1- *CHG group*: The surgical site will be largely disinfected using applicators of 2%
227 CHG-70% isopropanol (Chloraprep™, CareFusion). According to local practices,
228 antiseptic application will be preceded (two-step procedure) or not (one-step
229 procedure) by skin scrubbing with 4% CHG (Hibiscrub™, Molnlycke Health Care).
- 230 2- *PVI group*: The surgical site will be largely disinfected using sterile gauzes soaked
231 with 5% PVI-69% ethanol (Bétadine alcoolique™, MEDA Pharma SAS). According
232 to local practices, antiseptic application will be preceded (two-step procedure) or not
233 (one-step procedure) by skin scrubbing with 4% PVI (Bétadine Scrub™, MEDA
234 Pharma SAS).

235 In order to ensure respect of treatment group and to achieve traceability, individual boxes
236 containing all disinfecting products required for disinfecting the skin before surgery and
237 during patient care will be supplied. According to randomisation, each patient will have his
238 own box, which will follow him from the operating room to hospital discharge.

239 The following care procedures will be applied to all patients and controlled throughout the
240 duration of the study:

- 241 • At least one total body shower during the 24 h preceding surgery, using either plain
242 soap or antiseptic soap
- 243 • Hair removal if required with clipper (no shaving) before surgery
- 244 • Antibiotic prophylaxis according to the French recommendations [16] applied 30 min
245 prior to incision, and with appropriate reinjection if required for prolonged surgery.
246 No re-administration during the postoperative period.
- 247 • Antiseptic application by moving back and forth for at least 30 s, starting at the
248 incision site and then extending to the entire work area. The surgical field extends
249 from the jaw to the shoulders and down to the tip of both feet in case of surgery with
250 harvesting of the saphenous vein. In the event of surgery without saphenous vein
251 harvesting, the field stops at the knees. According to local practices, the antiseptic
252 solution will be applied once or twice, preceded or not by skin scrubbing with an
253 antiseptic soap.
- 254 • Application of large sterile drapes once the work area is dry.

255 In each centre, before the beginning of the inclusion, a list of care policy for prevention of SSI
256 (*Staphylococcus aureus* decontamination, antimicrobial-coated sutures, adhesive incises

1
2
3 257 drapes with antiseptics, antimicrobial dressings...) will be established and will not be
4
5 258 modified throughout the duration of the study.

6
7 259 **Study outcomes**

8
9 260 *Primary endpoint*

10
11 261 The primary outcome will be the proportion of patients undergoing either any re-sternotomy
12
13 262 occurring between Day 0 and Day 90 after surgery or any reoperation on saphen venous/radial
14
15 263 artery site occurring between Day 0 and Day 30 after surgery or both.

16
17 264 *Secondary endpoints*

- 18
19 265
- 20 • Proportion of patients with mediastinitis according to the Center for Disease Control
21 and Prevention (CDC) criteria [17] occurring by Day 90 after surgery and pathogens
22 involved.
23 267
 - 24 • Proportion of patients with deep incisional SSI at saphen venous/radial artery site,
25 superficial incisional SSI at sternal or saphen venous/radial artery sites according to
26 the CDC criteria [17] occurring by Day 30 after surgery and the pathogens involved.
27 269
 - 28 • Proportion of patients with sternal wound infection (SWI) requiring reoperation,
29 occurring by Day 90.
30 271
 - 31 • Proportion of patients with SSI at saphen venous/radial artery site requiring
32 reoperation, occurring by Day 30.
33 273
 - 34 • Proportion of patients with unexpected need for readmission to intensive care unit
35 (ICU) or re-hospitalisation.
36 274
 - 37 • Duration of ICU stay.
38 275
 - 39 • Duration of stay under mechanical ventilation.
40 276
 - 41 • Duration of hospital stay.
42 277
 - 43 • Duration of rehabilitation unit stay.
44 278
 - 45 • All-cause mortality at Day 90 of surgery.
46 279
 - 47 • Proportion of patients with local and systemic side effects possibly linked to antiseptic
48 use.
49 280
 - 50 281
 - 51 282
 - 52 283

53 284 Two independent assessors masked to the antiseptic group and to the event will review all
54 post-operative reports of patients needing re-sternotomy during the 90 days following surgery
55 285 and/or reoperation on saphen venous/radial artery site during the 30 days following surgery.
56
57 286 They will classify the case-report as:
58
59 287
60

- 288 • SWI (mediastinitis or superficial sternal SSI)
- 289 • And/or deep or superficial saphen venous/radial artery SSI
- 290 • Or no SSI according to CDC criteria

291 Disagreements between the two assessors will be resolved by consensus conference among all
292 outcome assessors.

293 **Data collection**

294 Independent clinical research assistants will be available at each participating hospital to help
295 in running the study and with data collection. Study documents will be de-identified and
296 stored for 15 years, as per the protocol for non-clinical trial notification (CTN) interventional
297 studies. Data will be entered into the web-based eCRF (CSOnline, Clinsight) and
298 electronically stored on double password-protected computers. Hard copies of data (clinical
299 research files) will be stored in a secure locked office. All personnel involved in data analysis
300 will be masked to study groups. Only the principal investigators and the statisticians will have
301 access to the final data set. The following data will be recorded:

302 *Baseline characteristics and preoperative data*

303 Demographic data (age, gender, height, weight and body mass index); American Society of
304 Anaesthesiologists physical status; EuroSCORE II; comorbidities (active smoking; insulin-
305 dependent diabetes; non-insulin-dependent diabetes; hypertension; hypercholesterolaemia;
306 chronic renal failure; COPD; history of cardiac surgery; atrial fibrillation; key laboratory
307 findings; use of preoperative *Staphylococcus aureus* decontamination; hair removal and
308 modality; number and type (soap with or without antiseptic) of preoperative showers.

309 *Intraoperative data*

310 Type of surgery of the heart (valve, coronary, combined surgery, other) or of the aorta; type of
311 scheduling (elective, semi-elective or emergency); skin scrubbing before skin antiseptics;
312 number of antiseptic applications; number of antiseptic products used; antibiotic prophylaxis:
313 molecule, dose, timing and possible redosing; use of iodophor-impregnated incise drapes;
314 number of internal thoracic arteries sampled; sampling of saphen vein or radial artery, site
315 open or endoscopic; length of surgery (incision to closure); duration of cardiopulmonary
316 bypass; minimal and maximal body temperature during surgery; volume infused during
317 surgery and type; number and types of blood transfusion during surgery; type of vasopressor
318 administered during surgery; use of mechanical cardiac support (extra-corporeal life support

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2
3 319 [ECLS] or intra-aortic balloon pump); adverse events (especially local and systemic side
4 effects possibly linked to antiseptic use).
5 320

6
7 321 *Postoperative data until hospital discharge*

8
9 322 Type and number of blood products given during the 48h following surgery; type and length
10 323 of vasopressor and/or inotropic drugs administered during the 48h following surgery; use of
11 324 mechanical cardiac support (ECLS, intra-aortic balloon pump); atrial fibrillation episode;
12 325 number and results of blood cultures; number, type and results of bacteriological sampling at
13 326 surgical site; wound status at surgical site (until dressing withdrawal): local signs of infection
14 327 (local incisional pain/tenderness, localized redness, heat or swelling, purulent drainage from
15 328 the superficial incision, superficial/deep incision spontaneously or deliberately opened by the
16 329 surgeon), status of dressing, date of dressing changes; physical examination (temperature,
17 330 chest pain, sternal instability); antibiotics used (molecule, duration and indication); results of
18 331 blood samples (standard lab values); duration of mechanical ventilation; length of stay in
19 332 ICU, surgical ward and high dependency unit; date of hospital discharge; reoperation at
20 333 sternal site or saphen venous/radial artery site occurring after surgery (date and reason); SSI
21 334 occurrence: type (superficial, deep, organ-space), site and date and hour of SSI diagnosis;
22 335 adverse events (especially local and systemic side effects possibly linked to antiseptic use)
23 336 and survival status (if the patient is deceased, date of death).
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36 337 *Postoperative data monthly after surgery (until 90 days following surgery)*

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38 338 Phone contact: date; SSI occurrence, date of diagnosis, site and type; planned or unplanned
39 339 surgical consultation; need for hospital readmission: date, total duration of hospital stay; need
40 340 for reoperation at sternal site (within 90 days following surgery) or at saphen venous/radial
41 341 artery site (within 30 days following surgery): date, reason; date of rehabilitation unit
42 342 discharge and survival status (if the patient is deceased, date of death).
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47 343 **Safety**

48
49 344 According to the French Public Health Code, all suspected unexpected serious adverse events
50 345 will be reported to the Agence Nationale de Sécurité du Médicament (ANSM). Adverse
51 346 events will be evaluated at each visit during clinical interview and physical examination. In
52 347 agreement with ANSM, all serious adverse events related to heart disease (except infections)
53 348 and not related to antiseptic use will not be declared immediately but will be reported in the
54 349 eCRF. Each serious adverse event will be described as completely as possible on the report
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2
3 350 form designed for this purpose. The initial report will be followed by complementary reports
4
5 351 of relevant information as soon as possible.

6 7 352 **Sample size calculation**

8
9 353 Assuming a 6% reoperation rate in the PVI group,[6] 1863 patients in each treatment arm will
10
11 354 be required to demonstrate a 33% reduction of reoperation rate with the use of 2% CHG-70%
12
13 355 isopropanol, with statistical risks at 5% and 20% for type I and type II errors, respectively.
14
15 356 The sample size calculation is based on the two-sided test. We are planning to enrol 4100
16
17 357 patients to take into account a maximum patient loss of 10%.

18 358 **Statistical analysis**

19
20 359 The data will be analysed blindly on an intention-to-treat basis. No interim analysis is
21
22
23 360 planned. Demographic data will be described as number and percentage or median and IQR
24
25 361 and compared with the χ^2 test or Mann-Whitney test, as appropriate. For primary analysis,
26
27 362 incidence of reoperation between groups will be compared with χ^2 test. We will assess
28
29 363 antiseptic efficacy with a marginal Cox model and adjusted for covariates that will be
30
31 364 significantly imbalanced between groups. We will calculate hazard ratios (HR) and 95% CIs,
32
33 365 as well as incidence density and Kaplan-Meier estimates. Proportions of each secondary
34
35 366 endpoint assessed at day 30 and day 90 will be compared using similar principles. We will use
36
37 367 chi-square tests. A multiple logistic regression will be computed with covariates clinically
38
39 368 relevant as regard as our outcomes (*Centre; Patients' characteristics*: age, gender, body mass
40
41 369 index, EuroSCORE II, active smoking, insulin-dependent diabetes, use of preoperative
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43 370 *Staphylococcus aureus* decontamination; *Intraoperative data*: type of surgery of the heart
44
45 371 [valve, coronary, combined surgery, other] or of the aorta, type of scheduling [elective, semi-
46
47 372 elective or emergency], skin scrubbing before skin antiseptics; number of antiseptic
48
49 373 application, use of iodophor-impregnated incise drapes, number of internal thoracic arteries
50
51 374 sampled, length of surgery, duration of cardiopulmonary bypass, minimal body temperature
52
53 375 during surgery, volume infused during surgery, use of mechanic cardiac support) and with
54
55 376 covariates statistically relevant (covariates with difference between groups < 0.20 in the

1
2
3 377 univariate analysis). All tests will be two-tailed, stratified by centre and unadjusted for
4
5 378 multiple comparisons. Analyses will be done with SAS version 9.4 and R software.
6
7

8 379 **Patient and Public Involvement**

9
10 380 The ethical committee, composed of patients' representatives, considered if the research is
11 381 conformed to patients' priorities, experience and preferences. Each patient, admitted in a
12 382 participating centre, is screened and enrolled by the attending physicians according to the
13 383 protocol. The burden of the intervention is assessed by patients themselves. Each patient, after
14 384 the end of the study, will have the opportunity to obtain the results if they are interested, all
15 385 information is provided at inclusion in consent and information forms. No patient was
16 386 involved in the recruitment to and the conduct of the study.
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23 387 **ETHICS AND DISSEMINATION**

24 388 **Research ethics approval**

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26 389 The clinical trial will be carried out in line with the principles of the Declaration of Helsinki,
27 390 the guideline for Good Clinical Practice of the International Conference on Harmonization, in
28 391 accordance with the French law No. 2012-300 of 5 March 2012 on research involving the
29 392 human person and with the Clinical Trials Directives 2001/20/EC and 2005/28/EC of the
30 393 European Parliament. Ethical aspects of this research project have been approved by the
31 394 ethics committee of Ambroise Paré Hospital (CPP Ile de France VIII, Boulogne-Billancourt,
32 395 France). The CLEAN 2 trial is registered at the European Clinical Trial Database on 27
33 396 December 2017 (EudraCT #2017-005169-33) and summarised at ClinicalTrials.gov with the
34 397 trial identification number NCT03560193.
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44 398 **Consent**

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46 399 Written informed consent will be requested for each patient prior to enrolment. The
47 400 investigators will provide clear and precise information to the patient about the protocol
48 401 before asking him/her for written informed consent.
49
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51

52 402 **Confidentiality**

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54 403 People with direct access to the data will take all necessary precautions to maintain
55 404 confidentiality. All data collected during the study will be rendered anonymous. Only initials
56 405 and inclusion number will be registered.
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60 406 **Dissemination policy**

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3 407 The results of the study will be released to the participating physicians, referring physicians
4 and medical community no later than one year after completion of the trial through
5 408
6 409 presentation at scientific conferences and publication in peer-reviewed journals.

8
9 410 The main manuscript will mention the name of the sponsor and all trial sites will be
10 411 acknowledged. All investigators having included or followed participants in the study will
11 412 appear with their names under “the CLEAN 2 investigators” in an appendix to the final
12 413 manuscript. Authorship will be done in accordance with the guidelines of the International
13 414 Committee of Medical Journal. No professional writer will be used.

17 415 **DISCUSSION**

20 416 This study will provide new knowledge in the field of SSI prevention, addressing questions
21 417 raised by the Cochrane review on preoperative skin antiseptics aimed at preventing surgical
22 418 wound infections after clean surgery.[18] In clean surgery, the majority of pathogens
23 419 responsible for infectious complications come from the skin and skin disinfection has the
24 420 potential to reduce both the frequency and severity of SSI in proportion to the efficacy of
25 421 disinfection. The choice of cardiac surgery is based on the severity of SSI with this surgery,
26 422 especially mediastinitis, which frequently requires reoperation. We selected centres with
27 423 experience in SSI prevention studies and already applying all the other SSI prevention
28 424 measures recommended by our national guidelines. Their number is limited so as to ensure
29 425 high quality of follow-up by independent clinical research assistants. Stratified randomisation
30 426 will protect against bias linked to potential variability in surgical practices between centres.
31 427 Individual boxes containing allocated disinfecting products will follow the patient from the
32 428 operating room to hospital discharge to ensure respect of treatment group and to facilitate
33 429 product traceability. The choice of reoperation as the main endpoint is not subject to
34 430 evaluation bias in an open study.

36 431 Our study will have several limitations. First, masking will not be feasible, because the two
37 432 antiseptic solutions differ in both colour and formulation. However, the microbiologists who
38 433 will perform all microbiological cultures will be unaware of treatment allocation. More
39 434 importantly, all cases of suspected SSI will be reviewed by masked independent assessors
40 435 based on internationally accepted definitions.[17] Second, the two antiseptic solutions contain
41 436 different alcoholic components and use different application methods. However, these
42 437 products will be used in their commercially available formulations in France and as
43 438 recommended by our national guidelines. Further studies will be necessary to determine the

1
2
3 439 more efficient type and concentration of alcohol to be combined with CHG or PVI as well as
4 440 the optimal concentration of CHG and PVI and optimal method for antiseptic application.
5
6 441 Third, we have chosen incidence of reoperation as the primary endpoint. They can be due to
7
8 442 non-infectious causes such as postoperative bleeding, valve-dysfunction etc..., for which the
9
10 443 impact of skin disinfection is probably low. However, their main advantage is to be a strong
11
12 444 unquestionable endpoint not subject to assessment bias in an open trial. Fourth, adherence to
13
14 445 the study protocol will not be regularly checked by formal audits. However, the health-care
15
16 446 providers will attend training sessions designed to homogenise skin preparation practices
17
18 447 across hospitals before starting the study and independent clinical research assistants will be
19
20 448 available at each participating hospital to monitor the conduct of the trial. Moreover, all study
21
22 449 centres will be required to follow French recommendations similar to CDC recommendations
23
24 450 for prevention of SSI with no modification allowed during the study period.

24 451 We will conduct the first large scale randomised trial adequately powered to compare the
25
26 452 efficacy and safety of CHX-alcohol over PVI-alcohol in reducing SSI after clean surgery.
27
28 453 Reducing SSI after surgery is associated with decreased length of hospital stay, mortality and
29
30 454 overall costs and increased patient satisfaction,[4] which should benefit both the patient and
31
32 455 the community. The trial is multicentre and almost all eligible patients will be included and
33
34 456 will benefit from all the measures recommended by our national guidelines (similar to CDC
35
36 457 guidelines) to prevent SSI. As a result, our findings will be reasonably extended to other
37
38 458 cardiac surgery centres, to other clean surgeries and, more generally, to all surgical
39
40 459 procedures performed worldwide, even if the proportion of skin pathogens involved in SSI is
41
42 460 lower than in clean surgery.

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43 44 462 **Trial status**

45
46 463 The current protocol is version 3.0 dated 12 September 2018. The trial is currently recruiting
47
48 464 patients. The inclusion process started on 17 September 2018 and the number of patients
49
50 465 included to date (22 January 2019) is 218. The estimated length of inclusion time is 18
51
52 466 months.

53
54 467

55 56 468 **CONTRIBUTOR SHIP STATEMENT**

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2
3 469 MB and OM conceived the study, coordinated its design, wrote the manuscript and drafted the
4 manuscript. PC, TK, LC, MD, PD, VE, EF, LL, DL, PL, NN, JYN, AO, JCR, BR, SR, JCL
5 470 and JFT read and were involved in critical appraisal and revision of the manuscript. SR and
6 471 JFT provided statistical expertise. All authors approved the final manuscript prior to
7 472 submission.
8 473

11 12 474 **COMPETING INTERESTS**

13
14
15 475 OM has received grant support from 3M and Carefusion-BD and honoraria for giving lectures
16 476 from 3M and Carefusion-BD.

17 18 19 477 **FUNDING**

20
21 478 This work is being funded by unrestricted research grants from the French Ministry of Social
22 479 Affairs and Health (#16-0619) and CareFusion/ Becton Dickinson. Funders will have no role
23 480 in the trial initiation, study design, choice of antiseptic products, data collection, data analysis,
24 481 data interpretation or writing of the report.

25 26 27 482 **DATA SHARING STATEMENT**

28
29 483 University Hospital of Poitiers is responsible for obtaining the agreement of all parties
30 484 involved in the study so as to guarantee direct access to all study sites, source data, source
31 485 documents, and reports.

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546 Figure 1. CONSORT diagram (CHG: chlorhexidine, PVI: povidone iodine)

For peer review only

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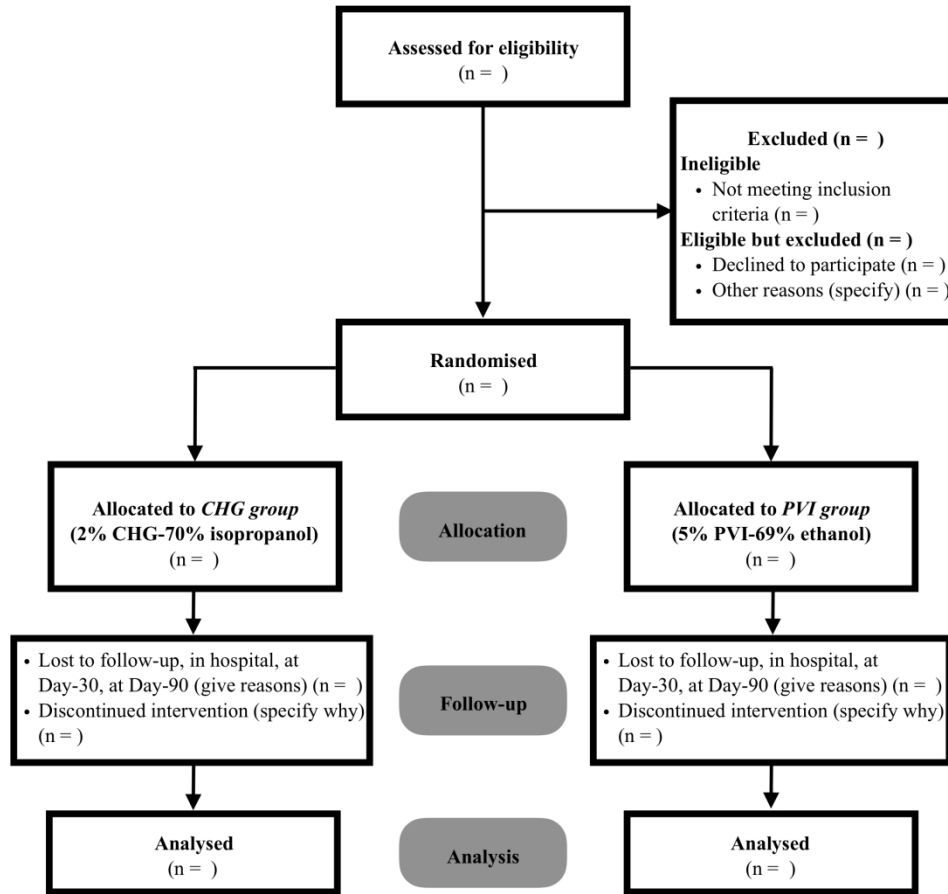


Figure 1. CONSORT diagram (CHG: chlorhexidine, PVI: povidone iodine)

209x209mm (300 x 300 DPI)



STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	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	4 & 13
	2b	All items from the World Health Organization Trial Registration Data Set	1, 3, 4, 7, 8, 9, 10, 12, 13, 14, 16
Protocol version	3	Date and version identifier	16
Funding	4	Sources and types of financial, material, and other support	17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 2, 3, 17
	5b	Name and contact information for the trial sponsor	3
	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	17
	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)	10
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	6
	6b	Explanation for choice of comparators	6, 7
Objectives	7	Specific objectives or hypotheses	7

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2	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, noninferiority, exploratory)	7
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7				
8	Methods: Participants, interventions, and outcomes			
9				
10	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
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15	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
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21	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9
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26		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)	n/a
27				
28				
29				
30				
31		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9, 11
32				
33				
34				
35				
36		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
37				
38				
39	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	10
40				
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47				
48	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)	9, 16
49				
50				
51				
52				
53				
54	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	13
55				
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60				

1
2 Recruitment 15 Strategies for achieving adequate participant enrolment to 7, 11
3 reach target sample size
4

5 **Methods: Assignment of interventions (for controlled trials)**
6

7 Allocation:

8
9 Sequence 16a Method of generating the allocation sequence (eg, 8
10 generation computer-generated random numbers), and list of any
11 factors for stratification. To reduce predictability of a
12 random sequence, details of any planned restriction (eg,
13 blocking) should be provided in a separate document that
14 is unavailable to those who enrol participants or assign
15 interventions
16
17

18 Allocation 16b Mechanism of implementing the allocation sequence (eg, 8
19 concealment central telephone; sequentially numbered, opaque, sealed
20 mechanism envelopes), describing any steps to conceal the sequence
21 until interventions are assigned
22
23

24 Implementation 16c Who will generate the allocation sequence, who will enrol 8
25 participants, and who will assign participants to
26 interventions
27

28 Blinding 17a Who will be blinded after assignment to interventions (eg, 10, 11, 13
29 (masking) trial participants, care providers, outcome assessors, data
30 analysts), and how
31
32

33 17b If blinded, circumstances under which unblinding is n/a
34 permissible, and procedure for revealing a participant's
35 allocated intervention during the trial
36

37 **Methods: Data collection, management, and analysis**
38

39 Data collection 18a Plans for assessment and collection of outcome, baseline, 11, 12
40 methods and other trial data, including any related processes to
41 promote data quality (eg, duplicate measurements,
42 training of assessors) and a description of study
43 instruments (eg, questionnaires, laboratory tests) along
44 with their reliability and validity, if known. Reference to
45 where data collection forms can be found, if not in the
46 protocol
47
48
49

50 18b Plans to promote participant retention and complete 9, 10, 11, 12
51 follow-up, including list of any outcome data to be
52 collected for participants who discontinue or deviate from
53 intervention protocols
54
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1				
2	Data	19	Plans for data entry, coding, security, and storage,	11
3	management		including any related processes to promote data quality	
4			(eg, double data entry; range checks for data values).	
5			Reference to where details of data management	
6			procedures can be found, if not in the protocol	
7				
8				
9	Statistical	20a	Statistical methods for analysing primary and secondary	13
10	methods		outcomes. Reference to where other details of the	
11			statistical analysis plan can be found, if not in the protocol	
12				
13		20b	Methods for any additional analyses (eg, subgroup and	13
14			adjusted analyses)	
15				
16		20c	Definition of analysis population relating to protocol non-	n/a
17			adherence (eg, as randomised analysis), and any	
18			statistical methods to handle missing data (eg, multiple	
19			imputation)	
20				
21				
22	Methods: Monitoring			
23				
24	Data monitoring	21a	Composition of data monitoring committee (DMC);	n/a
25			summary of its role and reporting structure; statement of	
26			whether it is independent from the sponsor and competing	
27			interests; and reference to where further details about its	
28			charter can be found, if not in the protocol. Alternatively,	
29			an explanation of why a DMC is not needed	
30				
31				
32		21b	Description of any interim analyses and stopping	n/a
33			guidelines, including who will have access to these interim	
34			results and make the final decision to terminate the trial	
35				
36				
37	Harms	22	Plans for collecting, assessing, reporting, and managing	11, 12
38			solicited and spontaneously reported adverse events and	
39			other unintended effects of trial interventions or trial	
40			conduct	
41				
42				
43	Auditing	23	Frequency and procedures for auditing trial conduct, if	n/a
44			any, and whether the process will be independent from	
45			investigators and the sponsor	
46				
47	Ethics and dissemination			
48				
49	Research ethics	24	Plans for seeking research ethics committee/institutional	14
50	approval		review board (REC/IRB) approval	
51				
52	Protocol	25	Plans for communicating important protocol modifications	15
53	amendments		(eg, changes to eligibility criteria, outcomes, analyses) to	
54			relevant parties (eg, investigators, REC/IRBs, trial	
55			participants, trial registries, journals, regulators)	
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2	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
3			7, 8, 14
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6		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
7			n/a
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9			
10	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
11			11, 12, 13, 17
12			
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16	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site
17			17
18			
19	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
20			11, 13, 17
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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 participation
25			n/a
26			
27			
28	Dissemination policy	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
29			15
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35		31b	Authorship eligibility guidelines and any intended use of professional writers
36			15
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39		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
40			n/a
41			
42	Appendices		
43			
44	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
45			n/a
46			
47	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
48			n/a
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*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

BMJ Open

Multicentre, open label, randomised, controlled clinical trial comparing 2% chlorhexidine – 70% isopropanol and 5% povidone iodine – 69% ethanol for skin antisepsis in reducing surgical-site infection after cardiac surgery: the CLEAN 2 study protocol

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Secondary Subject Heading :	Infectious diseases, Anaesthesia
Keywords :	Surgical site infection, skin antiseptis, Cardiac surgery < SURGERY, chlorhexidine, povidone iodine

SCHOLARONE™
Manuscripts

1
2
3 **1 Multicentre, open label, randomised, controlled clinical trial comparing 2%**
4 **2 chlorhexidine – 70% isopropanol and 5% povidone iodine – 69% ethanol for skin**
5 **3 antiseptics in reducing surgical-site infection after cardiac surgery: the CLEAN 2 study**
6 **4 protocol**

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22 91 **WORD COUNT**

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25 93 **KEYWORDS**

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27 94 Surgical site infection, skin antisepsis, cardiac surgery, chlorhexidine, povidone iodine
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96 ABSTRACT

97 **Introduction:** Surgical site infection (SSI) is the second most frequent cause of healthcare-
98 associated infection worldwide and is associated with increased morbidity, mortality and
99 healthcare costs. Cardiac surgery is clean surgery with low incidence of SSI, ranging from 2
100 to 5%, but with potentially severe consequences.

101 Perioperative skin antisepsis with an alcohol-based antiseptic solution is recommended to
102 prevent SSI, but the superiority of chlorhexidine (CHG)-alcohol over povidone iodine (PVI)-
103 alcohol, the two most common alcohol-based antiseptic solutions used worldwide, is
104 controversial. We aim to evaluate whether 2% CHG-70% isopropanol is more effective than
105 5% PVI-69% ethanol in reducing the incidence of reoperation after cardiac surgery.

106 **Methods and analysis:** The CLEAN 2 study is a multicentre, open label, randomised,
107 controlled clinical trial of 4100 patients undergoing cardiac surgery. Patients will be
108 randomised in 1:1 ratio to receive either 2% CHG – 70% isopropanol or 5% PVI – 69%
109 ethanol for perioperative skin preparation. The primary endpoint is the proportion of patients
110 undergoing any re-sternotomy between Day 0 and Day 90 after initial surgery and/or any
111 reoperation on saphenous vein/radial artery surgical site between Day 0 and Day 30 after
112 initial surgery. Data will be analysed on the intention-to-treat principle.

113 **Ethics and dissemination:** This protocol has been approved by an independent ethics
114 committee and will be carried out according to the principles of the Declaration of Helsinki
115 and the Good Clinical Practice guidelines. The results of this study will be disseminated
116 through presentation at scientific conferences and publication in peer-reviewed journals.

117 **Trial registration:** EudraCT 2017-005169-33 & NCT03560193.

118

119 STRENGTHS AND LIMITATIONS OF THIS STUDY

120 • This randomised study is aimed at being the largest one performed comparing the
121 efficacy of perioperative skin preparation with either alcohol-based CHG or alcohol-based
122 PVI in reducing severe postoperative complications.

123 • The primary endpoint, the incidence of any reoperation at both surgical sites, is a
124 predefined strong and unquestionable criterion, underscoring the need – and the risk of bias –
125 to assess the reality of SSI.

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3 126 • Limitations due to the lack of masking related to the nature of the intervention will be
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5 127 reduced by assessment of all SSIs by an adjudication committee masked to the antiseptic
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7 128 group.
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For peer review only

130 INTRODUCTION

131 Surgical site infection (SSI) is the second most frequent cause of healthcare-associated
132 infections with an incidence up to 19% depending of the type of surgery, and ranges from
133 simple wound discharge to life-threatening condition.[1–3] It is associated with increased
134 hospital stay, prolonged antibiotic use and occasional need for reoperation, and is responsible
135 for rising mortality and healthcare costs estimated at € 10 billion per year in the USA. [4]

136 Cardiac surgery is considered as clean surgery. Incidence of SSI is lower than with other
137 types of surgery, ranging from 2 to 5% depending on the definitions used, but its
138 consequences may be greater in terms of both frequency and severity.[5,6] Because pathogens
139 involved in SSI after clean surgery come mostly from skin, perioperative skin antisepsis plays
140 a major role in SSI prevention.

141 The most common antiseptic agents used for skin disinfection before surgery are aqueous or
142 alcoholic formulations of chlorhexidine (CHG) or povidone iodine (PVI), both of which are
143 available at various concentrations. Several studies have compared their respective efficacy
144 and safety in reducing SSI. Nevertheless, results have been contradictory, probably due to
145 different comparators (concentrations, combination with alcohol or water...), different SSI
146 definitions, and different lengths of follow-up.[7–11] In 2010, a meta-analysis of seven
147 randomised-controlled trials (including 3437 patients) compared CHG (at a concentration of
148 0.5 to 4%) with PVI or other iodophors (at a concentration of 7 to 10%) for preoperative skin
149 antisepsis in clean and clean-contaminated surgery.[12] The use of CHG was associated with
150 fewer SSIs (adjusted RR 0.64; 95%CI 0.51-0.80) compared with iodine. Another meta-
151 analysis of six randomised-controlled trials comparing CHG (at a concentration of 0.5 to 4%)
152 to PVI (at a concentration of 7.5 to 10%) for preoperative skin antisepsis yielded similar
153 findings [OR of 0.68 (0.50-0.94; p=0.019)].[13] However, in most studies CHG was
154 combined with alcohol and PVI was not, which meant that two antiseptics were being
155 compared to only one. A review conducted in 2012 was unable to draw any conclusion about
156 which surgical site antiseptic more effectively reduces SSI.[14] Recently, Tuuli and
157 colleagues were the first to conduct a large trial comparing CHG and PVI in alcoholic
158 formulations for skin disinfection before caesarean section.[9] Interestingly, both antiseptic
159 formulations used the same alcohol at the same concentration and both were applied similarly,
160 using an applicator. Although this was the first study demonstrating a benefit of 2% CHG-
161 70% isopropanol over 8.3% PVI-70% isopropanol, it was monocentre, and did not address all
162 potential methodological limits. Especially, the choice of superficial or deep surgical-site

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3 163 infection as primary endpoint assessed by the surgeon (the diagnosis was made by the treating
4 164 physician and verified through chart review by the principal investigator, who was unaware of
5 165 the study-group assignments) may generate interpretation biases in an open study. Moreover,
6 166 the one dual microbial source of pathogens of both skin and vaginal origins in SSI after
7 167 caesarean delivery and immune modulation in pregnancy raises questions about whether the
8 168 results of trials of preoperative skin antisepsis for caesarean delivery can be extrapolated to
9 169 other surgical procedures.

10 170 Furthermore, the possible superiority of CHG over PVI was not confirmed in a second
11 171 monocentre trial involving 1404 women requiring caesarean section.[8] Lastly, in a third
12 172 assessor-blinded, monocentre, randomised trial involving 802 patients scheduled for elective
13 173 clean-contaminated colorectal surgery, the use of PVI-alcohol failed to meet the criterion for
14 174 non-inferiority in SSI occurrence compared with CHG-alcohol.[11] These contradictory
15 175 results may explain the lack of universal use of CHG-alcohol for skin antisepsis in surgery
16 176 despite the recommendations of the World Health Organization (WHO).[15]

17 177 The prevalence and potential serious consequences of SSI in cardiac surgery, especially
18 178 mediastinitis, support a large randomised controlled trial in this setting. We hypothesize that
19 179 perioperative skin preparation with 2% CHG-70% isopropanol is more effective than 5%
20 180 PVI-69% ethanol as a means of preventing any reoperation after cardiac surgery.

21 181

22 182 **METHODS AND ANALYSIS**

23 183 **Trial design and setting**

24 184 The CLEAN 2 trial is an investigator-initiated, publicly-funded multicentre, randomised,
25 185 controlled, open-label clinical trial with concealed allocation of patients scheduled to undergo
26 186 cardiac surgery and to receive 1:1 either 2% CHG – 70% isopropanol or 5% PVI– 69%
27 187 ethanol for perioperative skin preparation. Randomisation will be carried out through a secure
28 188 web-based randomisation system and stratified by centre (Fig. 1).

29 189 The trial will take place at seven university and non-university French hospitals. All
30 190 participating centres perform more than 500 cardiac surgical procedures per year.

31 191 **Participant eligibility and consent**

32 192 During surgery or preoperative anaesthesia consultation, all consecutive patients will be
33 193 considered candidates for inclusion in the study if they meet all of the inclusion criteria and

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3 194 none of the exclusion criteria. Eligible patients will receive oral and written information and
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5 195 will be enrolled after having given written consent.
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7 196 **Inclusion criteria**
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- 9 197
- 10 • Adult patients (age \geq 18 years) admitted in one of the participating centres
 - 11 198 • Scheduled to undergo surgery of the heart (valve, coronary or combined surgery) or of
12 the aorta via median sternotomy
 - 13 199
 - 14 • Having signed informed consent form
 - 15 200

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17 201 **Exclusion criteria**
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- 19 202
- 20 • Patients with known allergies to CHG, PVI, isopropanol or ethanol
 - 21 203 • Surgery for heart transplantation
 - 22
 - 23 204 • Any signs of inflammation or sternal instability at the site of sternotomy or operation
24 for infection (sternal wound infection or endocarditis)
 - 25 205
 - 26 206 • History of cardiac surgery within 3 months preceding enrolment
 - 27
 - 28 207 • Participation in another clinical trial aimed at reducing SSI
 - 29
 - 30 208 • Patients already enrolled in this study
 - 31
 - 32 209 • Pregnant or breastfeeding women and potentially childbearing women without
33 effective contraception
 - 34 210
 - 35 211 • Patients not benefiting from a Social Security scheme or not benefiting from it through
36 a third party
 - 37 212
 - 38
 - 39 213 • Persons benefiting from enhanced protection, namely minors, persons deprived of
40 their liberty by a judicial or administrative decision and adults under legal protection.
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42
43 215 **Assignment of interventions**
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45 216 A computer-generated block-randomisation sequence will be performed by a statistician not
46 involved in either screening the patients or assessing outcomes. Randomisation will be carried
47 217 out using a secure web-based randomisation system with stratification by centre. The
48 218 randomisation will be accessible to investigators through user identification and a personal
49 password and will become effective following confirmation of inclusion and exclusion
50 219 criteria. Patients will be randomly assigned (1:1) to one of two study groups according to the
51 antiseptic solution used to disinfect the skin before surgery and during all dressing changes
52 220 (Fig. 1). To avoid randomisation of a patient with cancelled surgery, this will be done a few
53 221 days before or on the day of surgery.
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225 **Interventions**

- 226 1- *CHG group*: The surgical site will be largely disinfected using applicators of 2%
227 CHG-70% isopropanol (ChloraPrep™, CareFusion). According to local practices,
228 antiseptic application will be preceded (two-step procedure) or not (one-step
229 procedure) by skin scrubbing with 4% CHG (Hibiscrub™, Molnlycke Health Care).
- 230 2- *PVI group*: The surgical site will be largely disinfected using sterile gauzes soaked
231 with 5% PVI-69% ethanol (Bétadine alcoolique™, MEDA Pharma SAS). According
232 to local practices, antiseptic application will be preceded (two-step procedure) or not
233 (one-step procedure) by skin scrubbing with 4% PVI (Bétadine Scrub™, MEDA
234 Pharma SAS).

235 In order to ensure respect of treatment group and to achieve traceability, individual boxes
236 containing all disinfecting products required for disinfecting the skin before surgery and
237 during patient care will be supplied. According to randomisation, each patient will have his
238 own box, which will follow him from the operating room to hospital discharge.

239 The following care procedures will be applied to all patients and controlled throughout the
240 duration of the study:

- 241 • At least one total body shower during the 24 h preceding surgery, using either plain
242 soap or antiseptic soap
- 243 • Hair removal if required with clipper (no shaving) before surgery
- 244 • Antibiotic prophylaxis according to the French recommendations [16] applied 30 min
245 prior to incision, and with appropriate reinjection if required for prolonged surgery.
246 No re-administration during the postoperative period.
- 247 • Antiseptic application by moving back and forth for at least 30 s, starting at the
248 incision site and then extending to the entire work area. The surgical field extends
249 from the jaw to the shoulders and down to the tip of both feet in case of surgery with
250 harvesting of the saphenous vein. In the event of surgery without saphenous vein
251 harvesting, the field stops at the knees. According to local practices, the antiseptic
252 solution will be applied once or twice, preceded or not by skin scrubbing with an
253 antiseptic soap.
- 254 • Application of large sterile drapes once the work area is dry.

255 In each centre, before the beginning of the inclusion, a list of care policy for prevention of SSI
256 (*Staphylococcus aureus* decontamination, antimicrobial-coated sutures, adhesive incises

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3 257 drapes with antiseptics, antimicrobial dressings...) will be established and will not be
4
5 258 modified throughout the duration of the study.

6
7 259 **Study outcomes**

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9 260 *Primary endpoint*

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11 261 The primary outcome will be the proportion of patients undergoing either any re-sternotomy
12
13 262 occurring between Day 0 and Day 90 after surgery or any reoperation on saphenous
14
15 263 vein/radial artery site occurring between Day 0 and Day 30 after surgery or both.

16
17 264 *Secondary endpoints*

- 18
19 265
- 20 266 • Proportion of patients with mediastinitis according to the Center for Disease Control
21 267 and Prevention (CDC) criteria [17] occurring by Day 90 after surgery and pathogens
22 268 involved.
 - 23 269 • Proportion of patients with deep incisional SSI at saphenous vein/radial artery site,
24 270 superficial incisional SSI at sternal or saphenous vein/radial artery sites according to
25 271 the CDC criteria [17] occurring by Day 30 after surgery and the pathogens involved.
 - 26 272 • Proportion of patients with sternal wound infection (SWI) requiring reoperation,
27 273 occurring by Day 90.
 - 28 274 • Proportion of patients with SSI at saphenous vein/radial artery site requiring
29 275 reoperation, occurring by Day 30.
 - 30 276 • Proportion of patients with unexpected need for readmission to intensive care unit
31 277 (ICU) or re-hospitalisation.
 - 32 278 • Duration of ICU stay.
 - 33 279 • Duration of stay under mechanical ventilation.
 - 34 280 • Duration of hospital stay.
 - 35 281 • Duration of rehabilitation unit stay.
 - 36 282 • All-cause mortality at Day 90 of surgery.
 - 37 283 • Proportion of patients with local and systemic side effects possibly linked to antiseptic
38 284 use.

39 284 Two independent assessors masked to the antiseptic group and to the event will review all
40 285 post-operative reports of patients needing re-sternotomy during the 90 days following surgery
41 286 and/or reoperation on saphenous vein/radial artery site during the 30 days following surgery.
42 287 They will classify the case-report as:
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3 288 • SWI (mediastinitis or superficial sternal SSI)
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5 289 • And/or deep or superficial saphenous vein/radial artery SSI
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7 290 • Or no SSI according to CDC criteria
8

9 291 Disagreements between the two assessors will be resolved by consensus conference among all
10 292 outcome assessors.

13 293 **Data collection**

15 294 Independent clinical research assistants will be available at each participating hospital to help
16 295 in running the study and with data collection. Study documents will be de-identified and
17 296 stored for 15 years, as per the protocol for non-clinical trial notification (CTN) interventional
18 297 studies. Data will be entered into the web-based eCRF (CSOnline, Clinsight) and
19 298 electronically stored on double password-protected computers. Hard copies of data (clinical
20 299 research files) will be stored in a secure locked office. All personnel involved in data analysis
21 300 will be masked to study groups. Only the principal investigators and the statisticians will have
22 301 access to the final data set. The following data will be recorded:

29 302 *Baseline characteristics and preoperative data*

31 303 Demographic data (age, gender, height, weight and body mass index); American Society of
32 304 Anaesthesiologists physical status; EuroSCORE II; comorbidities (active smoking; insulin-
33 305 dependent diabetes; non-insulin-dependent diabetes; hypertension; hypercholesterolaemia;
34 306 chronic renal failure; COPD; history of cardiac surgery; atrial fibrillation; key laboratory
35 307 findings; use of preoperative *Staphylococcus aureus* decontamination; hair removal and
36 308 modality; number and type (soap with or without antiseptic) of preoperative showers.

42 309 *Intraoperative data*

44 310 Type of surgery of the heart (valve, coronary, combined surgery, other) or of the aorta; type of
45 311 scheduling (elective, semi-elective or emergency); skin scrubbing before skin antiseptics;
46 312 number of antiseptic applications; number of antiseptic products used; antibiotic prophylaxis:
47 313 molecule, dose, timing and possible redosing; use of iodophor-impregnated incise drapes;
48 314 number of internal thoracic arteries sampled; sampling of saphen vein or radial artery, site
49 315 open or endoscopic; length of surgery (incision to closure); duration of cardiopulmonary
50 316 bypass; minimal and maximal body temperature during surgery; volume infused during
51 317 surgery and type; number and types of blood transfusion during surgery; type of vasopressor
52 318 administered during surgery; use of mechanical cardiac support (extra-corporeal life support
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3 319 [ECLS] or intra-aortic balloon pump); adverse events (especially local and systemic side
4 effects possibly linked to antiseptic use).
5 320

6
7 321 *Postoperative data until hospital discharge*
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9 322 Type and number of blood products given during the 48h following surgery; type and length
10 323 of vasopressor and/or inotropic drugs administered during the 48h following surgery; use of
11 324 mechanical cardiac support (ECLS, intra-aortic balloon pump); atrial fibrillation episode;
12 325 number and results of blood cultures; number, type and results of bacteriological sampling at
13 326 surgical site; wound status at surgical site (until dressing withdrawal): local signs of infection
14 327 (local incisional pain/tenderness, localized redness, heat or swelling, purulent drainage from
15 328 the superficial incision, superficial/deep incision spontaneously or deliberately opened by the
16 329 surgeon), status of dressing, date of dressing changes; physical examination (temperature,
17 330 chest pain, sternal instability); antibiotics used (molecule, duration and indication); results of
18 331 blood samples (standard lab values); duration of mechanical ventilation; length of stay in
19 332 ICU, surgical ward and high dependency unit; date of hospital discharge; reoperation at
20 333 sternal site or saphenous vein/radial artery site occurring after surgery (date and reason); SSI
21 334 occurrence: type (superficial, deep, organ-space), site and date and hour of SSI diagnosis;
22 335 adverse events (especially local and systemic side effects possibly linked to antiseptic use)
23 336 and survival status (if the patient is deceased, date of death).
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36 337 *Postoperative data monthly after surgery (until 90 days following surgery)*
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38 338 Phone contact: date; SSI occurrence, date of diagnosis, site and type; planned or unplanned
39 339 surgical consultation; need for hospital readmission: date, total duration of hospital stay; need
40 340 for reoperation at sternal site (within 90 days following surgery) or at saphenous vein/radial
41 341 artery site (within 30 days following surgery): date, reason; date of rehabilitation unit
42 342 discharge and survival status (if the patient is deceased, date of death).
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47 343 **Safety**
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49 344 According to the French Public Health Code, all suspected unexpected serious adverse events
50 345 will be reported to the Agence Nationale de Sécurité du Médicament (ANSM). Adverse
51 346 events will be evaluated at each visit during clinical interview and physical examination. In
52 347 agreement with ANSM, all serious adverse events related to heart disease (except infections)
53 348 and not related to antiseptic use will not be declared immediately but will be reported in the
54 349 eCRF. Each serious adverse event will be described as completely as possible on the report
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3 350 form designed for this purpose. The initial report will be followed by complementary reports
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5 351 of relevant information as soon as possible.

6 7 352 **Sample size calculation**

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9 353 Assuming a 6% reoperation rate in the PVI group,[6] 1863 patients in each treatment arm will
10
11 354 be required to demonstrate a 33% reduction of reoperation rate with the use of 2% CHG-70%
12
13 355 isopropanol, with statistical risks at 5% and 20% for type I and type II errors, respectively.
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15 356 The sample size calculation is based on the two-sided test. We are planning to enrol 4100
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17 357 patients to take into account a maximum patient loss of 10%.

18 358 **Statistical analysis**

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21 359 The data will be analysed blindly on an intention-to-treat basis. No interim analysis is
22
23 360 planned. Demographic data will be described as number and percentage or median and IQR
24
25 361 and compared with the χ^2 test or Mann-Whitney test, as appropriate. For primary analysis,
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27 362 incidence of reoperation between groups will be compared with χ^2 test. We will assess
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29 363 antiseptic efficacy with a marginal Cox model and adjusted for covariates that will be
30
31 364 significantly imbalanced between groups. We will calculate hazard ratios (HR) and 95% CIs,
32
33 365 as well as incidence density and Kaplan-Meier estimates. Proportions of each secondary
34
35 366 endpoint assessed at day 30 and day 90 will be compared using similar principles. We will use
36
37 367 chi-square tests. A multiple logistic regression will be computed with covariates clinically
38
39 368 relevant as regard as our outcomes (*Centre; Patients' characteristics*: age, gender, body mass
40
41 370 *Staphylococcus aureus* decontamination; *Intraoperative data*: type of surgery of the heart
42
43 371 [valve, coronary, combined surgery, other] or of the aorta, type of scheduling [elective, semi-
44
45 372 elective or emergency], skin scrubbing before skin antisepsis; number of antiseptic
46
47 373 application, use of iodophor-impregnated incise drapes, number of internal thoracic arteries
48
49 374 sampled, length of surgery, duration of cardiopulmonary bypass, minimal body temperature
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51 375 during surgery, volume infused during surgery, use of mechanic cardiac support) and with
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53 376 covariates statistically relevant (covariates with difference between groups < 0.20 in the
54
55 377 univariate analysis). All tests will be two-tailed, stratified by centre and unadjusted for
56
57 378 multiple comparisons. Analyses will be done with SAS version 9.4 and R software.

58 379 **Patient and Public Involvement**

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60 380 The ethical committee, composed of patients' representatives, considered if the research is
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conformed to patients' priorities, experience and preferences. Each patient, admitted in a

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3 382 participating centre, is screened and enrolled by the attending physicians according to the
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5 383 protocol. The burden of the intervention is assessed by patients themselves. Each patient, after
6
7 384 the end of the study, will have the opportunity to obtain the results if they are interested, all
8
9 385 information is provided at inclusion in consent and information forms. No patient was
10
11 386 involved in the recruitment to and the conduct of the study.
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13 387

14 15 388 **ETHICS AND DISSEMINATION**

16 17 18 389 **Research ethics approval**

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20 390 The clinical trial will be carried out in line with the principles of the Declaration of Helsinki,
21
22 391 the guideline for Good Clinical Practice of the International Conference on Harmonization, in
23
24 392 accordance with the French law No. 2012-300 of 5 March 2012 on research involving the
25
26 393 human person and with the Clinical Trials Directives 2001/20/EC and 2005/28/EC of the
27
28 394 European Parliament. Ethical aspects of this research project have been approved by the
29
30 395 ethics committee of Ambroise Paré Hospital (CPP Ile de France VIII, Boulogne-Billancourt,
31
32 396 France). The CLEAN 2 trial is registered at the European Clinical Trial Database on 27
33
34 397 December 2017 (EudraCT #2017-005169-33) and summarised at ClinicalTrials.gov with the
35
36 398 trial identification number NCT03560193.

37 38 399 **Consent**

39
40 400 Written informed consent will be requested for each patient prior to enrolment. The
41
42 401 investigators will provide clear and precise information to the patient about the protocol
43
44 402 before asking him/her for written informed consent.

45 46 403 **Confidentiality**

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48 404 People with direct access to the data will take all necessary precautions to maintain
49
50 405 confidentiality. All data collected during the study will be rendered anonymous. Only initials
51
52 406 and inclusion number will be registered.

53 54 407 **Dissemination policy**

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56 408 The results of the study will be released to the participating physicians, referring physicians
57
58 409 and medical community no later than one year after completion of the trial through
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60 410 presentation at scientific conferences and publication in peer-reviewed journals.

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3 411 The main manuscript will mention the name of the sponsor and all trial sites will be
4
5 412 acknowledged. All investigators having included or followed participants in the study will
6
7 413 appear with their names under “the CLEAN 2 investigators” in an appendix to the final
8
9 414 manuscript. Authorship will be done in accordance with the guidelines of the International
10
11 415 Committee of Medical Journal. No professional writer will be used.

12 416 **Funding statement**

13
14 417 This work is being funded by unrestricted research grants from the French Ministry of Social
15
16 418 Affairs and Health (#16-0619) and CareFusion/ Becton Dickinson. Funders will have no role
17
18 419 in the trial initiation, study design, choice of antiseptic products, data collection, data analysis,
19
20 420 data interpretation or writing of the report.

21 421 **Conflict of interest**

22
23
24 422 OM has received grant support from 3M and Carefusion-BD and honoraria for giving lectures
25
26 423 from 3M and Carefusion-BD.

27 28 424 **DISCUSSION**

29
30
31 425 This study will provide new knowledge in the field of SSI prevention, addressing questions
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33 426 raised by the Cochrane review on preoperative skin antiseptics aimed at preventing surgical
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35 427 wound infections after clean surgery.[18] In clean surgery, the majority of pathogens
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37 428 responsible for infectious complications come from the skin and skin disinfection has the
38
39 429 potential to reduce both the frequency and severity of SSI in proportion to the efficacy of
40
41 430 disinfection. The choice of cardiac surgery is based on the severity of SSI with this surgery,
42
43 431 especially mediastinitis, which frequently requires reoperation. We selected centres with
44
45 432 experience in SSI prevention studies and already applying all the other SSI prevention
46
47 433 measures recommended by our national guidelines. Their number is limited so as to ensure
48
49 434 high quality of follow-up by independent clinical research assistants. Stratified randomisation
50
51 435 will protect against bias linked to potential variability in surgical practices between centres.
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53 436 Individual boxes containing allocated disinfecting products will follow the patient from the
54
55 437 operating room to hospital discharge to ensure respect of treatment group and to facilitate
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57 438 product traceability. The choice of reoperation as the main endpoint is not subject to
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59 439 evaluation bias in an open study.

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441 440 Our study will have several limitations. First, masking will not be feasible, because the two
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60 441 antiseptic solutions differ in both colour and formulation. However, the microbiologists who

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3 442 will perform all microbiological cultures will be unaware of treatment allocation. More
4
5 443 importantly, all cases of suspected SSI will be reviewed by masked independent assessors
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7 444 based on internationally accepted definitions.[17] Second, the two antiseptic solutions contain
8
9 445 different alcoholic components and use different application methods. However, these
10
11 446 products will be used in their commercially available formulations in France and as
12
13 447 recommended by our national guidelines. Further studies will be necessary to determine the
14
15 448 more efficient type and concentration of alcohol to be combined with CHG or PVI as well as
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17 449 the optimal concentration of CHG and PVI and optimal method for antiseptic application.
18
19 450 Third, we have chosen incidence of reoperation as the primary endpoint. They can be due to
20
21 451 non-infectious causes such as postoperative bleeding, valve-dysfunction etc., for which the
22
23 452 impact of skin disinfection is probably low. However, their main advantage is to be a strong
24
25 453 unquestionable endpoint not subject to assessment bias in an open trial. Fourth, adherence to
26
27 454 the study protocol will not be regularly checked by formal audits. However, the health-care
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29 455 providers will attend training sessions designed to homogenise skin preparation practices
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31 456 across hospitals before starting the study and independent clinical research assistants will be
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33 457 available at each participating hospital to monitor the conduct of the trial. Moreover, all study
34
35 458 centres will be required to follow French recommendations similar to CDC recommendations
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37 459 for prevention of SSI with no modification allowed during the study period.

38
39 460 We assumed a 33% reduction in reoperation with the use of alcoholic chlorhexidine in our
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41 461 study. This choice may appear too ambitious. However, it is based on the existence of several
42
43 462 surgical sites in the majority of patients, the major role of SSI in reoperation and the expected
44
45 463 effect of antiseptic choice on SSI prevention. In clean contaminated surgery, a 50% reduction
46
47 464 in SSI with alcoholic chlorhexidine use has been reported in digestive[7] or obstetrical[9]
48
49 465 surgery. In these types of surgery, a significant fraction of pathogens involved comes from the
50
51 466 digestive or gynaecological flora not accessible to the action of antiseptics. In intensive care,
52
53 467 an 85% reduction in infections related to short-term central venous and arterial catheters has
54
55 468 been reported with alcoholic chlorhexidine use.[19] As in clean surgery, the skin flora is the
56
57 469 main reservoir of pathogens involved in these infections, and the effectiveness of skin
58
59 470 disinfection is essential to prevent them. In total, if we consider that among the 6% of
60
471 reoperation in the povidone iodine group, half are related to an SSI (which is probably
472 underestimated), we can expect an incidence of reoperation in the chlorhexidine group
473 between 3.5% (hypothesis very favourable to alcoholic chlorhexidine use) and 4.5%
474 (hypothesis not very favourable to alcoholic chlorhexidine use). In the event of negative

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3 475 results, the choice of the antiseptic strategy could be based on the incidence of secondary
4 476 endpoints in both arms of our study, and finally, on the cost of antiseptic strategies, even if it
5 477 is insignificant compared to that of SSI.

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9 478 We will conduct the first large scale randomised trial adequately powered to compare the
10 479 efficacy and safety of CHX-alcohol over PVI-alcohol in reducing SSI after clean surgery.
11 480 Reducing SSI after surgery is associated with decreased length of hospital stay, mortality and
12 481 overall costs and increased patient satisfaction,[4] which should benefit both the patient and
13 482 the community. The trial is multicentre and almost all eligible patients will be included and
14 483 will benefit from all the measures recommended by our national guidelines (similar to CDC
15 484 guidelines) to prevent SSI. As a result, our findings will be reasonably extended to other
16 485 cardiac surgery centres, to other clean surgeries and, more generally, to all surgical
17 486 procedures performed worldwide, even if the proportion of skin pathogens involved in SSI is
18 487 lower than in clean surgery.
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28 489 **Trial status**

29
30 490 The current protocol is version 3.0 dated 12 September 2018. The trial is currently recruiting
31 491 patients. The inclusion process started on 17 September 2018 and the number of patients
32 492 included to date (12 February 2019) is 311. The estimated length of inclusion time is 18
33 493 months.
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38 494

39 40 495 **AUTHORS' CONTRIBUTIONS**

41
42
43 496 MB and OM conceived the study, coordinated its design, wrote the manuscript and drafted the
44 497 manuscript. PC, TK, LC, MD, PD, VE, EF, LL, DL, PL, NN, JYN, AO, JCR, BR, SR, JCL
45 498 and JFT read and were involved in critical appraisal and revision of the manuscript. SR and
46 499 JFT provided statistical expertise. All authors approved the final manuscript prior to
47 500 submission.
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For peer review only

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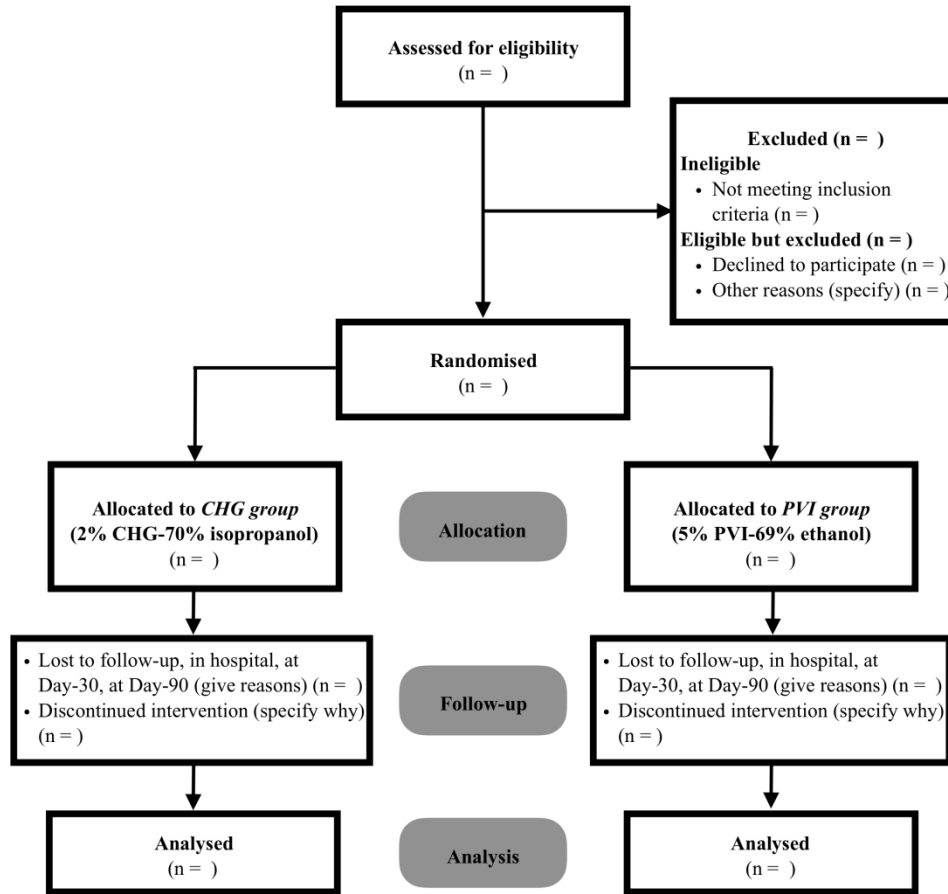


Figure 1. CONSORT diagram (CHG: chlorhexidine, PVI: povidone iodine)

209x209mm (300 x 300 DPI)



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	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	4 & 13
	2b	All items from the World Health Organization Trial Registration Data Set	1, 3, 4, 7, 8, 9, 10, 12, 13, 14, 16
Protocol version	3	Date and version identifier	16
Funding	4	Sources and types of financial, material, and other support	17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 2, 3, 17
	5b	Name and contact information for the trial sponsor	3
	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	17
	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)	10
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	6
	6b	Explanation for choice of comparators	6, 7
Objectives	7	Specific objectives or hypotheses	7

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2	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, noninferiority, exploratory)	7
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8	Methods: Participants, interventions, and outcomes			
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10	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
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15	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
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21	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9
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26		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)	n/a
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31		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9, 11
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36		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
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39	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	10
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48	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)	9, 16
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54	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	13
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2 Recruitment 15 Strategies for achieving adequate participant enrolment to 7, 11
3 reach target sample size
4

5 **Methods: Assignment of interventions (for controlled trials)**
6

7 Allocation:

8
9 Sequence 16a Method of generating the allocation sequence (eg, 8
10 generation computer-generated random numbers), and list of any
11 factors for stratification. To reduce predictability of a
12 random sequence, details of any planned restriction (eg,
13 blocking) should be provided in a separate document that
14 is unavailable to those who enrol participants or assign
15 interventions
16
17

18 Allocation 16b Mechanism of implementing the allocation sequence (eg, 8
19 concealment central telephone; sequentially numbered, opaque, sealed
20 mechanism envelopes), describing any steps to conceal the sequence
21 until interventions are assigned
22
23

24 Implementation 16c Who will generate the allocation sequence, who will enrol 8
25 participants, and who will assign participants to
26 interventions
27

28 Blinding 17a Who will be blinded after assignment to interventions (eg, 10, 11, 13
29 (masking) trial participants, care providers, outcome assessors, data
30 analysts), and how
31
32

33 17b If blinded, circumstances under which unblinding is n/a
34 permissible, and procedure for revealing a participant's
35 allocated intervention during the trial
36

37 **Methods: Data collection, management, and analysis**
38

39 Data collection 18a Plans for assessment and collection of outcome, baseline, 11, 12
40 methods and other trial data, including any related processes to
41 promote data quality (eg, duplicate measurements,
42 training of assessors) and a description of study
43 instruments (eg, questionnaires, laboratory tests) along
44 with their reliability and validity, if known. Reference to
45 where data collection forms can be found, if not in the
46 protocol
47
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50 18b Plans to promote participant retention and complete 9, 10, 11, 12
51 follow-up, including list of any outcome data to be
52 collected for participants who discontinue or deviate from
53 intervention protocols
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2	Data	19	Plans for data entry, coding, security, and storage,	11
3	management		including any related processes to promote data quality	
4			(eg, double data entry; range checks for data values).	
5			Reference to where details of data management	
6			procedures can be found, if not in the protocol	
7				
8				
9	Statistical	20a	Statistical methods for analysing primary and secondary	13
10	methods		outcomes. Reference to where other details of the	
11			statistical analysis plan can be found, if not in the protocol	
12				
13		20b	Methods for any additional analyses (eg, subgroup and	13
14			adjusted analyses)	
15				
16		20c	Definition of analysis population relating to protocol non-	n/a
17			adherence (eg, as randomised analysis), and any	
18			statistical methods to handle missing data (eg, multiple	
19			imputation)	
20				
21				
22	Methods: Monitoring			
23				
24	Data monitoring	21a	Composition of data monitoring committee (DMC);	n/a
25			summary of its role and reporting structure; statement of	
26			whether it is independent from the sponsor and competing	
27			interests; and reference to where further details about its	
28			charter can be found, if not in the protocol. Alternatively,	
29			an explanation of why a DMC is not needed	
30				
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32		21b	Description of any interim analyses and stopping	n/a
33			guidelines, including who will have access to these interim	
34			results and make the final decision to terminate the trial	
35				
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37	Harms	22	Plans for collecting, assessing, reporting, and managing	11, 12
38			solicited and spontaneously reported adverse events and	
39			other unintended effects of trial interventions or trial	
40			conduct	
41				
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43	Auditing	23	Frequency and procedures for auditing trial conduct, if	n/a
44			any, and whether the process will be independent from	
45			investigators and the sponsor	
46				
47	Ethics and dissemination			
48				
49	Research ethics	24	Plans for seeking research ethics committee/institutional	14
50	approval		review board (REC/IRB) approval	
51				
52	Protocol	25	Plans for communicating important protocol modifications	15
53	amendments		(eg, changes to eligibility criteria, outcomes, analyses) to	
54			relevant parties (eg, investigators, REC/IRBs, trial	
55			participants, trial registries, journals, regulators)	
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2	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7, 8, 14
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6		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
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10	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	11, 12, 13, 17
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16	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
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19	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	11, 13, 17
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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 participation	n/a
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28	Dissemination policy	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	15
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35		31b	Authorship eligibility guidelines and any intended use of professional writers	15
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39		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
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42	Appendices			
43				
44	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
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47	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	n/a
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