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# BMJ Open Skin antiseptics with chlorhexidine–alcohol versus povidone iodine–alcohol, combined or not with use of a bundle of new devices, for prevention of short-term peripheral venous catheter-related infectious complications and catheter failure: an open-label, single-centre, randomised, four-parallel group, two-by-two factorial trial: CLEAN 3 protocol study

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## ABSTRACT

**Introduction** Short peripheral intravenous catheters (PVCs) are the most frequently used invasive medical devices in hospitals. Unfortunately, PVCs often fail before the end of treatment due to the occurrence of mechanical, vascular or infectious complications, which prolongs hospitalisation and increases healthcare costs and mortality. Prevention of these complications is mainly based on the respect of hygiene rules and the use of biocompatible catheters. In critically ill patients, 2% chlorhexidine-alcohol is superior to 5% povidone iodine-alcohol for skin preparation before central venous and arterial catheters; whether this finding can be extended to PVC inserted in the wards remains speculative. Similarly, the use of new technologies such as catheters designed to minimise blood exposure, zero-reflux needleless connectors, disinfecting caps and flushing PVCs before and after each medication administration to maintain catheter patency are of theoretical interest to prevent PVC failure, but little scientific data support their routine use.

**Methods and analysis** The CLEAN 3 study is an open-label, single-centre, randomised, two-by-two factorial trial. One thousand patients visiting our emergency department and requiring hospital admission in the wards will be randomised to one of four strategies according to skin preparation and devices used. The two primary endpoints will be (1) the incidence of infectious complications related to the catheters (colonisation, local infection or bloodstream infection) and (2) the time between catheter insertion and catheter failure defined as any premature removal of PVC before end of treatment, other than for routine replacement.

**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

## Strengths and limitations of this study

- This large-scale study is the first to compare the commonly used antiseptics for skin disinfection before short peripheral venous catheter insertion, the most common device used in hospitalised patients, to prevent catheter infection.
- This study is also the first adequately powered study to evaluate if the use of a bundle of new devices delays complication occurrences leading to catheter failure.
- Limitation due to the lack of masking related to the nature of the interventions will be limited by assessment of the primary endpoints using predefined strong unquestionable criteria.

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 number** EudraCT 2018-A02535-50; NCT03757143.

## INTRODUCTION

Short peripheral intravenous catheters (PVCs) are the most frequently used invasive medical devices in hospitals<sup>1</sup>; about 330 millions are sold every year in the USA alone.<sup>2</sup> Unfortunately, PVCs often fail before the end of treatment due to the occurrence

of complications, which can be mechanical, vascular or infectious. Mechanical complications include occlusion, infiltration and accidental removal. Vascular complications include venous thrombotic occlusion and phlebitis. Infectious complications may be bacterial or fungal, and local or systemic bloodstream infections (catheter-related bloodstream infections [CR-BSIs]). The risk of CR-BSI is lower (0.2–0.7 episodes per 1000 catheter-days) than for other vascular catheters, but the far greater number of PVCs in use means that the absolute infection rates for PVCs approach the absolute infection rates for other vascular catheters.<sup>3</sup> Moreover, peripheral intravenous CR-BSIs are mainly due to *Staphylococcus aureus* while other vascular CR-BSIs are due to coagulase negative staphylococci.<sup>4</sup> *S. aureus* bloodstream infections are generally more severe, induce more endocarditis and other tissue infections and consequently, are associated with worse outcomes.

Complications lead to infusion failure and device replacement, which results in interrupted therapy, pain associated with replacement and increased healthcare costs for resources and staff time.<sup>5</sup> CR-BSIs prolong hospitalisation and increase treatment costs and mortality.<sup>6</sup> Prevention of these complications is based on the respect of hygiene rules and the use of biocompatible catheters. The choice of the best antiseptic solution for skin disinfection is key. While the use of alcoholic solutions is recommended, the superiority of alcoholic chlorhexidine (CHG) over alcoholic povidone iodine (PVI) is demonstrated only for short-term central venous and arterial catheters in critically ill patients.<sup>7–9</sup> Similarly, the use of new technologies such as catheters designed to minimise blood exposure, zero-reflux needleless connectors, disinfecting caps or flushing PVCs before and after each medication administration to maintain catheter patency are of theoretical interest, but little scientific data support their use in clinical practice.<sup>10–13</sup>

We hypothesise that (1) skin preparation with 2% CHG-70% isopropanol is more effective than 5% PVI-69% ethanol to prevent PVC-related infectious complications and (2) use of a bundle of devices including new PVCs, zero-reflux needleless connectors, disinfecting caps and single-use prefilled flush syringes extends the time between catheter insertion and catheter failure.

## METHODS AND ANALYSIS

### Trial design and setting

The CLEAN 3 study is an open-label, single-centre, randomised, four-parallel group, two-by-two factorial, investigator-initiated trial. Patients requiring PVC for an expected 48 hours will be randomised to one of four groups according to skin disinfection method and type of devices used. Randomisation will be carried out through a secure web-based randomisation system. Inclusions are expected to begin in January 2019 and continue until at least July 2019, once the number of catheters required has been reached.

Patients will be enrolled at the emergency department of the Poitiers University Hospital before being hospitalised in one of seven wards (acute geriatrics, hepato-gastroenterology, endocrinology, neurology, pneumology, internal medicine and downstream emergency units).

### Participant eligibility and consent

Any patient consulting at the emergency department of the University Hospital of Poitiers and needing the insertion of PVC will be screened for eligibility. 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 giving informed written consent.

### Inclusion criteria

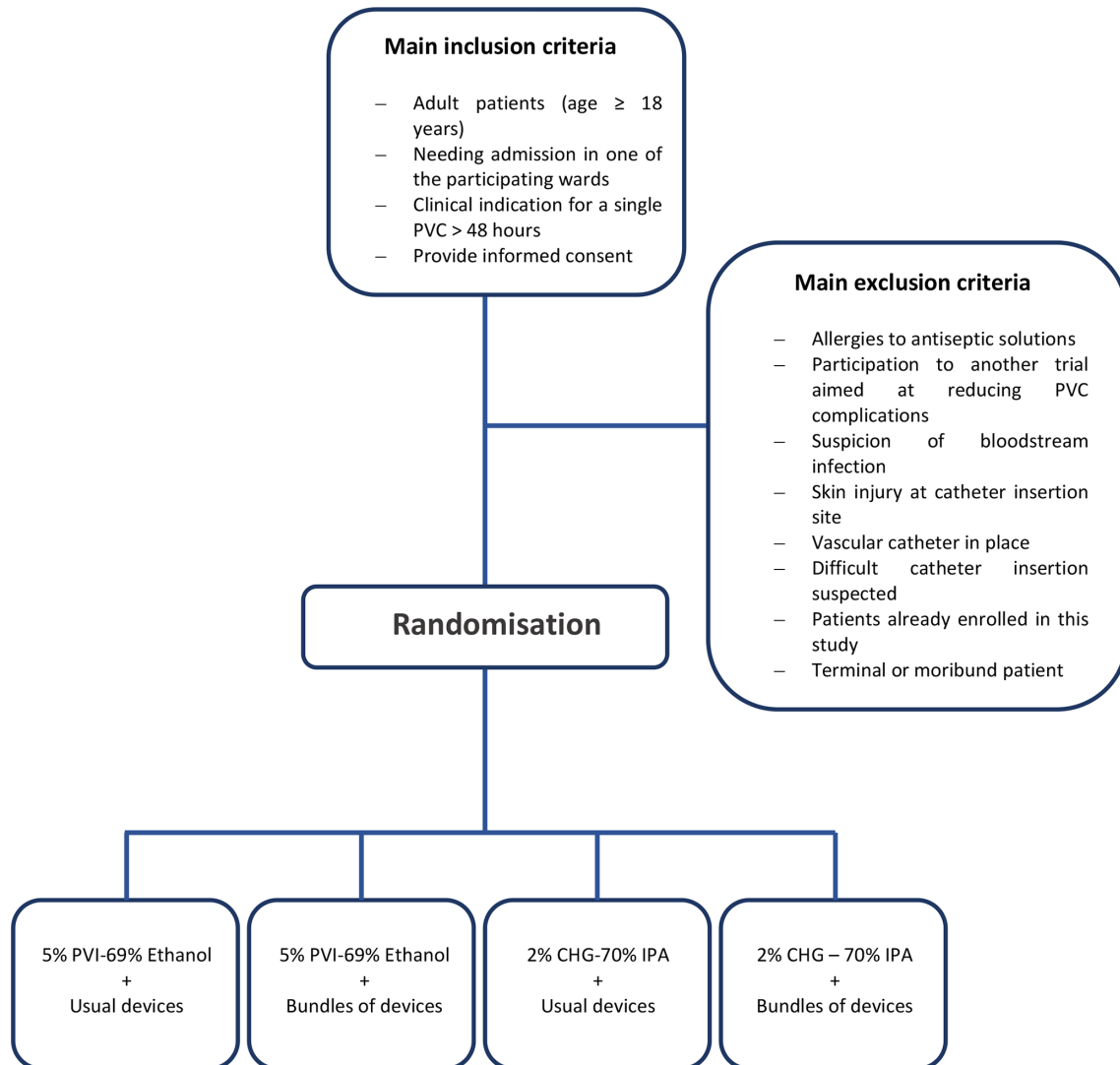
- ▶ Adult (age  $\geq 18$  years) patients needing admission in one of the participating wards.
- ▶ Having clinical indication for placement of a single PVC for at least 48 hours.
- ▶ Willing and able to provide informed consent.

### Exclusion criteria

- ▶ Known allergies to CHG, PVI, isopropanol or ethanol.
- ▶ Participation in another clinical trial aimed at reducing PVC complications.
- ▶ Suspicion of bloodstream infection at catheter insertion.
- ▶ Skin injury at catheter insertion site increasing the risk of catheter infection.
- ▶ PVC inserted extremely urgently, making it impossible to comply with the protocol.
- ▶ Intravascular catheter in place within the last 2 days, or within the last 2 weeks and with local signs of catheter complication.
- ▶ Difficult catheter insertion suspected (obesity, known intravenous drug users, non-visible venous network after placement of a tourniquet and so on).
- ▶ Patients already enrolled in this study.
- ▶ Terminal or moribund patient not expected to live more than 1 week.
- ▶ 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, adults under legal protection.
- ▶ Known pregnant or breastfeeding women.

### Sample size calculation

Assuming 12% of PVC colonisation rate in the PVI-alcohol group,<sup>3</sup> 712 patients will be required to detect a 50% reduction of PVC colonisation with the use of CHG-alcohol,<sup>7</sup> with bilateral statistical risks at 5% and 20% for type I and type II errors, respectively. We plan to enrol 1000 patients to take into account for the interaction between the two strategies (+30%) and a maximum catheter culture loss of 10%.



**Figure 1** Study flowchart. CHG, chlorhexidine; IPA, isopropanol; PVC, peripheral intravenous catheters; PVI, povidone iodine.

### Assignment of interventions

A computer-generated block-randomisation sequence with the use of permuted-block randomisation with varying block sizes will be performed by the statistician and will be carried out via Ennov System software. The statistician will not be involved in either screening the patients or assessing outcomes.

The randomisation process will be accessible to all physicians working in the emergency department through user identification and a personal password to access the website (<https://chu-poitiers.hugo-online.fr/CSOnline/>). It will become effective following confirmation of inclusion and exclusion criteria.

Patients will be assigned to one of four study groups (in a 1:1:1:1 randomisation scheme) according to (1) the skin disinfectant used before catheter insertion and (2) the type of PVC and additional materials used for the venous line (figure 1).

### Interventions

► Group 1: (1) The skin at catheter insertion site will be disinfected using sterile gauzes soaked with 5% (w/v)

PVI-69% (v/v) ethanol (Bétadine alcoolique, Mylan, Merignac, France); (2) The PVC will be the Insyte AutoguardBC Winged (Becton Dickinson [BD], Le Pont de Claix, France).

- Group 2: (1) The skin at catheter insertion site will be disinfected using sterile gauzes soaked with 5% (w/v) PVI-69% (v/v) ethanol (Bétadine alcoolique); (2) The PVC will be the Nexiva single port catheter with MaxZero needleless connector. PureHub Disinfecting Caps port protectors and 10 mL Posiflush prefilled saline syringes will also be used (all devices will be from BD).
- Group 3: (1) The skin at catheter insertion site will be disinfected using sterile applicators of 2% (w/v) CHG-70% (v/v) isopropanol (ChloraPrep, BD); (2) The PVC will be the Insyte AutoguardBC Winged (BD).
- Group 4: (1) The skin at catheter insertion site will be disinfected using sterile applicators of 2% (w/v) CHG-70% (v/v) isopropanol (ChloraPrep, BD); (2) The PVC will be the Nexiva single port catheter with



MaxZero needleless connector. PureHub Disinfecting Caps port protectors and 10 mL Posiflush prefilled saline syringes will also be used (all devices will be from BD).

In order to avoid any risk of confusion, kits containing all the necessary products according to the randomisation arm will be used from the emergency room and will follow patients to their room. Training for healthcare providers designed to homogenise skin preparation, PVC insertion and maintenance practices between units will be held before starting inclusions. Research nurses will visit the wards daily to ensure compliance with the protocol.

The following care will be applied at catheter insertion:

- ▶ Hair will be removed only if required with clipper (no shaving) before catheter insertion.<sup>14</sup> Hands of health caregivers will be disinfected with hydro-alcoholic solution and dressed with non-sterile gloves. To further minimise infection risk, healthcare providers should avoid wearing wristwatches, stoned rings, long sleeves and long fingernails.
- ▶ Skin will be disinfected with the assigned antiseptic solution applied by moving back and forth for at least 30 s.
- ▶ Assigned PVC will be inserted once the work area will be dry and taped with Tegaderm 1626W transparent dressings (3M, St Paul, Minnesota, USA). PVC can be inserted by any nurse or emergency physician working in the emergency department provided he/she has previously inserted at least 50 PVC.
- ▶ All other French recommendations (similar to Centers for Disease Control and Prevention [CDC] recommendations) for prevention of catheter-related infections will be applied and no modification will be allowed during the study period.
- ▶ No ultrasound guidance will be used during the study. Dressings will not be changed except if soiled or loose.

The following care will be applied during catheter use:

- ▶ Before any contact with the PVC or injection sites, hands of healthcare providers will be decontaminated using an alcohol-based hand rub or by washing with liquid soap and water if the hands are soiled or contaminated with blood or body fluids.
- ▶ In the control group, intravenous fluids or drugs administration will be made through a three-way stop cock (pre-assembled 3WSC intravenous set) after disinfection with an alcohol-based antiseptic. Intravenous fluids will be infused continuously in the absence of any contraindications.
- ▶ In the 'bundle' group, intravenous fluids or drugs administration will be made through the zero-reflux needleless connector, after removal of the disinfecting cap covering the needle-free luer connector. Before and after each drug administration, a 'pulse' flushing technique with 5 mL of sterile saline solution in a prefilled syringe will be used to flush the catheter and its extension, followed by administering positive pressure to seal the tube (by pushing the flushing solution while simultaneously clamping the extension

tubing). The pulse flushing consists of alternatively pushing and pausing in flushing with saline solution, creating a small vortex within the catheter. Recapping of the needle-free luer connector with a new disinfecting cap will be systematic. Intravenous fluids will be infused only if the patient needs them, not to avoid catheter occlusion, usually discontinuously.

- ▶ No restriction on products administered through the PVCs will be placed.
- ▶ The catheter dressing will not be redone unless it is soiled or not hermetic; in this case, the same antiseptic strategy will be applied.
- ▶ Peripheral blood for culture will be drawn in cases of fever (body temperature >38.5°C), hypothermia (body temperature <36.5°C) or chills. Ten millilitres of blood will be placed each in aerobic and anaerobic bottles. Blood cultures will be incubated at 37°C in a BacT/Alert system (bioMérieux, La-Balme-les-Grottes, France) for 7 days for aerobic bottles and 5 days for anaerobic bottles and monitored in accordance with the manufacturer's recommendations. All positive bottles will be systematically plated on Columbia blood-sheep agar and incubated under aerobic and anaerobic conditions.

The following care will be applied at catheter removal:

- ▶ Catheters will be removed only for completion of treatment, phlebitis, infiltration, occlusion, accidental removal or suspected infection and systematically at day 4. Investigators and research nurses will have no involvement in the decision to remove PVCs or to order cultures, only the physician in charge of the patient will be able to do so.
- ▶ After catheter removal, the distal 2–3 cm catheter segment will be aseptically removed and sent to the clinical microbiology laboratory for quantitative culture in a sterile, dry plastic container.<sup>15</sup> One millilitre of sterile distilled water will be dripped on the catheter and the tube will be vortexed for 1 min; 0.1 mL of the suspension will be sampled with a 10 µL calibrated pipette and plated over the whole surface of a 90 mm diameter 5% horse blood agar plate. Plates will be incubated at 35°C–37°C and examined daily for 2 days. Colonies of each species will be enumerated, counts will be corrected for the initial 1/10 dilution and quantitative results will be reported as colony-forming units per milliliter (cfu/mL).

Each participant will remain in the study until 48 hours after catheter removal or he/she decides to stop participating in the study. The length of hospital stay will be assessed at the end of the first hospital stay censored at Day 28.

## Study outcomes

### Primary endpoints

- ▶ The first primary endpoint will be the incidence of catheter-related infectious complications, and include catheter colonisation, local infection and CR-BSI.

- ▶ The second primary endpoint will be the time between catheter insertion and catheter failure defined as any premature removal of PVC before end of treatment, other than for routine replacement, and includes phlebitis, infiltration, occlusion, accidental catheter removal, local infection and CR-BSI, whichever occurred first.

### Secondary endpoints

- ▶ Number of phlebitis defined as two or more of the following present simultaneously: (1) patient-reported pain or tenderness (on questioning, then palpation by the research nurse) with a severity of 2 or more on a 10-point scale; (2) erythema extending at least 1 cm from the insertion site; (3) swelling, extending at least 1 cm from the insertion site; (4) purulent discharge or (5) palpable venous cord beyond the intravenous catheter tip.
- ▶ Number of infiltrations, defined as the infusion of non-blistering drug leaking through the normal vascular channel and resulting in the swelling of tissue peripheral to the puncture site.
- ▶ Number of catheter occlusions defined as the inability of the catheter to flush (not able to intravenously inject 1 mL of normal saline within 30s).
- ▶ Number of accidental catheter removal.
- ▶ Number of CR-BSI, defined as (1) at least one positive blood culture from a peripheral vein and (2) clinical signs of infection (ie, fever (body temperature  $>38.5^{\circ}\text{C}$ ), hypothermia (body temperature  $<36.5^{\circ}\text{C}$ ), chills or hypotension (Systolic blood pressure  $<90\text{ mm Hg}$ )); (3) no other apparent source of the bloodstream infection except the intravenous catheter (in situ within 48 hours of the bloodstream infection) and (4) a colonised intravenous catheter tip culture with the same organism (same species) as identified in the blood. For commensal microorganisms (coagulase-negative staphylococci, *Corynebacterium* spp. (except *Corynebacterium jeikeium*), *Lactobacillus* spp., *Bacillus* spp. and *Propionibacterium* spp., or viridans group *Streptococcus* isolates and *Clostridium perfringens*), at least two positive blood cultures will be required.
- ▶ Number of local infections, defined as organisms grown from purulent discharge with no evidence of associated bloodstream infection.
- ▶ Number of all-cause bloodstream infections, defined as any positive blood culture drawn from a peripheral vein while intravenous catheter in situ or for 48 hours after removal. For commensal microorganisms (coagulase-negative staphylococci, *Corynebacterium* spp. (except *C. jeikeium*), *Lactobacillus* spp., *Bacillus* spp. and *Propionibacterium* spp., or viridans group *Streptococcus* isolates and *C. perfringens*), at least two positive blood cultures will be required.
- ▶ Number of catheter colonisations defined as the culture of intravascular catheter tip showing at least 1000 cfu/mL.

- ▶ Type of pathogens involved in catheter colonisations, local infections, CR-BSI and all-cause bloodstream infections.
- ▶ Number of days the catheter remaining in place without complication.
- ▶ Length of first hospital stay censored at day 28.
- ▶ Incidence of local and systemic side effects possibly linked to antiseptic use.
- ▶ Patient's evaluation of pain at catheter insertion using visual analogue scale (VAS).
- ▶ Patient's satisfaction at catheter removal using VAS.
- ▶ Impact of venous line on patient's mobility at catheter removal using VAS.

Patients, clinical staff and research nurses will not be masked after allocation because of the nature of the intervention. However, laboratory staff will be masked for rating of all microbiological endpoints. Moreover, two assessors masked to the intervention will review all cases of bloodstream infections. Disagreements between the two assessors will be resolved by consensus conference among all outcome assessors.

### Data collection

Research nurses and clinical research assistants will 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 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 locked, secure 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 patients' characteristics

- ▶ Demographic data: age, gender, height, weight and body mass index.
- ▶ Smoker status.
- ▶ Comorbidities: insulin-dependent diabetes, hypercholesterolaemia, COPD, cardiac failure, renal failure, corticotherapy.
- ▶ Anticoagulant and/or antiplatelet aggregation treatment.
- ▶ Hair removal and modality.

### Characteristics of catheters

- ▶ Catheter type.
- ▶ Catheter gauge.
- ▶ Insertion side: left/right.
- ▶ Insertion site: cubital fossa/back of hand/inner forearm/lower forearm/mid forearm/outer forearm/wrist/upper arm/elbow flexure.
- ▶ Successful catheter insertion.
- ▶ Number of attempts.

- ▶ Pain felt by the patient using 10-point VAS (from 0=no pain to 10=maximum pain conceivable).

#### Daily parameters

Patients will be followed daily by research nurses as long as their catheter remains in place for 4 days, and the following parameters will be collected using digital tablets:

- ▶ Catheter still in place or time of catheter ablation. In case of catheter ablation, reason for catheter removal (no further indication, accidental removal, catheter complication, suspicion of infection or other).
- ▶ Intravenous drug administration during last 24 hours: antibiotics, heparin-therapy potassium, corticoids, hypertonic solutions or others specified products.
- ▶ Oral anticoagulant administration during last 24 hours.
- ▶ Maintenance fluids.
- ▶ Blood transfusion during the last 24 hours.
- ▶ Dressing change during the last 24 hours and indication.
- ▶ Number and results of blood cultures during the last 24 hours.
- ▶ Catheter complication: phlebitis, occlusion, infiltration around the catheter, local infection, CR-BSI.
- ▶ Blood cultures (number and results).
- ▶ Local and systemic side effects possibly linked to anti-septic use.
- ▶ Impact of venous line on patient's mobility using 10-point VAS.
- ▶ Overall satisfaction using 10-point VAS.
- ▶ Skin and systemic safety.

#### Parameters collected 2 days after catheter removal

The research nurses will visit the patients (or contact them by phone in case of discharge) and their files to collect the following parameters:

- ▶ Appearance of a new catheter complication: phlebitis, local infection, CR-BSI.
- ▶ Local or systemic side effects possibly linked to anti-septic use.
- ▶ Results of blood cultures (if any) and catheter tip culture.
- ▶ Skin and systemic safety.

#### Parameters collected 28 days after catheter insertion

- ▶ The research nurses will collect the length of the first hospital stay using the patient's file.

#### 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. Adverse events will be evaluated at each visit during clinical interview and physical examination. Each serious adverse event will be described as completely as possible on the report form designed for this purpose. The initial report will have to be followed by complementary reports of relevant information as soon as possible.

#### Patient and public involvement

Patients were not involved in the design or in the recruitment to and conduct of the study, nor in the assessment of burden of the intervention. Results will be disseminated to study participants on request.

#### Statistical analysis

Statistical analyses will be performed after the total number of subjects required will be reached. No interim analysis is planned.

The analyses will be performed by 2×2 factorial design 'inside the table' on all randomised patients (intention to treat analysis). Interaction between treatments strategy will be sought and the specific effects will be evaluated. An 'inside the table' analysis is planned because of an expected additive interaction between strategy effects. No antagonistic interaction between strategy effects is expected. Factorial trial remains the most valid means by which to evaluate whether combining two or more therapies achieves incremental benefits.<sup>16</sup>

#### Baseline characteristics and univariate analyses

Demographic data will be described. Point estimates (percentages, means, medians) and CI, SD or IQR will be given for the qualitative and quantitative variables as appropriate.

The Student's t-test will be used to compare the distributions of quantitative variables between treatment groups at inclusion. The Cochran-Mantel-Haenszel Chi-square test will be used to compare the distributions of qualitative variables between treatment groups at inclusion. Incidence density, Kaplan-Meier estimates and log-rank test will be used to compare the distributions of censored variables (censored data at days 6 and 28).

Due to the factorial design, randomised groups will be tested to ensure the comparability.

The proportions of catheters that are free of colonisation as a function of time they had been in place would be compared between groups using the log-rank test. The proportions of catheters failure as a function of time catheters had been in place would be also compared between groups using the log-rank test.

To test the interaction between treatments, a multivariable logistic-regression model that included the two randomised treatments and their interaction as parameters will be performed. In the analysis of the primary and secondary endpoints, a p-value <0.05 on the Wald chi-square test was considered to indicate statistical significance for the interaction term and to determine its inclusion or exclusion in the final model. A stepwise procedure to confirm the results of interaction testing will be performed.

#### Multivariate analyses

Primary endpoints will be modelled with a marginal Cox model adjusted for covariates (including study group) that will be significantly imbalanced between groups (p-value <0.20 in univariate analysis). HR and 95% CI



will be calculated. The Fine and Gray subdistribution hazard regression model, which extend the Cox model to competing risk data by considering the hazard function associated with the cumulative incidence function, will be used to compare strategies effects. Mortality before catheter removal is considered as a competing risk.

Analyses will be done with SAS V.9.4 and R software. All the tests will be two-tailed. Any p-value  $\leq 0.05$  will be considered significant. The analysis report will be presented in accordance with the Consolidated Standards of Reporting Trials Statement.<sup>17</sup>

Owing to a single-centre trial design and short-term study duration, no data monitoring committee will be established and no interim analyses will be conducted.

## ETHICS AND DISSEMINATION

### Consent

Written informed consent of the patient will be requested prior to the enrolment. The investigators will provide clear and precise information about the protocol to the patient before requesting him/her for written informed consent (information form and consent form appended).

### Confidentiality

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

### Dissemination policy

The results of the study will be released to the participating physicians, referring physicians and medical community no later than 1 year after the completion of the trial, through presentation at scientific conferences and publication in peer-reviewed journals.

The main manuscript will mention the name of the funder, and all the physicians and nurses involved in the project will be acknowledged. Authorship will be done in accordance with the guidelines of the International Committee of Medical Journal.

## DISCUSSION

Modern medicine is intimately linked to the increasing use of implanted medical devices such as PVC, which is the first vascular device inserted worldwide.<sup>1 2</sup> Despite their undeniable usefulness, they are responsible for a large number of complications. Bacteraemic and non-bacteraemic infections represent the most serious events but fortunately are rare. Catheter failure is much more common and leads to treatment interruption. Both complications may increase patients' dissatisfaction, burden of care, length of hospital stay, healthcare costs and mortality.

Preventing these complications is therefore essential. Although several improvements have been made over the last decades, some issues have remained unknown,

such as the best antiseptic solution to use for skin preparation and the value of new concepts such as needle-free connectors, disinfectant caps and regular flushing. To the best of our knowledge, CLEAN-3 will be the first large study powerful enough to explore these issues.

The combination of catheter colonisation, local infection and CR-BSI will be used as the primary endpoint to compare the efficacy of 2% CHG-alcohol over 5% PVI-alcohol. CR-BSI alone would have been more clinically relevant, but it would have taken more than 50 times as many catheters to reach a conclusion. Catheter colonisation is by far a much more common event and has been regularly used in the past as a surrogate for CR-BSI because catheter colonisation usually precedes CR-BSI.<sup>18 19</sup>

The time between catheter insertion and catheter failure was selected for the second primary endpoint. Catheter failure usually requires catheter replacement, which causes pain for patients and time loss for caregivers.<sup>5</sup> It also exposes patients to temporary interruption of treatment delivery, which can compromise their outcome.<sup>6</sup>

The strengths of our study include a relatively high number of catheters included, the training of all health-care staff in the use of the medical devices before starting inclusions, and the permanent presence of two clinical research nurses to ensure compliance with the protocol. Its weaknesses are the lack of masking related to the nature of the interventions, which is inherent to the difference in appearance of the products and devices compared. Nevertheless, robust and well-accepted criteria were chosen to define the different endpoints. In addition, the microbiologists who will be in charge of laboratory analyses will be masked to the treatment group. Finally, all bacteraemia, whether or not associated with PVC, will be reviewed by an adjudication committee masked to the study group.

Our results have the potential to modify the current recommendations on the prevention of PVC-related complications. The expected changes in practices should improve the quality of patient care and patient satisfaction. Although this is a single-centre study, the high number of patients included, the limited number of exclusion criteria and the participation of several wards suggest that the results will be extended to all emergency departments and wards worldwide.

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**Contributors** OM conceived the study and coordinated its design. JG and BD wrote the manuscript. OM, DF, JG, BD, RO, DC, CS, CP, SS read and were involved in

critical appraisal and revision of the manuscript. DF provided statistical expertise. All authors approved the final manuscript prior to submission.

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**Patient consent for publication** Not required.

**Ethics approval** The clinical trial will be carried out in line with the principles of the Declaration of Helsinki, the guideline for Good Clinical Practice of the *International Conference on Harmonisation*, in accordance with the French law No. 2012 – 300 of 5 March 2012 on research involving the human person and with the Clinical Trials Directives 2001/20/EC and 2005/28/EC of the European Parliament. Ethical aspects of this research project have been approved by the ethics committee of Sud-Ouest et Outre-Mer I (CPP SOOM I) and the National Agency for Drug Safety.

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## REFERENCES

- Keogh S, Flynn J, Marsh N, *et al*. Varied flushing frequency and volume to prevent peripheral intravenous catheter failure: a pilot, factorial randomised controlled trial in adult medical-surgical hospital patients. *Trials* 2016;17:348.
- Hadaway L. Short peripheral intravenous catheters and infections. *J Infus Nurs* 2012;35:230–40.
- Maki DG, Kluger DM, Crnich CJ. The risk of bloodstream infection in adults with different intravascular devices: a systematic review of 200 published prospective studies. *Mayo Clin Proc* 2006;81:1159–71.
- Mermel LA. Short-term peripheral venous catheter-related bloodstream infections: a systematic review. *Clin Infect Dis* 2017;65:1757–62.
- Tuffaha HW, Rickard CM, Webster J, *et al*. Cost-effectiveness analysis of clinically indicated versus routine replacement of peripheral intravenous catheters. *Appl Health Econ Health Policy* 2014;12:51–8.
- Maki DG. Risk Factors for Infusion-related Phlebitis with small peripheral venous catheters. *Ann Intern Med* 1991;114:845–54.
- Mimoz O, Lucet J-C, Kerforne T, *et al*. Skin antisepsis with chlorhexidine-alcohol versus povidone iodine-alcohol, with and without skin scrubbing, for prevention of intravascular-catheter-related infection (CLEAN): an open-label, multicentre, randomised, controlled, two-by-two factorial trial. *The Lancet* 2015;386:2069–77.
- Mimoz O, Chopra V, Timsit JF. What's new in catheter-related infection: skin cleansing and skin antisepsis. *Intensive Care Med* 2016;42:1784–6.
- Mimoz O, Chopra V, Widmer A. What's new in skin antisepsis for short-term intravascular catheters: new data to address old problems? *Intensive Care Med* 2016;42:2043–5.
- Frasca D, Dahyot-Fizelier C, Mimoz O. Prevention of central venous catheter-related infection in the intensive care unit. *Crit Care* 2010;14:212.
- Timsit JF, Rupp M, Bouza E, *et al*. A state of the art review on optimal practices to prevent, recognize, and manage complications associated with intravascular devices in the critically ill. *Intensive Care Med* 2018;44:742–59.
- Tabak YP, Jarvis WR, Sun X, *et al*. Meta-analysis on central line-associated bloodstream infections associated with a needleless intravenous connector with a new engineering design. *Am J Infect Control* 2014;42:1278–84.
- Clavier T, Ferguen M, Gouin P, *et al*. needle-free connector on the incidence of central venous catheter-related infections in surgical intensive care unit. *Aust Crit Care* 2018 (Published Apr 2018).
- Société Française d'Hygiène Hospitalière. Antisepsie de la peau saine avant un geste invasif chez l'adulte : recommandations pour la pratique clinique. 2016 <https://sf2h.net/wp-content/uploads/2016/05/Recos-Antisepsie-SF2H-2016.pdf>.
- Brun-Buisson C, Abrouk F, Legrand P, *et al*. Diagnosis of central venous catheter-related sepsis. Critical level of quantitative tip cultures. *Arch Intern Med* 1987;147:873–7.
- McAlister FA, Straus SE, Sackett DL, *et al*. Analysis and reporting of factorial trials: a systematic review. *JAMA* 2003;289:2545–53.
- Schulz KF, Altman DG, Moher D, *et al*. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;340:c332.
- Mimoz O, Villeminey S, Ragot S, *et al*. Chlorhexidine-based antiseptic solution vs alcohol-based povidone-iodine for central venous catheter care. *Arch Intern Med* 2007;167:2066.
- Rijnnders BJ, Van Wijngaerden E, Peetermans WE. Catheter-tip colonization as a surrogate end point in clinical studies on catheter-related bloodstream infection: how strong is the evidence? *Clin Infect Dis* 2002;35:1053–8.