2% chlorhexidine–70% isopropyl alcohol versus 10% povidone–iodine for insertion site cleaning before central line insertion in preterm infants: a randomised trial

Emily A Kieran, Anne O’Sullivan, Jan Miletin, Anne R Twomey, Susan J Knowles, Colm Patrick Finbarr O’Donnell

ABSTRACT

Objective To determine whether 2% chlorhexidine gluconate–70% isopropyl alcohol (CHX–IA) is superior to 10% aqueous povidone–iodine (PI) in preventing catheter-related bloodstream infection (CR-BSI) when used to clean insertion sites before placing central venous catheters (CVCs) in preterm infants.

Design Randomised controlled trial.

Setting Two neonatal intensive care units (NICUs).

Patients Infants <31 weeks’ gestation who had a CVC inserted.

Interventions Insertion site was cleaned with CHX–IA or PI. Caregivers were not masked to group assignment.

Main outcome measures Primary outcome was CR-BSI determined by one microbiologist who was masked to group assignment. Secondary outcomes included skin reactions to study solution and thyroid dysfunction.

Results We enrolled 304 infants (CHX–IA 148 vs PI 156) in whom 815 CVCs (CHX–IA 384 vs PI 431) were inserted and remained in situ for 3078 (CHX–IA 1465 vs PI 1613) days. We found no differences between the groups in the proportion of infants with CR-BSI (CHX–IA 7% vs PI 5%, p=0.631), the proportion of CVCs complicated by CR-BSI or the rate of CR-BSI per 1000 catheter days. Skin reaction rates were low (<1% CVC insertion episodes) and not different between the groups. More infants in the PI group had raised thyroid-stimulating hormone levels and were treated with thyroxine (CHX–IA 0% vs PI 5%, p=0.003).

Conclusions We did not find a difference in the rate of CR-BSI between preterm infants treated with CHX–IA and PI, and more infants treated with PI had thyroid dysfunction. However, our study was not adequately powered to detect a difference in our primary outcome and a larger trial is required to confirm our findings.

Trial registration This study was registered with the EU clinical trials register before the first patient was enrolled (EudraCT 2011-002962-19). (https://www.clinicaltrialsregister.eu)

INTRODUCTION

Central venous catheters (CVCs) are commonly used in preterm infants for the administration of parenteral nutrition (PN) and concentrated and vasoactive medications. Umbilical venous catheters (UVCs) and peripherally inserted central catheters (PICCs) are the most frequently used CVCs in newborns. Catheter-related bloodstream infection (CR-BSI) is the most common complication associated with CVCs in preterm infants. Late-onset sepsis (LOS) (ie, after 3 days of life) occurs in 20%–36% of very low birthweight (<1500 g) babies. The majority of LOS episodes are caused by CR-BSI. CR-BSI rates in newborns vary significantly between centres, with infection occurring more commonly in the most immature infants. Preterm infants who develop CR-BSIs have higher mortality rates, poorer growth and neurodevelopmental outcome, longer hospital stays and significantly higher overall estimated total hospital admission costs compared with those who do not.

To minimise the rate of CR-BSI, strict aseptic technique should be used when inserting and accessing CVCs. The most commonly available solutions used to disinfect the site prior to CVC insertion are chlorhexidine gluconate (CHX) of various concentrations either in aqueous solution or in combination with alcohol, which itself is an antiseptic agent, and povidone–iodine (PI) in aqueous solution or combined with alcohol. CHX has been shown to reduce the rate of infection compared with PI when used to disinfect skin prior to CVC insertion and surgery in randomised trials in adults. There is less evidence to guide practice in newborns.
Several studies have compared the two agents for CVC insertion site cleansing and CVC care in infants; however, only small numbers of preterm infants were enrolled, and few reported the primary outcome of CR-BSI. Skin burns have been reported in preterm infants exposed to CHX of various concentrations in both alcohol and aqueous solutions. The majority of tertiary NICUs use CHX of various concentrations combined with alcohol or water prior to CVC insertion in preterm infants. However, PI can also cause skin damage in preterm infants. Skin reactions to CHX combined with alcohol or water prior to CVC insertion, PI is still used by some clinicians. Infants were randomly allocated to the 2% chlorhexidine gluconate–70% isopropyl alcohol (CHX–IA) or PI group in a double lumen radio-opaque polyurethane UVCs and 28-gauge Premichat radio-opaque polyurethane PICCs, both Vygon, Ecouen, France).

Infants randomised to CHX–IA group had the CVC insertion site cleaned with 2% CHX with 70% IA (ChoraPrep 2% chlorhexidine w/v/isopropyl alcohol 70% v/v; Insight Health Limited, Wembley, UK). Each ampoule contained 0.67 mL of clear solution. The site was cleaned with one single use applicator for 30s and then allowed to dry naturally before CVC insertion. If a second ampoule was used, the reason for use was documented on the CVC checklist.

Infants randomised to PI group had the CVC insertion site cleaned with 10% PI w/w (Videne 10% w/w antiseptic solution; Adams Healthcare, Ecolab, Leeds, UK). Approximately 3 mL of brown PI was poured directly into a sterile dish, and a sterile cotton swab was dipped into it for 1–2s. The swab was squeezed to remove excess solution and used to clean the site for 30s. The area was allowed to dry naturally before CVC insertion.

Owing to the reported association with antiseptic solution use and skin damage in preterm infants, clinicians inserting CVCs were instructed to closely observe for any pooling of solution on the infant’s skin, for example, down the side of the abdomen or into skin creases, and any excess solution was removed using a sterile swab.

Decisions to remove CVCs and to perform blood cultures were at the discretion of treating clinicians. If blood cultures were taken, one paediatric aerobic blood culture bottle (Peds Plus/F Culture Vial; Becton Dickinson, Oxford, UK or BacT/ALERT PF culture bottle; BioMerieux, Marcy-l’Étoile, France) was used. Blood cultures were analysed on one of two commercial analysers, approved for use with paediatric samples (Bactec; Becton Dickinson, Oxford, UK or BacTAlert; BioMerieux, Marcy-l’Etoile, France). At both centres, CVCs could remain in place when sepsis was suspected. However, if the blood culture were positive, the CVC was removed, the tip (5 cm length, cut using sterile blade) was sent for culture and a further blood culture was taken from a different peripheral site. A second blood culture was not taken if the first was negative. The tips of CVC that were removed that were not suspected to be infected were not cultured. Only the external surface of the catheter was cultured using the method previously described by Maki et al. Infants at both centres suspected of having LOS
were empirically treated with fluocoxacillin and gentamicin as a first line. Vancomycin could subsequently be used if CRBSI was confirmed, and treatment was considered appropriate. Antibiotics for CRBSI were not given through a CVC that was suspected to be infected.

The primary outcome for our study was the number of infants with a CR-BSI. Infants were diagnosed with a CR-BSI if they were >72 hours of age and had a CVC in situ or removed within the previous 48 hours and met at least one of the following three criteria:

- a recognised pathogen (eg, Staphylococcus aureus and Candida species) in one peripheral blood culture (ie, not taken through CVC) that was not related to an infection at another site (eg, meningitis or skin abscess),
- a common skin commensal (eg, coagulase-negative Staphylococcus (CONS)) cultured from two or more peripheral blood cultures drawn on separate occasions,
- a common skin commensal (eg, CONS) isolated from one peripheral blood culture with a CVC tip culture growing >15 colony-forming units of a pure growth of the same organism.

Caregivers were not masked to the infants’ group assignment. The primary outcome for all infants was determined from blood and CVC tip culture results by one consultant microbiologist (SJK) who was masked to the infant’s group assignment.

We recorded clinically relevant secondary outcomes. Total number of CVCs and total catheter days per infant along with recognised complications of CVCs were recorded.

Any area of skin irritation, erythema, excoriation or breakdown that was in the distribution of contact with the investigational medicinal product, and brought to the attention of the research team, was reported as an adverse skin reaction caused by a study solution.

As is the routine practice for all preterm infants admitted to the participating centres, enrolled infants had a newborn screening card sent weekly until established on full enteral feeds. Screening cards for all newborns in Ireland are sent to the National Newborn Screening Laboratory. Thyroid-stimulating hormone (TSH) values from 8 to 15 mU/L trigger a request for a repeat sample, and if persistently >15 mU/L prompt a request for formal serum thyroid function tests. Any abnormal TSH levels on newborn screening card or subsequent serum TSH levels on newborn screening card or subsequent serum sample were recorded. Episodes of culture negative/suspected sepsis (defined as clinical signs of sepsis, for example, increased frequency of apnoea, tachycardia or temperature instability, with negative blood culture, and treated with ≥5 days antibiotics) were reported. All secondary outcomes were determined before discharge home from hospital unless stated otherwise.

To demonstrate a reduction in the rate of CR-BSI from 35% with PI to 20% with the use of CHX–IA with 80% power and a=0.05, we aimed to recruit 276 infants. We anticipated that a significant reduction in the rate of CR-BSI would allow for a death of extreme prematurity in the first 72 hours of life and would not reach the primary outcome. To allow for a death rate of 10% before 72 hours, we planned to recruit 304 infants. Results for CR-BSI were analysed per infant, per catheter and also reported per 1000 CVC days.44 Data for all randomised babies who met entry criteria were analysed using the intention-to-treat principle with PASW V.20 software (IBM, Armonk, New York, USA). We compared the primary outcome and dichotomous secondary outcomes with non-parametric tests (Fisher’s exact test), continuous secondary outcomes with parametric tests (Student’s t-test) and considered p values <0.05 statistically significant.

Results

A total of 310 infants were randomised at the NMH and CWIUH between November 2011 and September 2014 (151 CHX–IA and 159 PI) (figure 1). Six infants were withdrawn postrandomisation as they met the protocol-specified exclusion criteria (five with congenital anomalies and one infant born at 31 weeks). We enrolled 304 infants (CHX–IA 148 vs PI 156) in whom 815 CVCs—200 UVCs and 615 PICCs—(CHX–IA 384 vs PI 431) were inserted and remained in situ for 3078 (CHX–IA 1465 vs PI 1613) days. Data were analysed for all 304 infants. The majority of infants were randomised on the first day of life (day 0, table 1), and CVCs were inserted as soon as possible after randomisation. All enrolled infants had a CVC successfully inserted.

![Figure 1](http://fn.bmj.com/)

**Table 1** Patient demographics

<table>
<thead>
<tr>
<th></th>
<th>CHX–IA (n=148)</th>
<th>PI (n=156)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (weeks)*</td>
<td>27 (2)</td>
<td>27 (2)</td>
<td>0.558</td>
</tr>
<tr>
<td>Birth weight (g)*</td>
<td>1017 (289)</td>
<td>1014 (326)</td>
<td>0.92</td>
</tr>
<tr>
<td>Male†</td>
<td>81 (55)</td>
<td>69 (44)</td>
<td>0.067</td>
</tr>
<tr>
<td>Antenatal steroid exposure†</td>
<td>144 (97)</td>
<td>155 (99)</td>
<td>0.309</td>
</tr>
<tr>
<td>Clinical chorioamnionitis†</td>
<td>14 (9)</td>
<td>24 (15)</td>
<td>0.082</td>
</tr>
<tr>
<td>Multiple birth†</td>
<td>62 (42)</td>
<td>54 (35)</td>
<td>0.509</td>
</tr>
<tr>
<td>Apgar score at 1 min*</td>
<td>6 (2)</td>
<td>6 (2)</td>
<td>0.537</td>
</tr>
<tr>
<td>Apgar score at 5 min*</td>
<td>8 (2)</td>
<td>8 (2)</td>
<td>0.364</td>
</tr>
<tr>
<td>Ventilation prereandomisation†</td>
<td>64 (43)</td>
<td>78 (50)</td>
<td>0.143</td>
</tr>
<tr>
<td>UVC as first CVC†</td>
<td>102 (69)</td>
<td>100 (64)</td>
<td>0.221</td>
</tr>
<tr>
<td>Day of life randomised‡</td>
<td>96 (65)</td>
<td>104 (67)</td>
<td>0.809</td>
</tr>
<tr>
<td>UVC first inserted (CHX–IA 96, PI 104)</td>
<td>0 (0, 1)</td>
<td>0 (0, 0)</td>
<td>0.438</td>
</tr>
<tr>
<td>PICC first inserted (CHX–IA 52, PI 52)</td>
<td>1 (0, 1)</td>
<td>1 (0, 1)</td>
<td>0.121</td>
</tr>
<tr>
<td>Total CVCs</td>
<td>384 (431)</td>
<td>328 (431)</td>
<td>0.328</td>
</tr>
<tr>
<td>Total CVC days</td>
<td>1465 (1613)</td>
<td>1465 (1613)</td>
<td>0.400</td>
</tr>
<tr>
<td>Duration CVC in situ per patient (days)‡</td>
<td>9 (6, 12)</td>
<td>9 (6, 13)</td>
<td>0.553</td>
</tr>
</tbody>
</table>

Data are * mean (SD), †n (%), ‡ median (IQR). CR-BSI, 2% chlorhexidine–70% isopropl alcohol; CPAP, continuous positive airway pressure; CVC, central venous catheter; PI, 10% aqueous povidone–iodine; UVC, umbilical venous catheter.


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There were two protocol violations where infants randomised to one agent received the other when a second CVC insertion was attempted. All analyses presented were performed using a modified ‘intention-to-treat’ principle (ie, not including the six infants who met the exclusion criteria). We have not performed a separate per-protocol analysis.

The groups were well matched for demographic variables at study entry (table 1). Twenty of the 815 (2%) CVCs that were inserted became infected, 3 UVCs and 17 PICCs. There were no differences between the groups in the primary outcome of CR-BSI per patient (CHX–IA 10/148 (6.8%) vs PI 8/156 (5.1%), p=0.631; OR (95%CI) 0.746 (0.286–1.945)); nor differences when the data were analysed per catheter (CHX–IA 10/384 (2.6%) vs PI 10/431 (2.3%), p=0.824) or per 1000 catheter days (CHX–IA 6.8 vs PI 6.2) (table 2). The mean (SD) number of CVCs successfully inserted per infant was 3 (1), and median (IQR) CVC days per infant was 9 (6–13). Similar numbers of catheters were inserted in both groups and they were in situ for similar durations (table 3). The number of blood cultures taken from enrolled infants during their hospital admission was not different between the groups (table 3).

The rates of skin reaction were low and not different between the groups (per patient—CHX–IA 3/148 (2%) vs PI 2/156 (1%); per CVC episode—CHX–IA 3/384 (0.78%) vs PI 2/431 (0.46%). All reported skin reactions occurred in infants <28 weeks of GA. All five episodes resolved without consequence, and no infant required plastic surgery review or specialist treatment.

Raised TSH was detected in 12 infants on newborn screening; all were randomised to the PI group and occurred after PI exposure (none had a raised TSH on cards sent prior to PI). Ten of these 12 infants had raised TSH on serum sampling and eight were treated with thyroxine replacement therapy on the advice of paediatric endocrinologists. All eight infants had normal thyroid function tests after commencing on treatment and at hospital discharge. All were discharged home on thyroxine with endocrinology follow-up.

Other secondary outcomes are shown in table 3. More infants randomised to PI were treated with supplemental oxygen at 36 weeks of corrected GA (CGA) (CHX–IA 27 (18.2%) vs PI 47 (30%), p=0.017). There were no differences between the groups in any of the other secondary outcomes we measured. In particular, rates of LOS (defined as laboratory confirmed sepsis (positive blood or cerebral spinal fluid culture for a recognised pathogen) after 72 hours of age and not related to a CVC) were similar between the groups (table 3). Similar proportions of infants were treated for suspected sepsis during hospital admission (CHX–IA 13 (8.7%) vs PI 12 (7.7%), p=0.835).

We found no differences in outcomes according to subgroups of GA, type of catheter first inserted or participating centre.

### Table 2 Primary outcome

<table>
<thead>
<tr>
<th></th>
<th>CHX–IA (n=148)</th>
<th>PI (n=156)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome per infant*</td>
<td>10/148 (6.8)</td>
<td>8/156 (5.1)</td>
<td>0.631</td>
</tr>
<tr>
<td>Primary outcome per catheter*</td>
<td>10/384 (2.6)</td>
<td>10/431 (2.3)</td>
<td>0.824</td>
</tr>
<tr>
<td>Per 1000 catheter days</td>
<td>6.8/1000</td>
<td>6.2/1000</td>
<td>0.121</td>
</tr>
</tbody>
</table>

* n (%), † Fisher’s exact test.

### Table 3 Secondary outcomes

<table>
<thead>
<tr>
<th></th>
<th>CHX–IA (n=148)</th>
<th>PI (n=156)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin damage from IMP*</td>
<td>3 (2)</td>
<td>2 (1.3)</td>
<td>0.677</td>
</tr>
<tr>
<td>Raised TSH on screening*</td>
<td>0 (0)</td>
<td>12 (7.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Raised TSH in serum*</td>
<td>0 (0)</td>
<td>10 (6.4)</td>
<td>0.002</td>
</tr>
<tr>
<td>Treatment with thyroxine*</td>
<td>0 (0)</td>
<td>8 (5.1)</td>
<td>0.003</td>
</tr>
<tr>
<td>Confirmed LOS (non-CR-BSI)*</td>
<td>17 (11.5)</td>
<td>26 (16.7)</td>
<td>0.249</td>
</tr>
<tr>
<td>Suspected sepsis</td>
<td>13 (8.7)</td>
<td>12 (7.7)</td>
<td>0.825</td>
</tr>
<tr>
<td>Courses of antibiotics per patient†</td>
<td>2 (2.4)</td>
<td>3 (2.4)</td>
<td>0.588</td>
</tr>
<tr>
<td>Total days of antibiotics per patient‡</td>
<td>5 (2.12)</td>
<td>5 (2.12)</td>
<td>0.786</td>
</tr>
<tr>
<td>No of blood cultures performed per patient‡</td>
<td>3 (2.5)</td>
<td>3 (2.5)</td>
<td>0.319</td>
</tr>
</tbody>
</table>

* n (%), † median (IQR).

Data are * n (%), † median (IQR).

CGA, corrected gestational age; CHX–IA, 2% chlorhexidine–70% isopropyl alcohol; CRUSS, cranial ultrasound scan; IMP, investigational medicinal product; IVH, intraventricular haemorrhage; LOS, late-onset sepsis; NEC, necrotising enterocolitis; PI, 10% aqueous povidone–iodine; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity; TSH, thyroid-stimulating hormone.

Discussion

Our study is one of the few randomised trials of skin cleaning agents before CVC insertion performed in newborns. We did not find a difference in the rate of our primary outcome of CR-BSI between the two groups. However, the incidence of CR-BSI in our study population (5.9% of infants) was much lower than we anticipated at the time that the study protocol was prepared. This renders our study significantly underpowered to detect a difference in our primary outcome and is a major weakness. To demonstrate a treatment effect of the size that we postulated with the CR-BSI rate that we ultimately measured, we would need to study more than 2000 infants. Several factors could account for these lower than expected CR-BSI rates. Just prior to starting, routine use of sterile gowns and gloves when accessing CVCs (for PN bag changes and medication administration) and cleaning of CVC hubs with swabs containing 2% CHX–IA prior to accessing the line was introduced in both centres. Either or both of these changes to practice may have contributed to the decrease in CR-BSI rates. The use of standardised CVC checklists and care bundles is known to decrease CR-BSI infection rates in NICUs by up to 67%. The CVC insertion checklists introduced to aid consistency in the trial may have themselves contributed to decreased CR-BSI rates. Performing a study of CR-BSI may in itself have decreased CR-BSI rates as staff involved in CVC insertion and care may have become more attentive when inserting and handling CVCs.

A weakness of our study is that it was not masked. The solutions we used looked different—CHX–IA was colourless, whereas PI was brown—and so operators inserting CVCs and caregivers in the NICU were aware of the infants’ group assignment. The primary outcome for all infants was determined by one consultant microbiologist who reviewed all relevant laboratory results and who was masked to each infant’s group allocation. To decrease the risk of bias, we chose strict laboratory-based diagnostic criteria for our primary outcome of CR-BSI.
The numbers of blood cultures taken from infants and episodes of ‘culture negative/suspected sepsis’ during their hospital stay did not differ between the groups. We believe this indicates that infants were not treated systematically differently according to their group assignment.

To ensure consistency between study centres, operators in both hospitals used maximal sterile barrier precautions during CVC insertion. The same type of catheters were used and transparent dressings were used in all infants. Operators enrolling infants and inserting CVCs were given formal training in CVC insertion procedure prior to participating. A study-specific CVC checklist was completed after each CVC insertion and these were regularly reviewed by one of the investigators to ensure adherence to the study protocol.

Alcohol in 70% concentration can be used alone for CVC insertion site antisepsis. It has an instant effect and provides excellent cover against Gram-negative organisms, including *Escherichia coli*, the most frequent cause of Gram-negative CR-BSI in preterm infants. It was, however, shown to be less effective than 2% aqueous chlorhexidine for preventing CR-BSI in adults. For these reasons, alcohol is commonly used in combination with CHX or with PI for skin antisepsis. We chose to compare the effect of CHX combined with alcohol to aqueous PI as these solutions are widely used in neonatal units and were the two solutions in use in the participating centres prior to the study.

Different considerations apply to the insertion sites for UVCs and PICCs. Most often, UVCs are inserted within hours of birth through the usually sterile cut end of the umbilical stump and remain in situ for less than a week. PICCs are more often inserted a day or more after birth through skin that may be colonised and may remain in situ for more than a week. This implies that the risk of CR-BSI may be higher with PICCs and that insertion site antisepsis has a more important role in this setting. This underpinned our rationale for stratifying our randomisation by the type of CVC first inserted. Many preterm infants who have a UVC inserted subsequently have a PICC inserted. We designed this study to determine whether CHX–IA used before CVC insertion reduced CR-BSI in preterm infants and did not aim to determine differential effects for UVC or PICC insertion.

Though alcohol-containing solutions are often regarded as too harsh for open wounds and mucous membranes, we did not see adverse effects of CHX–IA during UVC insertion. We suspect that the pain that arises when alcohol is applied to open wounds is not an issue during UVC insertion as the umbilical cord does not have sensory innervation. We saw few skin reactions in our study population. We believe that minimising the amount of skin antisepsis has a more important role in this setting. This underpinned our rationale for stratifying our randomisation by the type of CVC first inserted. Many preterm infants who have a UVC inserted subsequently have a PICC inserted. We designed this study to determine whether CHX–IA used before CVC insertion reduced CR-BSI in preterm infants and did not aim to determine differential effects for UVC or PICC insertion.

Conclusions

We did not find a difference in the rate of CR-BSI between preterm infants who had their skin insertion site prior to CVC insertion cleaned with CHX–IA compared with PI, and more infants treated with PI had thyroid dysfunction and were treated with thyroxine. However, our study was not adequately powered to detect a difference between the groups in our primary outcome, and a larger trial is required to confirm our findings.

Contributors

EAK made substantial contributions to the conception and design of the study. She oversaw patient enrolment and conducted trial at the National Maternity Hospital and Coombe Women and Infants University Hospital. She also acquired the data. Together with CPFOD, she had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. She wrote the first draft of the manuscript. ADS oversaw patient enrolment and conducted trial at the Coombe Women and Infants University Hospital and acquired the data for infants enrolled at that site. IM made substantial contributions to the design of the study. He was the primary investigator at the Coombe Women and Infants University Hospital. ART made substantial contributions to the design of the study. She critically reviewed the trial protocol and final manuscript for important intellectual content. SIK made substantial contributions to the design of the study. She determined the primary outcome for all infants enrolled in the study. She critically reviewed the trial protocol and final manuscript for important intellectual content. CPFOD conceived and designed the study. He was the principal investigator overseeing the trial. He was the primary investigator at the National Maternity Hospital. Together with EAK, he had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. He redrafted the manuscript and revised it for important intellectual content. All authors approved this version of the manuscript and are in agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding

The trial was funded by the National Children’s Research Centre (NCRC), Dublin, Ireland.

Patient consent

Parental/guardian consent obtained.

Ethics approval

Research ethics board at the National Maternity Hospital and Coombe Women and Infants University Hospital. In addition, the study protocol was approved by the Health Products Regulatory Authority in Ireland.

Provenance and peer review

Not commissioned; externally peer reviewed.

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REFERENCES


