Effect of infusion set replacement intervals on catheter-related bloodstream infections (RSVP): a randomised, controlled, equivalence (central venous access device)–non-inferiority (peripheral arterial catheter) trial

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Summary

Background The optimal duration of infusion set use to prevent life-threatening catheter-related bloodstream infection (CRBSI) is unclear. We aimed to compare the effectiveness and costs of 7-day (intervention) versus 4-day (control) infusion set replacement to prevent CRBSI in patients with central venous access devices (tunnelled cuffed, non-tunnelled, peripherally inserted, and totally implanted) and peripheral arterial catheters.

Methods We did a randomised, controlled, assessor-masked trial at ten Australian hospitals. Our hypothesis was CRBSI equivalence for central venous access devices and non-inferiority for peripheral arterial catheters (both 2% margin). Adults and children with expected greater than 24 h central venous access device–peripheral arterial catheter use were randomly assigned (1:1; stratified by hospital, catheter type, and intensive care unit or ward) by a centralised, web-based service (concealed before allocation) to infusion set replacement every 7 days, or 4 days. This included crystalloids, non-lipid parenteral nutrition, and medication infusions. Patients and clinicians were not masked, but the primary outcome (CRBSI) was adjudicated by masked infectious diseases physicians. The analysis was modified intention to treat (mITT). This study is registered with the Australian New Zealand Clinical Trials Registry ACTRN12610000505000 and is complete.

Findings Between May 30, 2011, and Dec, 9, 2016, from 6007 patients assessed, we assigned 2944 patients to 7-day (n=1463) or 4-day (n=1481) infusion set replacement, with 2941 in the mITT analysis. For central venous access devices, 20 (1·78%) of 1124 patients (7-day group) and 16 (1·46%) of 1097 patients (4-day group) had CRBSI (absolute risk difference [ARD] 0·32%, 95% CI –0·73 to 1·37). For peripheral arterial catheters, one (0·28%) of 357 patients in the 7-day group and none of 363 patients in the 4-day group had CRBSI (ARD 0·28%, –0·27% to 0·83%). There were no treatment-related adverse events.

Interpretation Infusion set use can be safely extended to 7 days with resultant cost and workload reductions.

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Introduction

Many patient groups and therapies require a central venous access device or peripheral arterial catheter. These invasive devices can cause substantial patient harm from catheter-related bloodstream infection (CRBSI), requiring additional associated hospital days and costs.[1–3] CRBSIs account for around 70% of all health-care associated bloodstream infections[4] and are the most costly health-care associated infection, with an attributable cost of US$45 814 per case.[3]

Numerous CRBSI prevention guidelines exist, but the most effective known strategies are applied at the time of insertion.[5–7] Conversely, the subsequent catheter dwell represents the majority of time at risk, but has less supporting evidence for infection prevention.[5] One post-insertion intervention is the routine replacement of infusion sets. This requires the disconnection, discard, and replacement of all infusates, medications, tubing, and component parts at recurring intervals during catheter dwell.[8] This strategy assumes that although infusion sets might become contaminated during use, CRBSI can be avoided by intermittent replacement with new, sterile sets. The procedure was instigated after endemic outbreaks in the USA half a century ago, amidst which the Centers for Disease Control (CDC) recommended 24 hourly infusion set replacement.[9] Most contemporary guidelines recommend infusion set replacement every 4 days[4,5] with the CDC recommending replacement "no more frequently than 96 hours, but at least every 7 days".[6]

Because infusion set replacement requires one or more skilled nurses and substantial amounts of disposable

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Research in context

Evidence before this study

We searched MEDLINE, CINAHL, Embase, Cochrane Central Register of Controlled Trials, and international clinical trials registries for randomised, controlled trials comparing durations of infusion set use. Search terms included "Catheterisation", "Catheters, indwelling", "Parenteral Nutrition", "Infusions, intravenous", "Line change", "Administration/infusion set", "Transducer", "Tubing", "Replacement", "Timing", and "Time-frame". The search was not restricted by language or date. We also searched reference lists of articles identified by this strategy. We published a systematic review in 2013 with the last search being June, 2012; a repeat of this search in March, 2020, identified no additional trials.

Our review summarised 16 trials with a total of 5001 participants. The trials compared various timeframes of infusion set replacement, from 1 to 7 days. Many studies were of low to medium quality. No evidence was found for differences in catheter-related bloodstream infection (CRBSI) with more frequent infusion set replacement (risk ratio (RR) 1·06, 95% CI 0·67–1·69) although less frequent infusion set replacement reduced all-cause bloodstream infection (RR 0·72, 0·54–0·98). One study suggested that less frequent infusion set replacement increased mortality within the neonatal population (RR 1·84, 1·00–3·36). No evidence revealed interactions between the effects of frequency of set replacement and subgroups of infusion (parenteral nutrition or fat emulsions), participant (adults, children, or neonates), or catheter (arterial or venous) type.

Previous studies did not provide a conclusive answer as to the optimal timing for infusion set replacement. Only two small studies tested use beyond 4 days. Some studies were limited to particular groups of patients, and costs were not considered. We concluded that a large trial was needed.

Added value of this study

In this large, randomised, controlled, pragmatic trial in ten hospitals, adult and paediatric patients with central venous access devices or peripheral arterial catheters were randomised to infusion set replacement every 7 days, or 4 days (controls). The study showed that 7-day compared with 4-day infusion set replacement for the prevention of CRBSI was equivalent for central venous access devices and non-inferior for peripheral arterial catheters. Costs were lower in the 7-day infusion set replacement group.

Implications of all the available evidence

Our trial indicates that 7-day compared with 4-day replacement of infusion sets is safe. Our results confirm the findings of previous, smaller trials in patients in intensive care and in patients with cancer. Extension of use to 7 days can substantially reduce workload and health-care costs.

sterile equipment as well as pharmaceutical resources, the procedure affects workloads and costs. The optimal infusion set replacement frequency has not been established in randomised, controlled trials. Infusion sets might actually become contaminated during the handling required for the procedure, consistent with the source of most CRBSIs being direct contamination from health workers' hands.[6] A 2013 Cochrane review identified no superior time interval for infusion set replacement, low to medium quality evidence, and only two small randomised, controlled trials investigating set use for longer than 4 days.[8] We tested the efficacy and effect on costs of extending intervals for replacement of infusion sets from 4 to 7 days. Our aim was to provide high quality evidence to inform clinical practice guidelines that maintain patient safety and use resources wisely.

Methods

Study design and participants

We did a randomised, controlled, equivalence, assessor-masked trial at nine government-run and one private (eight adult and two paediatric), teaching hospitals in Australia. The trial was designed to separately test an equivalence hypothesis for central venous access devices and a non-inferiority hypothesis for peripheral arterial catheters (owing to low baseline CRBSI); otherwise the protocol was identical for both devices. Initially, the trial was designed to test the central venous access device hypothesis separately for peripherally inserted central catheters (PICCs) and other central venous access devices, but these were merged into one central venous access device cohort on the advice of the data safety monitoring committee at an interim review. Only one central venous access device or peripheral arterial catheter per patient episode of hospitalisation was studied. Human research ethics committee (HREC) approval was obtained in Queensland, New South Wales Hospitals, and Western Australia, and from Griffith University, QLD, Australia. The RSVP study protocol has been published.[10]

We recruited across hospital inpatient units (medical, surgical, cancer, and intensive care units [ICUs], except for neonatal ICUs). Patients were adults, children, or infants (of any age) with a central venous access device (PICC, tunnelled cuffed or non-tunnelled central venous access device, or totally implanted port) or peripheral arterial catheter, in place for at least 24 h and expected to remain in place for at least 7 days, with infusion set(s) attached. We excluded patients with a bloodstream infection within the previous 48 h, whose catheters had been in situ for more than 96 h, or who had had their original infusion set(s) already routinely replaced. Patients were screened for eligibility by research nurses and the study was explained to them or their representative. Informed written consent was

obtained or waived as per local ethics committee requirements.[10]

Randomisation and masking

Randomisation was computer-generated per participant by a centralised, computerised service, purpose built by Griffith University's eResearch Services. The research nurse contacted the service at the time of each patient's study entry (allocation concealed until this point). We used randomly varied block sizes, stratified by catheter type (central venous access device–cuff central venous access device–PICC–port–peripheral arterial catheter), hospital (including adult and paediatric), and intensive care or ward setting, in a 1:1 ratio. Randomisation was to infusion set replacement every: 7 days, or 4 days (controls). Patients and clinical staff were unable to be masked to allocation owing to the nature of the intervention. The primary endpoint and other infection endpoints were adjudicated by a masked infectious diseases physician and processed by a masked microbiologist. A study manager trained and supervised the research nurses, did site visits, and audited data quality and randomisation compliance.

Procedures

The day of catheter insertion was designated as day 1. Subsequently, the intervention group had their infusion set(s) discarded and replaced every 7 days and the control group every 4 days. Infusion sets included fluid bags or syringes, infusion tubing, and any burettes, transducers, extension tubing, or 3-way stopcocks present. Infusion sets included crystalloids (eg, saline), medication infusions (eg, sedation), non-lipid parenteral nutrition, and pressure monitoring infusions (saline or heparin saline). Excluded were lipids, inotropes, chemotherapy, cyclosporin, and blood products—these followed institutional or manufacturer protocols which were typically at least 24 h, or for inotropes when the bag needed replenishing, or when the patient was haemodynamically stable. All infusion sets were replaced on the allocated day, regardless of how long individual components had been in place.

Preparation of new sets and the replacement procedure were done by one or two clinical nurses (two if complex) by means of hand hygiene, the Aseptic Non-Touch Technique, and decontamination of the connection point before disconnection. Researchers did not do the intervention. Medication infusions were prepared by manufacturers, the local pharmacy, or clinical nurses by means of the Aseptic Non-Touch Technique. Patients were followed up until catheter removal, infusions had ceased for 21 days, or if discharged home with the central venous access device in situ.

Research staff provided protocol training, but all care was provided by hospital staff. Catheter type and size were based on patient or treatment factors, with antimicrobial central venous access devices generally preferred in patients in the ICU and all other catheters non-impregnated. Heparinised catheters, antimicrobial connectors and in-line filters were not used. Procedures were consistent with CDC and epic3 guidelines, including full sterile barrier precautions for central venous access device insertion and sterile gloves and drape for peripheral arterial catheter insertion; skin preparation with 2% chlorhexidine gluconate in 70% isopropyl alcohol; sterile occlusive transparent dressings; and disinfection of needleless connectors with 70% isopropyl alcohol before each access.[4,6] Blood, tip, and exudate cultures were done in response to clinical suspicion of infection (new fever, chills, or hypotension), not routinely, consistent with clinical practice guidelines.[11] Microbiologists were masked and used existing hospital pathology protocols. Catheters were removed as clinically indicated, not routinely.

Patient and catheter characteristics were recorded at baseline. Thereafter, all intravenous therapy and infusion set replacements were recorded by bedside nurses and audited by research nurses. At completion of trial participation, we collected the reason for catheter removal, dwell time, and outcome variables. Microbiological results were collected up to 48 h post-catheter removal. All data were entered into password-protected portable electronic devices with a purpose-built interface (initially Microsoft Access then REDCap: Research Electronic Data Capture). Clinical staff did not have access to these data.

For more on **REDCap** see project-redcap.org

To further assess the risk of infusion set colonisation, if research staff were available when the sets were replaced, we swabbed the old set (burette port, burette spike, and injection ports) and sampled saline flush effluent through the 3-way stopcock and extension tubing. These samples were placed in saline, vortexed, plated onto growth media, and incubated for 24 h. Bacteria were identified by means of selective media and matrix assisted laser desorption or ionisation time of flight mass spectrometry. Bacterial load was determined semiquantitatively by assessing total colony forming units (CFUs).

Outcomes

The primary endpoint was CRBSI, which was centrally assessed by masked infectious diseases physicians (EGP, NR) who reviewed deidentified data extracted from hospital records. CRBSI was defined as a bacteraemia or fungaemia (with clinical manifestations of infection and no other identifiable source) and at least one positive blood culture from a peripheral vein, plus matching organism(s) found on the catheter tip (>15 CFUs on semiquantitative culture); or, two blood cultures (one from catheter, one from peripheral vein) with matching organism(s) that met the criteria for differential time to positivity (growth of catheter-drawn blood at least 2 h before growth from a peripheral vein blood culture).[11]

For the **Aseptic Non-Touch Technique** see http://www.antt.org/ANTT_Site/home.html

Secondary outcomes comprised catheter tip colonisation (>15 CFUs);[6] infusion set colonisation (≥10^3 CFU/mL);[12,13]

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all-cause bloodstream infection (laboratory-confirmed bloodstream infection [LCBI]); during the study, new National Healthcare Safety Network definitions differentiated LCBI–central line-associated bloodstream infection (CLABSI) from mucosal barrier injury–LCBI, so we also reported CLABSI (no apparent source other than the catheter, and at least two sets of positive blood cultures required for common commensals);[14] all-cause mortality at hospital discharge; catheter time in situ;[6] individual infusion sets used per patient (eg, one bag of saline with associated infusion tubing equalled one set); and, costs of consumables and staff time for doing all infusion set replacement procedures per patient.[10]

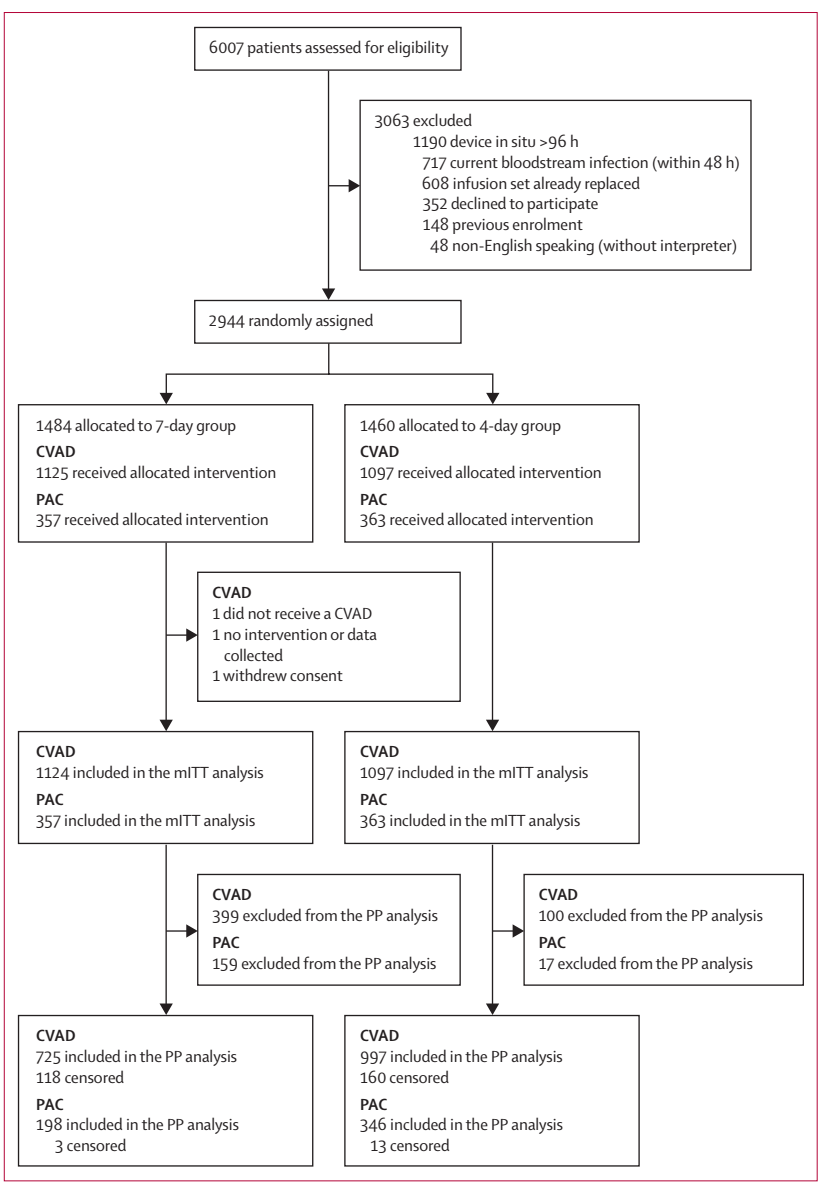

Figure 1: **Trial profile**
CVAD=central venous access device. PAC=peripheral arterial catheter. mITT=modified intention to treat. PP=per protocol.

Serious adverse events including all-cause bloodstream infection, mortality or new admission to ICU were adjudicated for possible trial-relatedness by the masked infectious diseases physicians (EGP, NR) and reported to the HRECs. The safety of participants, recruitment rates, and data quality were overseen by an independent data and safety monitoring committee (DSMC), which reviewed masked data on two occasions. There were no early stopping rules.

Detailed resource use was recorded for 20 infusion set replacements, with five per device for peripheral arterial catheters, PICCs, tunnelled cuffed, and non-tunnelled central venous access devices. Ports were not recorded owing to low numbers. We measured nursing time to gather equipment, prepare new infusion sets, communicate with the patient or family, decontaminate connection points, disconnect old infusion sets, connect new infusion sets, dispose of waste, and document the procedure. Infusion set and other procedural equipment costs were taken from purchasing contracts and published wage rates (2019).[15]

Statistical analysis

Initial sample size calculations were done separately for the three device types. We chose a conservative equivalence hypothesis (±2% margins, p=0·05) for PICCs (baseline CRBSI PICC 2·4%) and other central venous access devices (baseline CRBSI 2·6%), which required 1371 central venous access devices per group and 1268 PICCs per group (originally calculated for a two-sided 90% CI). We chose a non-inferiority approach for peripheral arterial catheter, considering further reduction from baseline 0·8% CRBSI was of low clinical importance (2% margin, p=0·05) requiring 340 peripheral arterial catheters per group. Equivalence (two-sided) and non-inferiority (one-sided) decisions were thus based on the 95% CIs of the absolute risk difference between study groups. At the second DSMC review, owing to slower than anticipated recruitment, the committee recommended that central venous access devices and PICCs be merged into one central venous access device cohort with 1110 central venous access devices required per group (estimated control group CRBSI 1·9%, equivalence hypothesis ±2% margins), with the peripheral arterial catheter sample size unchanged. We considered this acceptable because CRBSI incidence in hospitalised patients is similar for central venous access device subtypes,[16,17] and because guideline recommendations and hospital policies about infusion set replacement do not discriminate by central venous access device type.[4–6]

Data cleaning involved checks of missing, outlier, and improbable values, with additional source data verification by the project manager. We summarised categorical data as counts and proportions, and continuous or ordinal data as means (SD) or medians (IQR) if not normally distributed. Group characteristics at baseline were tabulated. Missing data were not imputed.

	7-day group (n=1481)	4-day group (n=1460)
Total days studied	17 196	17 438
Adults	1293 (87·3%)	1259 (86·2%)
Age, years	59·0 (47–68)	57·0 (45–67)
Paediatrics	188 (12·7%)	201 (13·8%)
Age, years	3·2 (0·9–10·0)	2·3 (0·8–8·0)
Male	935 (63·1%)	915 (62·7%)
Female	546 (36·9%)	545 (37·3%)
Hospital day at entry	5 (3–9·5)	4 (3–8)
Diagnosis		
Medical—general	452 (30·5%)	483 (33·1%)
Medical—haematology	322 (21·8%)	318 (21·8%)
Emergency surgical	236 (16·0%)	225 (15·4%)
Elective surgical	152 (10·3%)	134 (9·2%)
Cardiac surgical	122 (8·2%)	117 (8·0%)
Trauma	110 (7·4%)	108 (7·4%)
Oncology (medical or surgical)	70 (4·7%)	61 (4·2%)
Burns	16 (1·1%)	14 (1·0%)
Intensive care unit patients	912 (61·6%)	931 (63·8%)
Intensive care unit APACHE II	19·7 (6·8)	19·8 (7·1)
Catheter on right side of body	950 (64·2%)	934 (64·0%)
Diabetes	232 (15·7%)	229 (15·7%)
Leukopenia (white cell count <1·0 × 10⁹ per L at trial entry)	71 (4·8%)	77 (5·3%)
Catheter type		
CVAD	1124 (75·9%)	1097 (75·1%)
Tunnelled cuffed or implanted port	203 (13·7%)	197 (13·5%)
Non-tunnelled	486 (32·8%)	489 (33·5%)
PICC	435 (29·4%)	411 (28·2%)
PAC	357 (24·1%)	363 (24·9%)
Vein—CVAD		
Internal jugular	323 (66·5%)	320 (65·4%)
Femoral	97 (20%)	108 (22·1%)
Subclavian	62 (12·8%)	58 (11·9%)
Other (eg, external jugular)	4 (1·3%)	3 (0·6%)
Vein—PICC		
Basilic	298 (68·5%)	286 (69·6%)
Brachial	88 (20·2%)	94 (22·9%)
Cephalic	27 (6·2%)	20 (4·9%)
Saphenous	11 (2·5%)	5 (1·2%)
Other (eg, axilla)	11 (2·5%)	6 (1·5%)
Artery—PAC		
Radial	293 (82·1%)	294 (81·0%)
Femoral	27 (7·6%)	28 (7·7%)
Dorsalis pedis	12 (3·4%)	12 (3·3%)
Other	25 (7·0%)	29 (8·0%)
Power PICC	84 (8·5%)	86 (9·0%)
Lumens		
1	412 (27·8%)	419 (28·7%)
2	499 (33·7%)	461 (31·6%)
3	265 (17·9%)	275 (18·9%)
≥4	305 (20·6%)	303 (20·8%)
Inserted by		
Doctor	1255 (84·7%)	1250 (85·9%)
Nurse	119 (8·0%)	104 (7·1%)
Other (eg, radiographer)	107 (7·2%)	102 (7·0%)
Multiple attempts	67 (4·6%)	58 (4·0%)
Technology guided (eg, ultrasound or fluoroscopy)	1027 (69·8%)	1039 (72·0%)
Insertion location		
Intensive care	592 (40·0%)	620 (42·5%)
Procedure room	78 (5·3%)	54 (3·7%)
Radiology	442 (29·8%)	423 (29·0%)
Operating theatre	289 (19·5%)	262 (18·4%)
Other hospital	30 (2·0%)	34 (2·3%)
Emergency	45 (3·0)	49 (3·4)
Other (eg, ward)	5 (0·3%)	11 (0·7%)
Received intravenous antibiotics	1240 (83·6%)	1241 (85·1%)
Received intravenous heparin lock or flush	156 (10·5%)	157 (10·8%)
Received intravenous heparin infusion	101 (6·8%)	120 (8·2%)

Data are n (%), median (IQR), or mean (SD). APACHE=Acute Physiology Assessment and Chronic Health Evaluation. CVAD=central venous access device. PICC=peripherally inserted central catheter. PAC=peripheral arterial catheter.

Table 1: **Baseline characteristics**

The primary analysis was modified intention to treat (mITT), which excluded only those randomly assigned patients whose catheter insertion was cancelled, who withdrew their consent for data to be analysed, or who had no intervention and no data collection. The patient was the unit of measurement (a small number of patients might have been recruited more than once owing to repeated admissions at one or more participating hospitals; these were treated independently), and analyses were done separately for central venous access devices and peripheral arterial catheters. We calculated the relative incidence rates of CRBSI per 100 devices and per 1000 catheter days with absolute risk difference and 95% CIs to summarise the effectiveness of each intervention. Kaplan-Meier survival curves (with log rank Mantel-Cox test) compared CRBSIs over time. Multivariate Cox regression was used to calculate hazard ratios (HRs) and 95% CIs for CRBSI, adjusted for stratification factors.

The primary outcome was also analysed in the per protocol population. This excluded patients whose catheter was removed before 4 days (never received an infusion set replacement), and those whose infusion

set replacement occurred on the incorrect day (eg, 4-day patients whose infusion sets were changed after 7 days). Because patients could potentially remain on the study for many weeks or months, and have many infusion set replacements, we included them in the analysis for the period during which they received the correctly timed replacements, with censoring if they subsequently received an incorrectly timed replacement.

Secondary endpoints were compared between groups by means of parametric (Cox regression) or non-parametric (Wilcoxon rank sum) tests. Infusion set colonisation was

	7-day group	p value	4-day group	Overall
Primary endpoint (mITT—CVADs)				
n	1124 (14 698 days)	..	1097 (14 817 days)	2221 (29 515 days)
CRBSI per patient	20 (1·78%)	..	16 (1·46%)	36/2221 (1·62%)
Absolute risk difference	0·32% (−0·73 to 1·37)	..	..	..
CRBSI per 1000 days	1·36 (0·8 to 2·0)	..	1·08 (0·6 to 1·6)	1·22 (0·8 to 1·6)
CRBSI HR	1·33 (0·69 to 2·57)	0·40	..	..
Per protocol				
CRBSI per patient	18/725 (2·48%)	..	16/997 (1·60%)	34/1722 (1·97%)
Absolute risk difference	0·88% (−0·50 to 2·25)	..	..	..
CRBSI HR	1·23 (0·63–2.41)	0·55	..	..
Primary endpoint (mITT—PACs)				
n	357 (2498 days)	..	363 (2620 days)	720 (5118 days)
CRBSI per patient	1 (0·28%)	..	0	1/720, 0·13%
Absolute risk difference (95% CI)	0·28% (−0·27 to 0·83)	..	..	..
CRBSI per 1000 days*†	0·40 (0 to 1·2)	1·00	0	0·20 (0 to 0·6)
Per protocol				
CRBSI per patient	1/198 (0·51%)	..	0/346 (0%)	1/544 (0·18%)
ARD	0·51% (−0·48 to 1·49)	..	..	..
Secondary outcomes (CVADs)				
Infusion set colonised	4/39 (10·3%)	1·00	7/60 (11·7%)	11/99 (11·1%)
Tip colonised‡	26 (2·3%)	..	22 (2·0%)	48 (2·2%)
Tip colonised per 1000 days	1·8	..	1·5	1·6
HR	1·35 (0·76 to 4·63)	0·31	..	..
All-cause bloodstream infection	183 (16·3%)	..	168 (15·3%)	351 (15·8%)
All-cause bloodstream infection per 1000 days	12·5	..	11·3	11·9
HR	1·17 (0·95 to 1·45)	0·14	..	..
Central line-associated bloodstream infection	62 (5·5%)	..	48 (3·6%)	110 (5·0%)
Central line-associated bloodstream infection per 1000 days	4·2	..	3·2	3·7
HR	1·38 (0·94 to 2·02)	0·96	..	..
All-cause mortality	42 (3·7%)	..	56 (5·1%)	98 (4·4%)
All-cause mortality per 1000 days	2·9	..	3·8	3·3
HR	0·77 (95% CI 0·52 to 1·15)	0·20	..	..
Infusion sets§ replaced	5 (3 to 7)	<0·0001	6 (3 to 11)	5·7 (3 to 9)
CVAD dwell	9·1 (6·3 to 17·1)	0·67	9·0 (6·0 to 18·0)	9·1 (6·2 to 17·2)
Serious adverse event—intensive care unit admission	9 (1·6%)	..	9 (1·6%)	18 (1·6%)
Serious adverse event—intensive care unit admission per 1000 days	1·9	..	1·7	1·8
HR	1·01 (95% CI 0·40 to 2·54)	1·00	..	..
Serious adverse event—death or intensive care unit admission	51 (4·5%)	..	65 (5·9%)	116 (5·2%)
Serious adverse event—death or intensive care unit admission per 1000 days	3·5	..	4·4	3·9
HR	0·81 (0·56 to 1·18)	0·27	..	..

(Table 2 continues on next page)

	7-day group	p value	4-day group	Overall
(Continued from previous page)				
Secondary outcomes (PACs)				
Infusion set colonised¶	0/12 (0%)	..	0/7 (0%)	0/19 (0%)
Tip colonised‡	2 (0·56%)	..	5 (1·38%)	7 (0·97%)
Tip colonised per 1000 days	0·80	..	1·91	1·37
HR	0·40 (0·08 to 2·09)	0·28	..	..
All-cause blood stream infection (laboratory-confirmed bloodstream infection)	37 (10·4%)	..	48 (13·2%)	85 (11·8%)
All-cause blood stream infection (laboratory-confirmed bloodstream infection) per 1000 days	14·8	..	18·3	16·6
HR	0·83 (0·54 to 1·28)	0·40	..	..
Central line-associated bloodstream infection	6 (1·68%)	..	10 (2·75%)	16 (2·22%)
Central line-associated bloodstream infection per 1000 days	2·4	..	3·8	3·1
HR	0·64 (95% CI 0·23 to 1·76)	0·39	..	..
All-cause mortality	26 (7·3%)	..	24 (6·6%)	50 (6·9%)
All-cause mortality per 1000 days	10·4	..	9·2	9·8
HR	1·17 (0·67 to 2·04)	0·58	..	..
Infusion sets§ replaced	1 (1 to 2)	<0·0001	2 (2 to 3)	1 (2 to 2)
PAC dwell	6·0 (4·6 to 8·1)	0·10	6·7 (4·8 to 8·7)	6·5 (4·7 to 8·5)
Serious adverse event—intensive care unit admission*	0	..	0	0
Serious adverse event—death or intensive care unit admission	26 (7·3%)	..	24 (6·6%)	50 (6·9%)
Serious adverse event—death or intensive care unit admission per 1000 days	10·4	..	9·2	9·8
HR	1·17 (0·67 to 2·04)	0·58	..	..

Data are n (%), HR (95% CI), % (95% CI), or median (IQR). mITT=modified intention to treat. HR=hazard ratio. CVAD=central venous access device. CRBSI=catheter-related bloodstream infection. PAC=peripheral arterial catheter. ARD=absolute risk difference. *HR not calculated due to low event rate. †95% CI not calculated due to low event rate. ‡Tips cultured on clinical suspicion of infection (CVAD 7-day n=301; 4-day n=307. PAC 7-day n=357; 4-day n=363). §1 infusion set=for example one fluid bag, a burette chamber, and tubing. ¶p value not calculated owing to low event rate.

Table 2: **Study outcomes by treatment group (per patient analysis, Cox regression, adjusted for intensive care unit or ward setting)**

compared between groups by means of two-sided Fisher's exact test.

p value of less than 0·05 was considered to indicate significance for all comparisons. A two-sided superiority framework was used outside of the primary comparisons. All statistical analyses were done with Stata (SE version 15.1). All reported CIs were calculated by means of Stata's functions.

We estimated the distribution of the difference in costs incurred by means of the 7-day versus 4-day policy from the perspective of public hospitals. We did not include information on CRBSI treatment costs or health effects. We harvested information about the number of sets replaced per patient and multiplied this by the amount of nurse time in minutes to have a set changed and included the costs of employment for nursing staff; and we also included the consumables that were expected to be used for a typical infusion set change. We used a parametric gamma model for the total number of infusion sets replaced per patient (appendix pp 2–3); a bootstrap with replacement procedure for the time taken, based on five estimates per device type that arose from a time and motion study; the observed times are shown in the appendix (p 1); employment costs were assumed to be for Nursing Stream Grade 5 Registered Nurse and Grade 6 Clinical Nurse[15] with hourly wage rates inflated by 35% to account for the full costs of employment and then divided by 60 for a per minute cost. Consumables were estimated on the basis of observed quantities of resources by catheter type (appendix pp 1–2). We then considered 1000 random picks from these distributions to estimate the expected difference in costs. The results are reported separately for central venous access devices and for peripheral arterial catheters. The overall change to costs was estimated by a weighted mean with PICC costs used for implanted ports owing to similar local patterns of infusion set use and insufficient port observations (appendix p 3). We report the distributions of the change to costs incurred, with the probability that the 7-day policy has lower cost than the 4-day policy. A rational decision maker would accept as optimal a probability of greater than 0·5 that one policy is lower

See Online for appendix

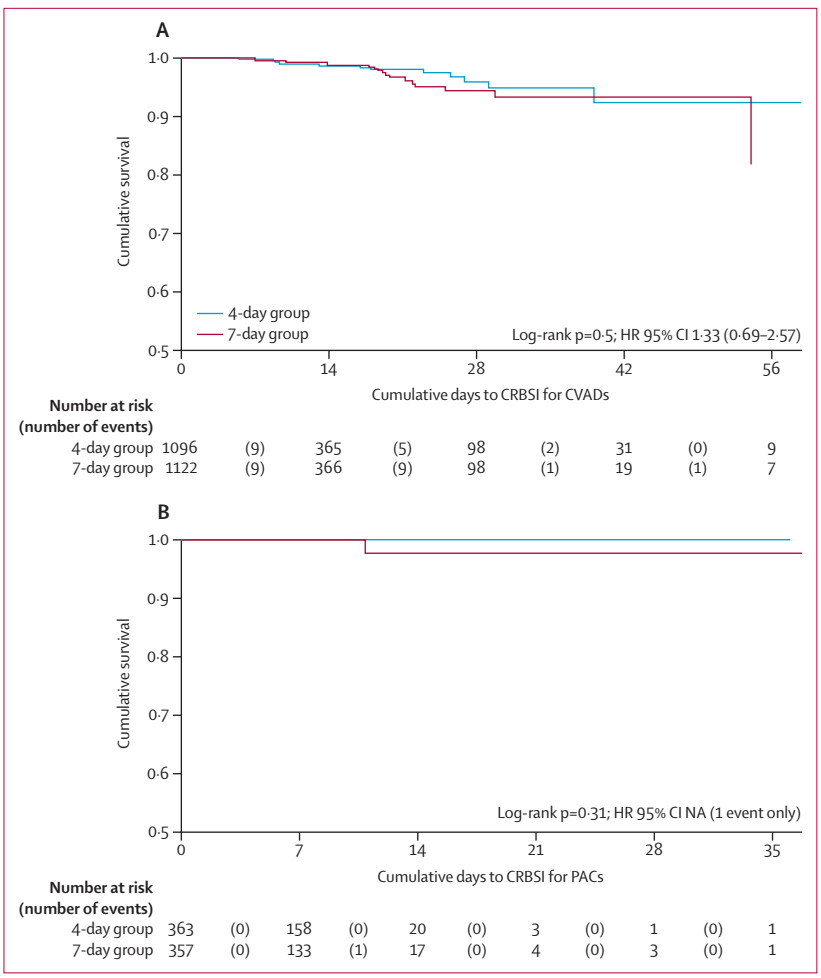

***Figure 2*: Kaplan-Meier plot from CRBSI for CVADs (A) and for PACs (B)**
For A, CVADs, dwell data was missing for one 4-day group and two 7-day group patients. CRBSI=catheter-related bloodstream infection. CVAD=central venous access device. HR=hazard ratio. PAC=peripheral arterial catheter. NA=not applicable.

cost than another.[18] An independent DSMC was used. This trial is registered with the Australian New Zealand Clinical Trials Registry, ACTRN12610000505000.

Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors commented on drafts and approved the final report.

Results

Between May 30, 2011, and Dec 9, 2016, we screened 6007 patients and enrolled 2944 (figure 1). We randomly assigned 1484 participants (1127 central venous access device; 357 peripheral arterial catheter) to 7-day infusion set replacements and 1460 (1097 central venous access device; 363 peripheral arterial catheter) to 4-day infusion set replacements. Patient accrual ended when the planned sample size was reached, with slight over recruitment owing to concurrent multi-site recruitment. Of 2944 randomly assigned patients, 2941 (99·9%) patients (2552 adults, 389 children) were included in the primary mITT analysis. Baseline patient and catheter characteristics are shown in table 1.

For central venous access devices, 20 (1·78%) of 1124 patients in the 7-day group had CRBSI (absolute risk difference [ARD] 0·32%, 95% CI –0·73 to 1·37), compared with 16 (1·46%) of 1097 patients in the 4-day group (table 2). Thus, the equivalence hypothesis was accepted. CRBSI per 1000 days was not different (7-day 1·36, 4-day 1·08, HR 1·33 (0·69 to 2·57), p=0·40, table 2), and time to CRBSI was similar between groups (p=0·45, figure 2A). More central venous access devices were removed for suspected CRBSI (366 [16·5%] of 2221) than were confirmed (36 [9·8%] of 366; group difference p=0·57). The absolute risk difference of CRBSI was within the 2% equivalency margin for both PICCs and other central venous access devices (appendix p 3).

For peripheral arterial catheters, one (0·28%) of 357 patients in the 7-day group had CRBSI (ARD 0·28%, 95% CI –0·27% to 0·83%), compared with 0 of 363 patients in the 4-day group (table 2). The non-inferiority hypothesis was therefore accepted. CRBSI survival was similar between groups (p=0·31, figure 2B). More peripheral arterial catheters (72 [10%] of 720) were removed for suspected CRBSI than were confirmed (one [0·14%] of 720).

The 37 CRBSI cases occurred in all device types (table 3), with 20 (54%) confirmed by tip culture, and the remainder by differential time to positivity. There were 16 responsible microorganisms, most (62·2%) being Gram-positive bacteria (table 3).[19] Common commensals were implicated in 17 (40·5%) of 37 CRBSIs; of which 14 (82·3) of 17 were isolated from the blood on more than one occasion.

Neither central venous access devices nor peripheral arterial catheters had significant between-group differences for the secondary endpoints of all-cause bloodstream infection, CLABSI, catheter tip colonisation, mortality, or median catheter dwell (table 2).

The microbiological substudy for the secondary endpoint of set colonisation included 118 patients and sampled more than 500 specimens from multiple infusion sets—less than planned owing to research staff availability at time of replacement. 12 sets were colonised from 11 central venous access devices and no peripheral arterial catheters with 3-way stopcocks (nine [75%] of 12) most often colonised, followed by line ports (two [17%] of 12) and bag spikes (one [8%] of 12; appendix pp 4–5). Central venous access device infusion set colonisation was not significantly different between groups (table 2). Coagulase-negative staphylococci, particularly *Staphylococcus haemolyticus*, predominated. Five (45·5%) of the 11 patients had a concurrent bloodstream infection (one CLABSI, three LCBI–MBI, one primary bloodstream infection). There were no species-matched bacteria from blood and infusion sets.

	7-day group (n=21*)	4-day group (n=16)
Central venous access device—recognised pathogen		
Gram negative		
Enterobacter cloacae†	1 (cuff CVAD)	3 (1 internal jugular CVAD, 1 cuff CVAD, 1 PICC)
Acinetobacter baumannii complex	2 (1 femoral CVAD, 1 PICC)	1 (femoral CVAD)
Pseudomonas aeruginosa	1 (cuff CVAD)	2 (2 PICC)
Klebsiella oxytoca†	..	1 (internal jugular CVAD)
Klebsiella pneumoniae†	..	1 (internal jugular CVAD)
Serratia marcescens†	..	1 (femoral CVAD)
Gram positive		
Staphylococcus aureus—methicillin-sensitive *S aureus*	1 (port)	1 (PICC)
Methicillin-resistant *S aureus**	2 (2 cuff CVAD)	..
Streptococcus agalactiae (group B)	1 (cuff CVAD)	..
Enterococcus faecalis*	..	1 (internal jugular CVAD)
Enterococcus faecium (vancomycin-resistant *Enterococci*)*	1 (cuff CVAD)	..
Lactobacillus sp*	..	1 (PICC)
Common commensal (Gram positive)		
Staphylococcus epidermidis	6 (1 cuff CVAD, 2 PICC, 3 internal jugular CVAD)	2 (2 cuff CVAD)
*Streptococcus mitis**	4 (4 cuff CVAD)	2 (2 cuff CVAD)
Staphylococcus hominis	1 (internal jugular CVAD)	..
Coagulase negative *Staphylococcus*—other	1 (internal jugular CVAD)	..
Peripheral arterial catheter—recognised pathogen (yeast)		
Candida parapsilosis†	1	..

CRBSI= catheter-related bloodstream infection. Cuff CVAD=tunnelled cuffed central venous access device. CVAD=non-tunnelled central venous access device. PICC=peripherally inserted central catheter. Port=totally implanted port. *Total number of microorganisms reported is higher than the number of CRBSI as there was a single case (cuff CVAD) presenting with *both* a recognised pathogen (*S aureus*) and a common commensal (*S mitis*). †Mucosal barrier injury organisms (National Healthcare Safety Network).

Table 3: **Microorganisms responsible for CRBSI in 37 patients**

	7-day group	4-day group	Difference
PAC	n=357	n=363	..
Mean per patient	75 (49)	118 (85)	−43 (97)
Median	65 (61)	96 (106)	−32 (110)
Range per patient	2 to 333	2 to 566	−491 to 210
Consumable costs (only)			
Mean per patient	59 (40)	97 (69)	−38 (79)
Median	49 (48)	79 (84)	−28 (88)
Time costs (only)			
Mean per patient	14 (11)	22 (18)	−8 (19)
Median	11 (13)	18 (20)	−6 (20)
Time (only), min			
Mean per patient	14 (12)	24 (19)	−10 (21)
Median	11 (12)	19 (20)	−7 (21)
CVAD	n=1124	n=1097	..
Mean per patient	339 (168)	823 (420)	−483 (432)
Median	311 (207)	747 (552)	−436 (554)
Range per patient	37 to 1174	119 to 2760	−2314 to −465
Consumable costs (only)			
Mean per patient	174 (78)	432 (231)	−258 (242)
Median	166 (101)	383 (301)	−226 (303)
Time costs (only)			
Mean per patient	162 (105)	371 (258)	−209 (245)
Median	136 (117)	309 (273)	−159 (259)
Time (only) min			
Mean per patient	178 (113)	405 (266)	−228 (257)
Median	148 (125)	348 (316)	−174 (285)

Data are mean (SD) and median (IQR). PAC=peripheral arterial catheter. CVAD=central venous access device.

Table 4: **Per patient costs (AU$) from staff time and consumables from infusion set replacement procedures**

For the secondary outcome of set use, for both central venous access devices and peripheral arterial catheters, the 7-day group had a median of one less infusion set replacement procedure and one less individual infusion set replaced, per patient, compared with the 4-day group (all p<0·0001, table 2).

Relative to the 4-day group, the 7-day group had mean cost savings of AU$483 (central venous access device) and AU$43 (peripheral arterial catheter; table 4). The posterior distribution of the cost differences revealed probability of lower cost with 7-day infusion set replacement of 89% for central venous access device (appendix p 6), and 66% for peripheral arterial catheter (appendix p 6). The median nursing time saved with 7-day replacement (compared with 4-day) was 174 min (maximum 1610 min) for central venous access devices, and 7 min (maximum 179 minutes) for peripheral arterial catheter.

Table 2 displays serious adverse events which did not differ between groups (central venous access devices p=0·27, peripheral arterial catheters p=0·58). After adjudication, none were related to the intervention and no patient died from CRBSI.

Discussion

Vascular catheters are the source of one-third of health-care associated bloodstream infections[20] and routine infusion set replacement has been an infection prevention strategy for half a century, despite scarce evidence. In our large, pragmatic, randomised, controlled trial of 7-day use versus 4-day use, the equivalence hypothesis for CRBSI was accepted for central venous access devices, as was the non-inferiority hypothesis for peripheral arterial catheters. These findings were consistent as a proportion of catheters, as rates per 1000 catheter days, on survival, and per protocol

analyses. The intervention was tested in a high acuity cohort, which included intensive care and patients with cancer, and complex infusions such as parenteral nutrition. We pragmatically studied a range of catheter types in both children and adults, because infusion set replacement affects all groups and because expert bodies do not differentiate between these when making recommendations about the frequency of infusion set replacement.[4–6] Most international guidelines recommend infusion set replacement "no more frequently than 96 h"[4] or "no more frequently than 96 h but at least every 7 days".[5,6] Our results indicate that infusion set replacement every 7 days is as safe as every 4 days, providing level I evidence to inform clinical practice guidelines.

Our results extend a systematic review which found no significant difference in CRBSI with infusion set replacement at intervals up to 4 days, and no large trials studying use beyond this timepoint.[8] Our findings are consistent with two smaller trials[21,22] and support infusion set replacement being extended to a weekly procedure. This is practical and aligns with the recommended 7-day replacement of both catheter dressings and needleless connectors.[5]

We have shown the high probability that 7-day rather than 4-day replacement of infusion sets will reduce costs (AU$483 per central venous access device; AU$43 per peripheral arterial catheter). Our economic analysis supports the adoption of a 7-day over a 4-day policy. The Australian State of Queensland purchased 26 500 central venous access devices and 33 700 peripheral arterial catheters in 2016 for government hospitals alone, so savings from implementation could approach AU$15 million per annum which is AU$3 per head of Queensland's population.[23] In the USA with use of 3 million and the UK with use of 250 000 central venous access devices, in 2012,[24] savings will be far greater. Our results indicate that a 7-day infusion set replacement policy will avoid, on average, one replacement procedure per catheter (each procedure can have multiple sets). Accompanying nursing time savings for patients with complex needs were up to 26·8 h over the life of the central venous access device (with many infusions and central venous access device dwell up to 159 days or 22 weeks), or 3·0 h per peripheral arterial catheter. A 7-day infusion set replacement policy will also reduce the considerable environmental and cost effect of infusion set manufacture and disposal.[25]

Routine infusion set replacement commenced in 1970–71 in response to more than 100 CRBSI cases in the USA, later traced to manufacturer contamination.[9] Although infusion set replacement is imperative for known or suspected contamination, RCTs have never investigated routine replacement per se (compared with no routine replacement), and replacement intervals tested have not been shown to prevent CRBSI.[8] Infusate contamination can undoubtably occur during manufacture, or from the hands of clinical staff while they are manipulating infusion sets.[6,11] So consideration of why routine replacement of infusion sets has not shown benefit is warranted. It might reflect a similar degree of chance that the new infusion set is contaminated during the procedure, as that an existing contaminated set is replaced with a sterile one. In addition, since poor technique by staff inserting or accessing catheters can allow microorganisms to immediately enter the catheter or bloodstream, the risk caused by such lapses might not be reversible by infusion set replacement. Meticulous infection prevention at all steps from catheter insertion to removal remains crucial to prevent CRBSI.

Our central venous access device cohort studied several catheter subtypes and had an overall CRBSI rate of 1·22/1000 days, consistent with published rates.[16] CRBSI is primarily a research and clinical diagnosis, but we also reported the common surveillance measure of CLABSI, which did not differ between study groups.[7] The National Healthcare Safety Network criteria to exclude mucosal barrier injury associated infections from CLABSI meant that central venous access device CLABSI was 110 (5%) of 2221 instead of 351 (15·8%) of 2221 (ie, all-cause bloodstream infections), and CLABSI was similar in cancer and ICU patients.[19] We noted the clinical challenge to diagnose CRBSI—ten times more central venous access devices and peripheral arterial catheters were removed for suspected CRBSI than were confirmed. This highlights the large number of catheters that might be unnecessarily removed and replaced, increasing risk to patients and health-care costs.

Both CRBSI and colonised infusion sets predominantly reflected Gram-positive bacteria, typically coagulase negative staphylococci and other skin residents, suggesting they came from the hands of staff in the case of contaminated infusate.[11] However, a range of gastrointestinal and environmental microorganisms commonly implicated in CRBSI including Gram-negative bacteria and fungi were also isolated.[6] Our substudy found 11 (9·3%) of 118 patients tested had one or multiple parts of the infusion set colonised; colonisation prevalence of 20% has been previously reported.[26] Although this seems incongruent with the low CRBSI incidence, microorganisms on infusion set surfaces might have been in a non-mature (preshedding) state, or patients might have been on antibiotics or had adequate immune function to resist infection. *Bacillus* was identified in infusate, an environmental organism known to proliferate in infusion fluids at room temperature and to cause CRBSI.[27] Most colonisation occurred at three-way stopcocks (typically used for higher acuity patients or blood sampling); this further questions their use.[28] All colonised sets were from long term central venous access devices, consistent with previous findings of low (0·4%) colonisation rates for short-term catheters,

and uncommon intraluminal colonisation before day 10 of catheter dwell.[29,30] Long-term central venous access devices appear most at risk of infusion set contamination owing to multiple system accesses, suggesting a lower threshold for their replacement if infection is suspected (and the catheter is retained).

The strengths of this study were its randomised, multisite design, centralised randomisation, blinded outcome assessment, and negligible loss to follow-up. Our mITT analysis excluded only three randomly assigned patients. Generalisability was maximised by hospital-wide recruitment of adults and paediatrics, clinical staff doing the intervention, the usual care approach to microbiological patient testing, and inclusion of multiple catheter types (central venous access devices and peripheral arterial catheters represent >80% of all vascular catheters).[20] Our expectation that catheters would remain in situ for at least 7 days was met and was long enough to test the intervention, adding to external validity.

Study limitations included the non-masking of patients and clinical staff, but risk of bias was reduced by clearly defined data collected by research staff, masked microbiology laboratory staff, and the primary and other outcome adjudication by masked infectious disease physicians. CLABSI might have been under-reported if clinical staff did not order blood cultures;[31] however our rigorous prospective approach to assessing all positive blood cultures for CLABSI promoted validity. Although our results apply to the most common infusions, they should not be extrapolated to blood, lipid, inotrope, chemotherapy, and cyclosporin infusions, or to low birthweight neonates. We were not able to test hypotheses individually for central venous access device types; however our merged central venous access device cohort was large, with similar distribution of central venous access device subtypes per group, and CRBSI between-group differences were within the equivalence margin for device sub-types, providing reassurance that the results probably apply to all central venous access devices. The cost analyses did not have direct observation of implanted ports, and conservatively used saline as the infusate cost, whereas infusions can be higher cost (eg, local cost of parenteral nutrition AU$89·56 per bag, propofol AU$35·85/100 mL bottle). Cost estimates were based on very few observed replacement times which caused large uncertainty in the estimated ranges of cost saving. This had little effect on decision uncertainty since the 7-day strategy will be cost saving for any reduction in infusion set times, owing to the clinically equivalent outcomes. Further, CRBSI treatment costs were omitted from cost analyses, but the lack of observed clinical differences in infections justifies this approach.

Millions of vascular catheters are inserted worldwide each year, and a policy change for infusion set replacement from every 4 to every 7 days will have significant cost and workload benefits. A modern, efficient health-care sector requires us to question traditional practices and routine procedures, including disinvestment where evidence shows they are ineffective. It is our hope that by reducing the frequency of this nursing procedure, more time is available for other basics of infection prevention, such as hand hygiene and aseptic access, insertion site decontamination and sterile dressing, regular catheter assessment with timely removal, and education of the patient and family in CRBSI prevention.

Contributors

CMR, NMM, and JW were responsible for study conception. CMR, NMM, MRM, NG, JW, AC, DM, JRG, DAL, JFF, JY, RJC, and NCG were responsible for protocol design and funding application. NMM, ENL, NR, JW, AC, JRG, DAL, JFF, JY, FJG, MM, EA, RJC, NCG, AD, AP, AR, and EGP were responsible for patient recruitment and treatment. DM and MAC were responsible for microbiological experiments and analysis. NG was responsible for health economic analysis. NR and EGP did the infection adjudication. NMM and ENL were responsible for overall project management. CMR, MRM, NMM, and ENL were responsible for data management and had access to all of the data. MRM did the statistical analysis. CMR was responsible for the first draft and coordinating the manuscript. All authors had full access to the study data and had final responsibility for the decision to submit for publication. All authors were responsible for critical review of drafts and approval of the final manuscript.

Declaration of interests

CMR's employer has received on her behalf from manufacturers of vascular access products: investigator-initiated research grants and unrestricted educational grants from BD-Bard and Cardinal Health; and consultancy payments for educational lectures and expert advice from 3M, and BD-Bard. NMM's employer has received on her behalf from manufacturers of vascular access products investigator-initiated research grants and unrestricted educational grants from BD-Bard and Cardinal Health; and consultancy payments for educational lectures from 3M. ENL's employer has received on her behalf from manufacturers of vascular access products an investigator-initiated research grant from Cardinal Health; and a conference scholarship from Angiodynamics. AC's employer has received on her behalf from manufacturers of vascular access products investigator-initiated research grants from Cardinal Health. EA's employer has received on his behalf from manufacturers of vascular access products: investigator-initiated research grants from BD-Bard. All other authors declare no competing interests.

Data sharing

Data sharing procedures will be described once all publications have been completed.

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