Central venous access devices for the delivery of systemic anticancer therapy (CAVA): a randomised controlled trial

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Summary

Background Hickman-type tunnelled catheters (Hickman), peripherally inserted central catheters (PICCs), and totally implanted ports (PORTs) are used to deliver systemic anticancer treatment (SACT) via a central vein. We aimed to compare complication rates and costs of the three devices to establish acceptability, clinical effectiveness, and cost-effectiveness of the devices for patients receiving SACT.

Methods We did an open-label, multicentre, randomised controlled trial (Cancer and Venous Access [CAVA]) of three central venous access devices: PICCs versus Hickman (non-inferiority; 10% margin); PORTs versus Hickman (superiority; 15% margin); and PORTs versus PICCs (superiority; 15% margin). Adults (aged ≥18 years) receiving SACT (≥12 weeks) for solid or haematological malignancy from 18 oncology units in the UK were included. Four randomisation options were available: Hickman versus PICCs versus PORTs (2:2:1), PICCs versus Hickman (1:1), PORTs versus Hickman (1:1), and PORTs versus PICCs (1:1). Randomisation was done using a minimisation algorithm stratifying by centre, body-mass index, type of cancer, device history, and treatment mode. The primary outcome was complication rate (composite of infection, venous thrombosis, pulmonary embolus, inability to aspirate blood, mechanical failure, and other) assessed until device removal, withdrawal from study, or 1-year follow-up. This study is registered with ISRCTN, ISRCTN44504648.

Findings Between Nov 8, 2013, and Feb 28, 2018, of 2714 individuals screened for eligibility, 1061 were enrolled and randomly assigned, contributing to the relevant comparison or comparisons (PICC *vs* Hickman n=424, 212 [50%] on PICC and 212 [50%] on Hickman; PORT *vs* Hickman n=556, 253 [46%] on PORT and 303 [54%] on Hickman; and PORT *vs* PICC n=346, 147 [42%] on PORT and 199 [58%] on PICC). Similar complication rates were observed for PICCs (110 [52%] of 212) and Hickman (103 [49%] of 212). Although the observed difference was less than 10%, non-inferiority of PICCs was not confirmed (odds ratio [OR] 1·15 [95% CI 0·78–1·71]) potentially due to inadequate power. PORTs were superior to Hickman with a complication rate of 29% (73 of 253) versus 43% (131 of 303; OR 0·54 [95% CI 0·37–0·77]). PORTs were superior to PICCs with a complication rate of 32% (47 of 147) versus 47% (93 of 199; OR 0·52 [0·33–0·83]).

Interpretation For most patients receiving SACT, PORTs are more effective and safer than both Hickman and PICCs. Our findings suggest that most patients receiving SACT for solid tumours should receive a PORT within the UK National Health Service.

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See **Online** for appendix

Introduction

Cancer requiring systemic anticancer therapy (SACT) is common. Between March, 2017, and February, 2018, the SACT dataset for Public Health England recorded 175 520 patients aged 25 years and older receiving the therapy.[1] Intravenous SACT administration can be given through a peripheral cannula, a short catheter (midline) into an upper arm vein, or a central venous access device (CVAD). CVADs are indicated when the duration of SACT is 3 months or longer or there are no adequate peripheral veins.[2] Furthermore, CVADs can be used to withdraw blood and administer other agents such as radiographic contrast media, both of which are very common in these patients.[3] CVADs include Hickman-type tunnelled catheters (Hickman), peripherally inserted central catheters (PICCs), and totally implanted ports (PORTs), which deliver drugs and fluids into a large central vein (typically the superior vena cava). This method avoids local vein damage from the irritant nature of SACT, which can rapidly occlude peripheral arm veins and cause tissue necrosis with extravasation.

Decision-making processes behind the choice of device are poorly understood globally. PICC usage has increased over the past decade and is now the dominant strategy in many western European countries and the USA. This increase could be due to ease of insertion and removal by nurse-led teams, technical issues such as the avoidance of the vital structures in the neck including the risk of pneumothorax, and perceived

Research in context

Evidence before this study

An extensive search was done on MEDLINE and Embase from inception of the analysis to Dec 31, 2012, with no language restrictions. Relevant keywords and permutations of search terms relating to central venous access devices (CVADs) and totally implantable ports were combined with those relating to cancer and chemotherapy; subsequently, validated search filters for randomised controlled trials and observational studies were applied to the search output. Long-term CVADs are usually required for patients receiving systemic anticancer therapy (SACT) of 3 or more months duration. There are three devices commonly used (peripherally inserted central catheters [PICCs], Hickman-type tunnelled catheters [Hickman], and totally implanted ports [PORTs]). Which device a patient receives or is offered is not standardised and often depends on what is available locally, the service delivery model, prompt placement, and cost. PICCs have become increasingly popular due to low cost and easy placement by nurse-led teams; however, several systematic reviews have identified the poor evidence base for its use and its heterogeneous nature. Much of the evidence compared only Hickman-type devices with PORTs, were small trials with mainly surgical placement, and usually had no quality of life (QOL) or costings data. More recently in 2020, two randomised trials comparing PICCs with PORTs have suggested a higher adverse event rate with PICCs. One of these trials only studied patients with breast cancer. Neither compared all three devices. Due to the scarcity of good evidence, neither the European Society for Medical Oncology nor the American Society of Clinical Oncology makes any specific recommendations regarding the type of device to be used. In 2011, the UK National Institute for Health Research Health Technology Assessment programme commissioned a call for research comparing these three devices.

Added value of this study

The Cancer and Venous Access (CAVA) trial is the largest randomised trial to compare these devices (PICCs, Hickman, and PORTs) and the only one to include all three, to our knowledge. It is also the only trial to include robust QOL data and a full economic analysis. There was little difference between PICCs and Hickman in terms of complications. CAVA showed that PORTs reduced the adverse event rate by approximately 50% compared with Hickman and PICCs. A device specific QOL instrument showed no difference between PICCs and Hickman, but a preference for PORTs. PORTs were associated with the highest total costs; however, after allowing for the dwell time of the devices, there was no difference between PICCs and Hickman, but the cost associated with PORTs was lower when compared with PICCs and Hickman.

Implications of all the available evidence

CAVA is a high-quality, pragmatic, randomised controlled trial offering strong evidence to change clinical practice so that most patients receiving SACT for solid tumours should receive a PORT. The challenge now is to change the service delivery model so that PORTs can be provided in a more timely and cost-effective manner. There will still be a small group in whom the other devices are preferred. Guidelines should be updated to reflect this new evidence.

lower upfront costs. PORTs, by contrast, are the most expensive and least frequently used of the three devices.

A systematic review[4] and pilot randomised controlled trial[5] comparing PORTs with Hickman have suggested that PORTs might be superior in terms of adverse events and quality of life (QOL) and possibly more cost-effective. A further systematic review evaluated the complications and costs of PICCs compared with PORTs.[6] On the basis of 15 cohort studies, PICCs were associated with an increased risk of complications including thrombosis, occlusion, infection, malposition, and accidental removal compared with PORTs. Two further randomised controlled trials comparing PICCs with PORTs both indicated a higher adverse event rate with PICCs.[7,8] The existing evidence is however heterogeneous regarding study population, design, and overall quality; data for QOL and cost-effectiveness are also scarce. Currently, there is no direct comparison of the three devices to our knowledge. Consequently, neither the European Society for Medical Oncology nor the American Society of Clinical Oncology makes specific recommendations regarding the type of device.[2,9] Furthermore, changes in practice are being driven by other sources of information such as appropriateness criteria using scenario-based modelling.[10,11]

In 2011, the UK National Institute for Health Research Health Technology Assessment (NIHR HTA) programme commissioned the Cancer and Venous Access (CAVA) trial with associated qualitative research, which aimed to evaluate the acceptability, clinical effectiveness, and cost-effectiveness of all three devices.

Methods

Study design and participants

CAVA was a pragmatic, open-label, multicentre, mixed methods, randomised controlled trial of three routinely used CVADs: Hickman, PICCs, and PORTs. Patients were recruited from 18 UK oncology units (appendix p 1). Patients aged 18 years or older expected to receive SACT for 12 weeks or more to treat solid or haematological malignancy, and in whom CVAD insertion was possible via a suitable upper body vein, but for whom there was clinical uncertainty about the best device, were screened by their consulting clinician or nursing team during routine appointments, before being randomly assigned. Reasons for exclusion were: treatment or life expectancy of less than 3 months; previous random assignment to

CAVA; CVADs removed within 2 weeks before random assignment; active infection; need for high-flow volume CVADs; or need for CVADs to be placed in a lower body vein.

All patients provided written informed consent. Ethical approval was received from the West of Scotland Research Ethics Service (REC 1; reference 13/WS/0056). The trial protocol has been published prospectively.[12]

Randomisation and masking

Eligible patients were randomly assigned through one of four randomisation options: (1) Hickman versus PICCs versus PORTs (2:2:1 to over-recruit to the non-inferiority comparison); (2) PICCs versus Hickman (1:1); (3) PORTs versus Hickman (1:1); or (4) PORTs versus PICCs (1:1). Clinicians could choose from these options depending on patient needs and local practice. Treatment allocations were obtained from the Cancer Research UK Glasgow Clinical Trials Unit.

Randomisations were done using minimisation algorithms incorporating random components. The stratification factors were: centre, body-mass index (BMI; <20, 20 to <30, 30 to <40, ≥40 kg/m²), CVAD history (no previous devices fitted, ≥1 device fitted ≤3 months before study, ≥1 device fitted >3 months before study), type of cancer (haematological malignancies, solid tumours), and planned treatment mode (inpatient, outpatient). The study was necessarily open-label with all parties aware of treatment allocation.

Procedures

Hickman are tunnelled under the skin before exiting and have a Dacron cuff, which allows tissue ingrowth, to improve catheter anchorage and reduce infection risk. These are inserted via the jugular or subclavian vein. Removal requires minor surgical dissection to free the Dacron cuff. PICCs are placed using an upper arm vein. Removal simply involves withdrawing the device usually at the bedside. Maintenance for both typically involves regular dressing change and weekly line flushing.

PORTs are completely implanted (usually on the chest wall) with nothing exiting the skin; there is no long-term dressing and flushing is typically only required monthly. The catheter is placed via the jugular or subclavian vein. The PORT has to be accessed through the skin with a non-coring needle each time it is used. PORTs are the most complicated to insert and remove, requiring minor surgical procedures.

Ultrasound is used to target access veins for all three devices, which are inserted by various specialists (ie, nurse practitioners, interventional radiologists, anaesthetists, and surgeons). The primary operator varies depending on the device used. This variation is associated with different practices in different hospital sites and countries. The pragmatic nature of the study meant that insertion-related procedures, aftercare, management of complications, and removal were not controlled and followed usual practices at each centre. The comparisons were of three different types of CVAD and their overall package of care.

Outcomes

The primary outcome was overall complication rate, a composite of infection (suspected or confirmed) or mechanical failure. This outcome comprised the following individual components: inability to aspirate blood, infection associated with the device (suspected, confirmed, or exit site), definitions stated in the appendix (pp 3–4), venous thrombosis related to the device (confirmed with imaging), pulmonary embolus related to the device, mechanical failure (ie, line fracture, line separation from chest wall port, exposure of line cuff, exposure of chest wall port or breakdown of wound, chest wall port dislodgement, line fallen out, or line migration requiring intervention), and other. The bundling of these different types of complications is justified in that they all interfere with the care pathway, can interrupt therapy, and require provider attention.

There were eight secondary outcomes. The first was the incidence of individual complications: inability to aspirate blood, suspected catheter-related bloodstream infection, laboratory-confirmed bloodstream infection, exit site infection, venous thrombosis related to the device, pulmonary embolus related to device, mechanical failure, and other. Secondly, we assessed complications per catheter week: the number of complications divided by number of weeks that the device was in place. The third was time to first complication from randomisation. Patients without complications were censored at device removal or last available date on-study (ie, last chemotherapy date, last status assessment date, or date of death) if the device was still in place at the end of the study. The fourth was duration of chemotherapy treatment interruptions, overall and by complication. The fifth was health-related QOL measured by the EQ-5D three-level version, including the visual analogue score for general health.[13] The sixth was cancer QOL, measured by the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life of Cancer Patients Questionnaire (QLQ-C30), comprising five functional scales, nine symptom scales, and a global health status score.[14] The seventh was venous access device-specific QOL from a questionnaire comprising 16 questions (appendix pp 5–6).[5] The final secondary outcome was cost comprising device cost, device insertion cost, and unplanned follow-up costs (ie, hospital admissions and outpatient visits). Data were collected monthly until device removal for a maximum of 12 months.

Statistical analysis

The sample size was based on three hypotheses. The first was that PICCs are non-inferior to Hickman. Assuming that the Hickman complication rate is 55%, PICCs would

be considered non-inferior if their complication rate is no more than 10% higher, 65%. This 10% non-inferiority margin corresponds to an odds ratio (OR; PICCs to Hickman) limit of 1·519. To rule out this difference with 80% power with a one-sided significance level of 2·5%, we required 778 patients (1:1 ratio; 389 per group). The second hypothesis was that PORTs are superior to Hickman. Assuming that the Hickman complication rate is 55%, we aimed to detect a 15% reduction with PORTs, based on the 40% complication rate for PORTs reported in the pilot study.[5] To detect this difference with 95% power with a two-sided significance level of 5%, we required 550 patients (1:1 ratio; 275 per group). The third hypothesis was that PORTs are superior to PICCs. Assuming that the PICCs complication rate is 55%, we aimed to detect a 15% reduction with PORTs, based on the 40% complication rate for PORTs reported in the pilot study.[5] To detect this difference with 80% power

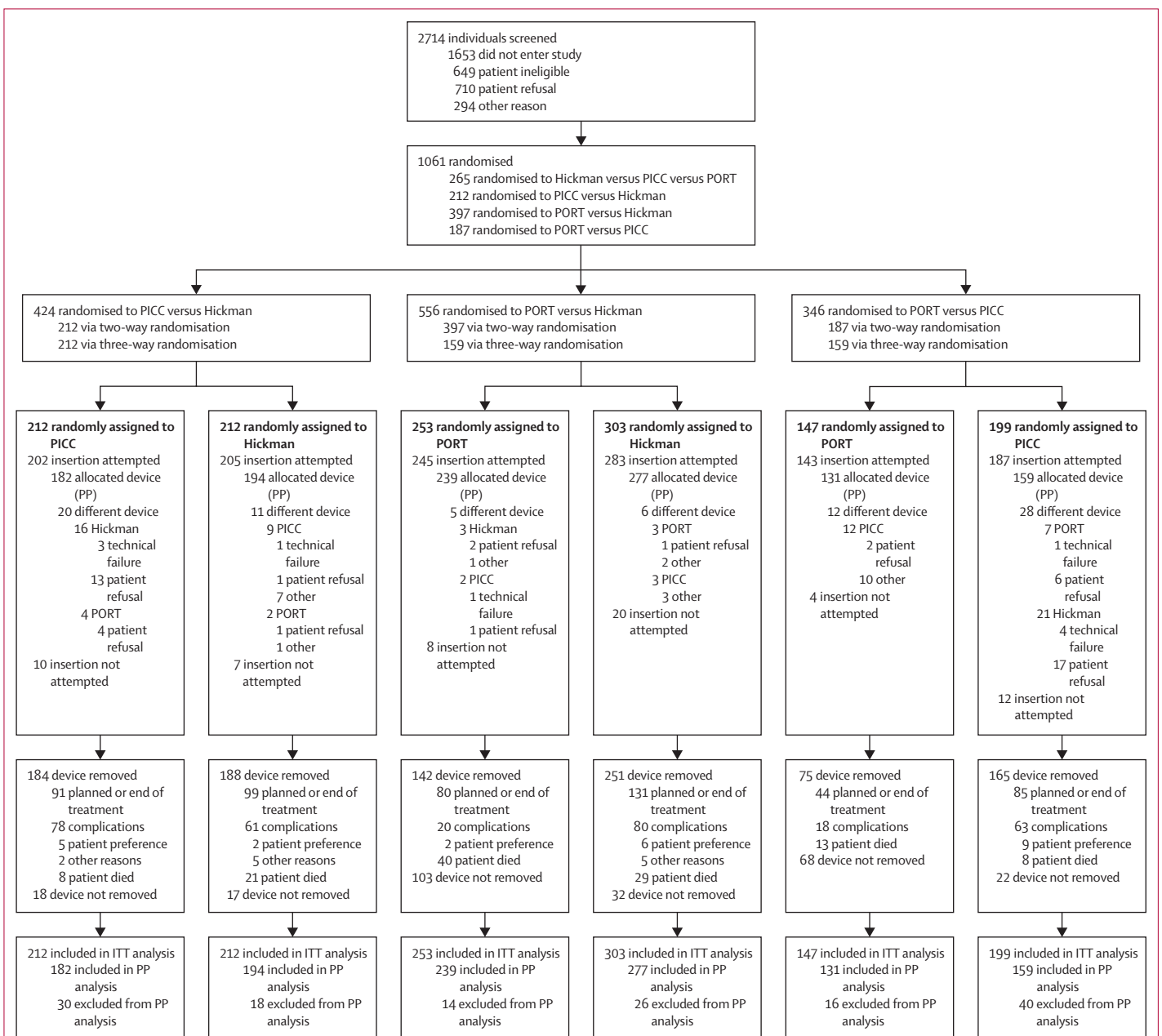

Figure 1: **Trial profile**
The total number of patients contributing to the comparisons is higher than the total number of patients randomly assigned as patients entering the study via the three-way randomisation contributed to two comparisons. Hickman=Hickman-type tunnelled catheters. PICCs=peripherally inserted central catheters. PORTs=totally implanted ports. PP=per-protocol. ITT=intention-to-treat.

with a two-sided significance level of 5%, we required 342 patients (1:1 ratio; 171 per group).

The statistical analyses were done separately for the three pairwise comparisons and were based on the intention-to-treat (ITT) populations, defined as all randomly assigned patients; study groups were based on the device patients were assigned at random assignment as opposed to the device fitted, if these differed. Per-protocol (PP) sensitivity analyses were undertaken for the primary analysis of each comparison, excluding patients not fitted with the device assigned at randomisation.

The primary endpoint was complication rate, analysed using logistic regression including study group, randomisation stratification factors, and whether the data came from the relevant two-way or three-way randomisation. The binary stratification factors of treatment mode and type of cancer were excluded due to small numbers of patients in one category (inpatient and haematological cancers) across all comparisons (≤13% inpatient and ≤10% haematological). BMI, device history, and centre were re-parameterised for the same reason. BMI was dichotomised into less than 30 kg/m² and 30 kg/m² or more, previous device history was categorised as yes or no, and centre retained the six sites with the highest recruitment (Beatson West of Scotland Cancer Centre, Glasgow, UK; Freeman Hospital, Newcastle upon Tyne, UK; Newcastle upon Tyne Hospitals, Newcastle upon Tyne, UK; St James's University Hospital, Leeds, UK; The Christie National Health Service (NHS) Foundation Trust and Charing Cross Hospital, Manchester, UK; and Imperial College Healthcare, London, UK), and the remaining were combined and termed other centre. The incidence of venous thrombosis was compared using the same approach. The total duration of treatment interruption was compared using the Mann-Whitney *U* test overall and for each complication.

Network meta-analysis of the four randomisation options was also done to combine direct and indirect evidence, thus generating a more precise estimate of the relative treatment effects.[15] Direct evidence was based on the head-to-head randomisation options, whereas indirect evidence was based on the estimates of the direct estimates from the other two comparisons.

Multiple imputations were applied to missing EQ-5D index value data[16] before estimating the area under the curve[17] for each patient, which was standardised by the period on study and adjusted by subtracting the baseline value (value reported before the device was fitted). These index value scores were compared across groups using a Mann-Whitney *U* test. The same approach was taken for the EQ-5D visual analogue scale for health. The p values for the index values and health state scores were adjusted for multiple comparisons using the false-discovery rate approach (calculated using the p.adjust function [fdr option]) of the stats library in R, version 3.6.2.[18] EORTC QLQ-C30 data were imputed and analysed in the same way as the EQ-5D data. p values were obtained for the differences between groups for the five functional scales (ie, physical, role, emotional, cognitive, social), nine symptom scales (ie, fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, financial difficulties) and the global health status score, and these were also adjusted for multiple comparisons. The worst responses for each question from the venous access device questionnaire were summarised and compared across groups via the Mann-Whitney *U* test, and the p values for the individual questions were adjusted for multiple comparisons.

Mean total costs were estimated by fitting a generalised linear model with γ distribution and log link, adjusting for age, sex, BMI, device history, and study group. Based on the estimation of the final statistical model, the predicted mean total cost associated with each device was estimated. Cost per catheter week was calculated by dividing time on device (catheter weeks) per patient by total cost per patient. The same regression approach used for total costs was used to estimate cost per catheter week. Non-parametric bootstrapping (1000 iterations) was used to estimate 95% CIs for the total mean cost and total mean cost per catheter week.

Statistical analyses were done using SAS, version 9.3 or 9.4, and SAS Enterprise Guide, version 5.0 or 7.1, with the exception of the quality of life analyses (IBM SPSS Statistics for Windows, version 23.0 or 25.0), adjustments for multiple testing (R Core Team, 2018), and the health economic analyses (Stata, version 14). An independent data monitoring committee reviewed the data annually six times throughout the study and found no concerns with the safety, efficacy, or management of the study at any stage. This study is registered with ISRCTN, ISRCTN44504648.

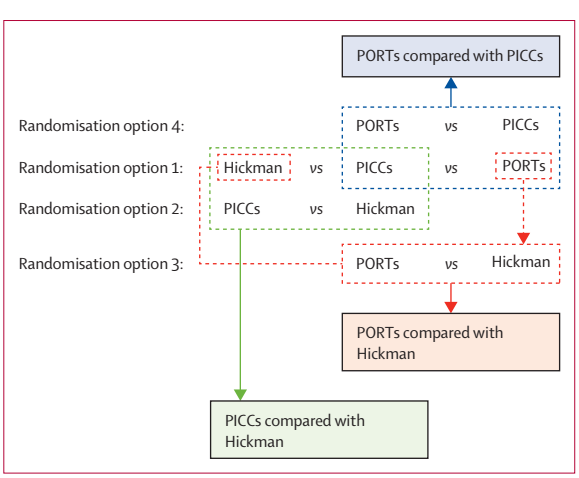

Figure 2: **Four randomisation options for three comparisons**
Hickman=Hickman-type tunnelled catheters. PICCs=peripherally inserted central catheters. PORTs=totally implanted ports.

	PICCs *vs* Hickman		PORTs *vs* Hickman		PORTs *vs* PICCs	
	PICCs (n=190)	Hickman (n=207)	PORTs (n=243)	Hickman (n=280)	PORTs (n=137)	PICCs (n=171)
Primary operator						
Nurse	128 (67%)	47 (23%)	59 (24%)	97 (35%)	3 (2%)	125 (73%)
Radiographer	10 (5%)	15 (7%)	5 (2%)	10 (4%)	3 (2%)	7 (4%)
Anaesthesiologist	7 (4%)	42 (20%)	27 (11%)	36 (13%)	14 (10%)	5 (3%)
Radiologist	24 (13%)	96 (46%)	144 (59%)	133 (48%)	107 (78%)	18 (11%)
Doctor	1 (<1%)	4 (2%)	7 (3%)	4 (1%)	5 (4%)	1 (1%)
Surgeon	3 (2%)	1 (<1%)	0	0	5 (4%)	0
Other	16 (8%)	1 (<1%)	0	0	0	13 (8%)
Missing	1 (<1%)	1 (<1%)	1 (<1%)	0	0	2 (1%)
Setting						
Theatre	11 (6%)	61 (30%)	57 (24%)	50 (18%)	28 (20%)	5 (3%)
Procedure or treatment room	103 (54%)	39 (19%)	9 (4%)	86 (31%)	1 (1%)	61 (36%)
Radiology department	50 (26%)	103 (50%)	171 (70%)	140 (50%)	106 (77%)	42 (25%)
Bedside	12 (6%)	0	0	0	0	44 (26%)
Other	14 (7%)	4 (2%)	5 (2%)	4 (1%)	2 (2%)	17 (10%)
Missing	0	0	1 (<1%)	0	0	2 (1%)
Type of anaesthesia						
Local only	188 (99%)	180 (87%)	216 (89%)	268 (96%)	115 (84%)	168 (98%)
Local and conscious sedation	1 (<1%)	26 (13%)	27 (11%)	12 (4%)	17 (12%)	1 (1%)
General anaesthesia	0	0	0	0	5 (4%)	0
Missing	1 (<1%)	1 (<1%)	0	0	0	2 (1%)
Prophylactic antibiotics given						
Yes	3 (2%)	4 (2%)	34 (14%)	2 (1%)	24 (18%)	3 (2%)
No	179 (94%)	199 (96%)	200 (82%)	272 (97%)	109 (80%)	160 (94%)
Missing	8 (4%)	4 (2%)	9 (4%)	6 (2%)	4 (3%)	8 (5%)
Type of dressing applied						
Non-antimicrobial	159 (84%)	144 (70%)	226 (93%)	221 (79%)	121 (88%)	140 (82%)
Antimicrobial	29 (15%)	60 (29%)	10 (4%)	58 (21%)	12 (9%)	25 (15%)
Missing	2 (1%)	3 (1%)	7 (3%)	1 (<1%)	4 (3%)	6 (4%)

Data are n (%). Table excludes patients with no device fitted and patients in whom technical insertion failure prevented a device from being fitted. PICCs=peripherally inserted central catheters. Hickman=Hickman-type tunnelled catheters. PORTs=totally implanted ports. Other primary operators include (but are not limited to) advanced practitioners, specialist nurses, and senior operating department practitioners.

Table 1: **Procedure details for all comparisons**

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Nov 8, 2013, and Feb 28, 2018, of 2714 individuals screened for eligibility, 1061 patients were enrolled and randomly assigned, contributing to the relevant comparison or comparisons (PICCs *vs* Hickman n=424, 212 [50%] on PICCs and 212 [50%] on Hickman; PORTs *vs* Hickman n=556, 253 [46%] on PORTs and 303 [54%] on Hickman; and PORTs *vs* PICCs n=346, 147 [42%] on PORTs and 199 [58%] on PICCs; figures 1, 2). Procedural details associated with device insertion including operator specialism, setting, type of anaesthesia, and antibiotic use are shown in table 1. Hickman were most commonly placed by radiologists (46–48%), followed by nurses (23–35%) and anaesthetists (13–20%). PICCs were most commonly placed by nurses (67–73%). PORTs were most commonly placed by radiologists (59–78%), followed by nurses (2–24%) and anaesthetists (10–11%). With the exception of five patients in the PORT group who received a general anaesthetic, all devices were inserted under local anaesthetic. The use of prophylactic antibiotics was uncommon (≤2% for Hickman and PICCs; 14–18% for PORTs), and non-antimicrobial dressing was most commonly applied across all three devices (≥70% for all devices). Manufacturer details, catheter diameter and material, presence of a Groshong valve, and CT pump compatibility are provided in the appendix (p 8).

For the PICCs versus Hickman comparison, 424 patients (212 in each group) were included (figure 1). The two-way and the three-way randomisation options contributed equal numbers of patients to each group.

All patients were included in the ITT analysis. Device insertion was attempted in 202 (95%) patients randomly assigned to PICCs and 205 (97%) patients randomly assigned to Hickman. Of these patients, 20 (10%) of 202 in the PICCs group and 11 (5%) of 205 in the Hickman group received a different device from that assigned. The PP population only consisted of patients who received the device they were randomly assigned to (182 [86%] to PICCs and 194 [92%] to Hickman).

Patient characteristics were generally similar at baseline (table 2). Most patients (222 [52%] of 424) had metastatic solid tumours. 224 (61%) of 369 of the patients with solid tumours had colorectal primary tumours; a greater proportion was seen in the Hickman group (120 [65%] of 184 *vs* 104 [56%] of 185) than in the PICCs group. The proportion of patients with pancreatic cancer was greater in the PICCs group (27 [15%] of 185 versus 15 [8%] of 184) than in the Hickman group. There were no differences between the groups in any baseline QOL measure.

Peri-procedural complications were rare in both groups: two (1%) in the Hickman group and four (2%) in the PICCs group (data not shown). There were no pneumothoraces, arterial punctures, mediastinal damage, haemorrhage, or cardiac arrythmias. The tip of the catheter lay in the superior vena cava or right atrium in 181 (87%) of 207 with Hickman and 165 (87%) of 190 with PICCs (data not shown).

Overall complication rates were similar (110 [52%] of 212 with PICCs *vs* 103 [49%] of 212 with Hickman; table 3). However, it could not be concluded that PICCs had significant non-inferiority (10% margin) to Hickman in terms of complication rate via the primary analysis (OR 1·15 [95% CI 0·78–1·71]) or the network meta-analysis (OR 1·10 [0·78–1·55]; appendix p 9). The PP analysis drew the same conclusion. PICCs were in situ for a shorter duration than Hickman (113 days for PICC, 158 days for Hickman; difference in median of 45 days). PICCs were associated with a higher number of complications per catheter week (0·12 [SE 0·02]) than Hickman (0·07 [0·01]). Device removal as a result of complications was common in both groups (78 [42%] of 184 PICCs and 61 [32%] of 188 Hickman). PICCs were associated with higher rates of inability to aspirate blood (45 [21%] PICCs *vs* 33 [16%] Hickman) and mechanical failure (31 [15%] PICCs *vs* seven [3%] Hickman). By contrast, Hickman were associated with higher rates of all types of infections than PICCs (23 [11%] PICCs *vs* 63 [30%] Hickman). Similar rates of venous thrombosis, pulmonary embolism, and other complications were reported; the analysis of venous thrombosis data was not significant (p=0·36). No significant differences were seen in QOL as measured by the EQ-5D or the EORTC QLQ-C30 (appendix pp 10–12). The device-specific QOL instrument showed a significant benefit in favour of Hickman for two of the 16 questions (hygiene and hobbies), but this significance was lost when adjusted for multiple testing (appendix p 13). Compliance with QOL questionnaires reduced with time so that by 1 year, only 29% (four of 14) of patients with PICCs and 13% (two of 15) of patients with Hickman returned data for any of the three questionnaires (appendix p 14). The use of PICCs compared with Hickman was associated with a substantially lower total cost (difference in costs –£1553 [95% CI –2639 to –468]). However, when catheter dwell times were taken into account, the difference in cost per catheter week was substantially reduced (–£126 [–279 to 28]). A detailed breakdown of total costs are provided in appendix (p 15).

556 patients were included in the PORTs (n=253) versus Hickman (n=303) comparison (figure 1). The two-way randomisation contributed 71% of the patients. All patients were included in the ITT analysis. Device insertion was attempted in 245 (97%) patients randomly assigned to PORTs and 283 (93%) patients randomly assigned to Hickman. Of these patients, five (2%) patients originally assigned to PORTs and six (2%) patients originally assigned to Hickman received a different device from that assigned. The PP population only consisted of patients who received the device they were randomly assigned to receive (239 [94%] PORTs and 277 [91%] Hickman).

Patient characteristics were similar at baseline (table 2). 347 (62%) of 556 patients had metastatic solid tumours. 306 (59%) of 515 patients with solid tumours had colorectal primary tumours. There were no differences between the groups in any baseline QOL measure.

Peri-procedural complications were rare in both groups: four (1%) with Hickman and three (1%) in PORTs (data not shown). There were two arterial punctures in the Hickman group. There were no pneumothoraces, mediastinal damage, haemorrhages, or cardiac arrythmias. The tip of the catheter lay in the superior vena cava or right atrium in 248 (89%) of 280 with Hickman and 210 (86%) of 243 with PORTs (data not shown).

PORTs were significantly superior to Hickman in terms of complication rate in the primary analysis (OR 0·54 [95% CI 0·37–0·77]). The network meta-analysis and PP analysis drew the same conclusion. PORTs were in situ for a substantially longer period than Hickman (165 days for Hickman, 367 days for PORTs; difference in median of 202 days; table 3). PORTs were associated with 0·02 (SE 0·00) number of complications per catheter week compared with 0·06 (0·01) in the Hickman group. Device removal as a result of complications was far less frequent in the PORTs group (20 [14%]) than in the Hickman group (80 [32%]). PORTs were associated with substantially lower rates of laboratory-confirmed blood-stream infections (14 [6%] PORTs *vs* 49 [16%] Hickman) and exit site infections (10 [4%] PORTs *vs* 26 [9%] Hickman); however, suspected catheter-related blood-stream infection was slightly higher in the PORTs group (19 [8%]) than in the Hickman group (15 [5%]). Venous thrombosis was rare (three [1%] patients in the PORT

	PICCs *vs* Hickman		PORTs *vs* Hickman		PORTs *vs* PICCs	
	PICCs (n=212)	Hickman (n=212)	PORTs (n=253)	Hickman (n=303)	PORTs (n=147)	PICCs (n=199)
Age, years						
Mean (SD)	62 (11)	61 (12)	59 (13)	60 (13)	61 (12)	61 (13)
Range	19–85	20–87	19–86	20–87	28–86	19–84
Gender						
Women	102 (48%)	96 (45%)	112 (44%)	151 (50%)	81 (55%)	107 (54%)
Men	110 (52%)	116 (55%)	141 (56%)	152 (50%)	66 (45%)	92 (46%)
Body-mass index, mg/kg²*						
<20	10 (5%)	12 (6%)	13 (5%)	16 (5%)	9 (6%)	8 (4%)
20 to <30	145 (68%)	145 (68%)	171 (68%)	209 (69%)	98 (67%)	139 (70%)
30 to <40	51 (24%)	49 (23%)	61 (24%)	70 (23%)	36 (25%)	47 (24%)
≥40	6 (3%)	6 (3%)	8 (3%)	8 (3%)	4 (3%)	5 (3%)
Ethnicity						
White	204 (96%)	210 (99%)	246 (97%)	293 (97%)	137 (93%)	182 (92%)
Asian	3 (1%)	1 (<1%)	4 (2%)	1 (<1%)	3 (2%)	5 (3%)
South East Asian	0	0	1 (<1%)	0	3 (2%)	0
Afro-Caribbean	1 (<1%)	1 (<1%)	2 (1%)	3 (1%)	3 (2%)	6 (3%)
Other	0	0	0	1 (<1%)	1 (1%)	4 (2%)
Missing	4 (2%)	0	0	5 (2%)	0	2 (1%)
Type of cancer*†						
Solid tumour	185 (87%)	184 (87%)	235 (93%)	280 (92%)	142 (97%)	190 (96%)
Colorectal	104 (56%)	120 (65%)	138 (59%)	168 (60%)	65 (46%)	89 (47%)
Breast	21 (11%)	21 (11%)	27 (12%)	42 (15%)	22 (16%)	27 (14%)
Pancreas	27 (15%)	15 (8%)	16 (7%)	18 (6%)	12 (9%)	25 (13%)
Other	31 (17%)	28 (15%)	54 (23%)	48 (17%)	43 (30%)	48 (25%)
Missing	2 (1%)	0	0	4 (1%)	0	1 (<1%)
Haematological malignancy	27 (13%)	28 (13%)	18 (7%)	23 (8%)	5 (3%)	9 (5%)
Acute myeloid leukaemia	7 (26%)	11 (39%)	5 (28%)	13 (57%)	2 (40%)	1 (11%)
High-grade non-Hodgkin lymphoma	5 (19%)	8 (29%)	4 (22%)	3 (13%)	0	4 (44%)
Hodgkin disease	4 (15%)	3 (11%)	4 (22%)	3 (13%)	0	1 (11%)
Other	10 (37%)	6 (21%)	5 (28%)	3 (13%)	3 (60%)	2 (22%)
Missing	1 (4%)	0	0	1 (4%)	0	1 (11%)
Metastatic disease (patients with solid tumours only)						
Yes	114 (62%)	108 (59%)	156 (66%)	191 (68%)	93 (66%)	123 (65%)
No	68 (37%)	76 (41%)	79 (34%)	85 (30%)	48 (34%)	65 (34%)
Missing	3 (2%)	0	0	4 (1%)	1 (1%)	2 (1%)
Patients being administered fluorouracil	137 (65%)	143 (68%)	179 (71%)	198 (65%)	91 (62%)	122 (61%)
Planned treatment mode*						
Inpatient	17 (8%)	19 (9%)	25 (10%)	26 (9%)	5 (3%)	6 (3%)
Outpatient	195 (92%)	193 (91%)	228 (90%)	277 (91%)	142 (97%)	193 (97%)
Device history*						
No previous device	181 (85%)	180 (85%)	198 (78%)	239 (79%)	123 (84%)	168 (84%)
≥1 previous device inserted >3 months before study entry	26 (12%)	26 (12%)	46 (18%)	53 (18%)	21 (14%)	27 (14%)
≥1 previous device inserted <3 months before study entry	5 (2%)	6 (3%)	9 (4%)	11 (4%)	3 (2%)	4 (2%)
Baseline quality of life scores						
EQ5D index value	0·7 (0·3; −0·3 to 1·0)	0·8 (0·2; −0·2 to 1·0)	0·7 (0·3; −0·1 to 1·0)	0·7 (0·3; −0·3 to 1·0)	0·8 (0·2; 0·0 to 1·0)	0·8 (0·2; 0·0 to 1·0)
EQ5D health state score	70·6 (20·7; 10·0 to 100·0)	70·3 (18·6; 10·0 to 100·0)	71·0 (21·0; 0·0 to 100·0)	69·4 (19·8; 0·0 to 100·0)	74·3 (17·5; 30·0 to 100·0)	73·6 (19·6; 20·0 to 100·0)
QLQ-C30 global health status	65·3 (22·6; 0·0 to 100·0)	68·0 (21·1; 0·0 to 100·0)	66·0 (21·9; 0·0 to 100·0)	64·2 (22·1; 0·0 to 100·0)	67·8 (19·9; 0·0 to 100·0)	69·8 (20·6; 0·0 to 100·0)

Data are n (%), or mean (SD; range), unless specified. PICCs=peripherally inserted central catheters. Hickman=Hickman-type tunnelled catheter. PORTs=totally implanted ports. QLQ-C30=Quality of Life of Cancer Patients Questionnaire. *Stratification factor. †Percentages for type of cancer are calculated from the number of patients with either solid tumours or haematological malignancies.

Table 2: **Baseline characteristics for all comparisons**

	PICCs *vs* Hickman		PORTs *vs* Hickman		PORTs *vs* PICCs	
	PICCs (n=212)	Hickman (n=212)	PORTs (n=253)	Hickman (n=303)	PORTs (n=147)	PICCs (n=199)
Number of complications						
0	102 (48%)	109 (51%)	180 (71%)	172 (57%)	100 (68%)	106 (53%)
≥1	110 (52%)	103 (49%)	73 (29%)	131 (43%)	47 (32%)	93 (47%)
Complication type						
Inability to aspirate blood						
Patients	45 (21%)	33 (16%)	38 (15%)	42 (14%)	23 (16%)	37 (19%)
Complications	66 (38%)	43 (25%)	63 (48%)	60 (30%)	33 (39%)	55 (40%)
Venous thrombosis						
Patients	13 (6%)	10 (5%)	3 (1%)	7 (2%)	3 (2%)	22 (11%)
Complications	14 (8%)	10 (6%)	3 (2%)	7 (4%)	3 (4%)	24 (17%)
Pulmonary embolism						
Patients	6 (3%)	4 (2%)	3 (1%)	4 (1%)	3 (2%)	1 (<1%)
Complications	6 (4%)	4 (2%)	3 (2%)	4 (2%)	3 (4%)	1 (1%)
Any infection						
Patients	23 (11%)	63 (30%)	36 (14%)	77 (25%)	18 (12%)	16 (8%)
Complications	27 (16%)	78 (46%)	47 (36%)	102 (51%)	24 (28%)	16 (12%)
Laboratory confirmed bloodstream infection						
Patients	10 (5%)	41 (19%)	14 (6%)	49 (16%)	8 (5%)	7 (4%)
Complications	11 (6%)	43 (25%)	16 (12%)	54 (27%)	9 (11%)	7 (5%)
Suspected catheter-related bloodstream infection						
Patients	10 (5%)	18 (9%)	19 (8%)	15 (5%)	8 (5%)	5 (3%)
Complications	12 (7%)	23 (14%)	21 (16%)	16 (8%)	11 (13%)	5 (4%)
Exit site infection						
Patients	4 (2%)	19 (9%)	10 (4%)	26 (9%)	4 (3%)	4 (2%)
Complications	4 (2%)	22 (13%)	10 (8%)	32 (16%)	4 (5%)	4 (3%)
Mechanical failure						
Patients	31 (15%)	7 (3%)	2 (1%)	9 (3%)	4 (3%)	21 (11%)
Complications	31 (18%)	7 (4%)	2 (2%)	9 (5%)	4 (5%)	21 (15%)
Other						
Patients	23 (11%)	16 (8%)	14 (6%)	17 (6%)	16 (11%)	19 (10%)
Complications	29 (17%)	18 (11%)	14 (11%)	18 (9%)	18 (21%)	22 (16%)
Total number of complications	173	170	132	200	85	139
≥1 severe SIR complications,* percentage of patients with complications	28 (25%)	52 (50%)	33 (45%)	62 (47%)	16 (34%)	24 (26%)
Median device dwell time, days	113 (106–123)	158 (140–175)	367 (324–393)	165 (149–177)	393 (324–393)	119 (109–130)
Complications per catheter week	0·12 (0·02)	0·07 (0·01)	0·02 (0·00)	0·06 (0·01)	0·05 (0·02)	0·13 (0·02)
Infective complications per catheter week	0·02 (0·01)	0·04 (0·01)	0·01 (0·00)	0·03 (0·01)	0·02 (0·01)	0·02 (0·01)
Non-infective complications per catheter week	0·10 (0·02)	0·04 (0·01)	0·01 (0·00)	0·03 (0·01)	0·04 (0·02)	0·10 (0·02)
Planned removal or end of treatment	91 (50%)	99 (53%)	80 (56%)	131 (52%)	44 (59%)	85 (52%)
Removal due to complications	78 (42%)	61 (32%)	20 (14%)	80 (32%)	18 (24%)	63 (38%)
Removal due to other reasons	15 (8%)	28 (15%)	42 (30%)	40 (16%)	13 (17%)	17 (10%)
Total devices removed, percentage device insertions attempted	184 (91%)	188 (92%)	142 (58%)	251 (89%)	75 (52%)	165 (88%)
Total cost, £	1708 (1153–2262)	3262 (2227–4296)	2436 (1927–2946)	2481 (2007–2954)	2706 (1899–3513)	1041 (764–1316)
Cost per catheter week, £	248 (161–336)	374 (244–505)	210 (120–300)	257 (161–353)	263 (133–394)	304 (153–455)

Data are n (%), mean (SE), mean (95% CI), or median (95% CI), unless specified. Percentages for complications are calculated out of the total number of complications in that group. PICCs=peripherally inserted central catheters. Hickman=Hickman-type tunnelled catheters. PORTs=totally implanted ports. *Classed as Society of Interventional Radiology classification C or worse (see appendix p 7).

Table 3: **Outcomes for all comparisons**

group and seven [2%] in the Hickman group), and not significantly different between groups (p=0·56). Other complication rates were similar in both groups. No statistically significant differences in QOL were seen as measured by the EQ-5D or the EORTC QLQ-C30 (appendix pp 10–12). By contrast, the device-specific QOL

instrument did show a significant benefit in favour of PORTs for 11 of the 16 questions (appendix p 13). Compliance with QOL questionnaires reduced with time so that by 1 year, only 49% (56 of 114) of patients with PORTs and 37% (11 of 30) of patients with Hickman returned data for any of the three questionnaires (appendix p 14). PORTs compared with Hickman were associated with a lower total cost (difference in costs –£45 [95% CI –744 to 655]) and lower cost per catheter week (–£47 [–166 to 73]). The difference was not significant.

346 patients were included in the PORTs (n=147) versus PICCs (n=199) comparison (figure 1). The two-way randomisation contributed 54% of the participants. All participants were included in the ITT analysis. Device insertion was attempted with 143 (97%) patients randomly assigned to PORTs and 187 (94%) patients randomly assigned to PICCs. Of these patients, 12 (8%) in the PORT group and 28 (15%) in the PICC group received a different device from that assigned. The PP population only consisted of participants who received the device they were randomly assigned to (131 [89%] to PORTs and 159 [80%] to PICCs).

Patient characteristics were similar at baseline (table 2). 216 (62%) of 346 patients had metastatic solid tumours. 154 (46%) of 332 patients with solid tumours had colorectal primary tumours. No differences were observed between the groups in any baseline QOL measure.

Peri-procedural complications were rare in PICCs (six [4%]). There were no pneumothoraces, arterial punctures, mediastinal damage, haemorrhages, or cardiac arrythmias (data not shown). No complications in PORTs were recorded. The catheter tip lay in the superior vena cava or right atrium in 153 (89%) of 171 with PICCs and 123 (90%) of 137 with PORTs (data not shown).

PORTs were associated with significantly lower complication rates than PICCs via the primary analysis (OR 0·52 [95% CI 0·33–0·83]). The network meta-analysis and PP analysis drew the same conclusion. PORTs were in situ for a substantially longer period than PICCs (119 days for PICCs, 393 days for PORTs; difference in median of 274 days; table 3). PORTs were associated with 0·05 (SE 0·02) complications per catheter week compared with 0·13 (0·02) in the PICCs group. Device removal as a result of complications was less frequent in the PORTs group (24%) than the PICCs group (38%). Mechanical failure was reported in four (3%) patients with PORTs compared with 21 (11%) with PICCs. Venous thrombosis was reported in three (2%) patients with PORTs but 22 (11%) with PICCs (p=0·0024). Although infection rates (any type) were reported in a greater proportion of patients in the PORTs group than in the PICCs group (18 [12%] with PORTs *vs* 16 [8%] with PICCs), the mean number of infections per catheter week was similar (0·02 in both groups; data not shown). There was a significant difference favouring PICCs over PORTs in terms of EQ-5D index value. We found no further significant differences in the QOL as measured by the EQ-5D health state score or the EORTC QLQ-C30 (appendix pp 10–12). By contrast, the device-specific QOL instrument showed a significant benefit in favour of PORTs for eight of the 16 questions (appendix p 13). Compliance with QOL questionnaires reduced with time so that by 1 year, only 39% of patients with PORTs and 32% of patients with PICCs returned data for any of the three questionnaires (appendix p 14). PORTs compared with PICCs were associated with a substantially higher cost (difference in costs £1665 [95% CI 766 to 2564]). However, when catheter dwell time was taken into account, the reverse was observed (difference in cost per catheter week –£41 [–227 to 147]).

Discussion

CAVA recruited 1061 participants and is, to our knowledge, the largest trial to date to compare Hickman, PORTs, and PICCs for SACT administration. It is also the only mixed methods study, incorporating extensive qualitative research and a health economic evaluation, from the UK NHS perspective. The qualitative results have been published separately,[19,20] and the full health economic evaluation will shortly be available in the NIHR HTA report, along with results of the clinical outcomes not specifically included in this paper.[21] The comparison between PORTs and Hickman showed a significant reduction in the overall complication rate of around 50% with PORTs. This difference was mainly driven by the difference in infections (25% with Hickman *vs* 14% with PORTs). Slightly more than double the number of Hickman were removed than PORTs due to a complication. Venous thrombosis was uncommon but twice as frequent with Hickman. Hickman were associated with higher total costs than PORTs (difference in cost £45) and when adjusted for the longer dwell time of PORTs (£47 per catheter week), although these differences were not significant. Given the clinical benefit and the small difference in cost, there seems little justification for placing a Hickman provided a PORT is deemed clinically appropriate.

The comparison between PORTs and PICCs showed a significant reduction in the overall complication rate of around 50% with PORTs. This difference was largely explained by a reduction in both mechanical and thrombotic complications with PORTs. The risk of a patient having a venous thrombosis was around five times higher with a PICC than with a PORT (2% *vs* 11%). This result has been reported by several other groups[7,8,22] and could be related to the presence of the PICC in a much smaller calibre arm vein over a longer length than a centrally placed PORT. Pulmonary embolus was rare but more common in the PICC group. We found infection rate to be a little higher with PORTs than with PICCs (12% *vs* 8%). This finding was unexpected given that there is no external component with a PORT, so one would expect fewer infections;

however, others have reported this finding previously.[7] The observation could be due to the skin being breached by the access needle every time a PORT is used and skin bacteria being introduced via the needle.[23] Another possibility is a learning curve phenomenon in the aftercare of PORTs in centres in which PORTs were recently introduced. Further, skin inflammation around the PORT from drug extravasation due to a misplaced needle could be confused with infection. PORTs were more than twice the cost of PICCs (total cost £2706 *vs* £1041). However, when dwell time was taken into consideration, PORTs were slightly cheaper (£263 *vs* £304 per catheter week). These data suggest, that in patients with metastatic solid cancers receiving palliative chemotherapy in which the expected duration of SACT is expected to exceed 3 months, or where patients are likely to receive multiple lines of SACT over a prolonged period, PORTs offer a distinct advantage to PICCs, with lower complication rates at similar costs.

The comparison between Hickman and PICCs showed no difference in complication rates but was underpowered to conclude non-inferiority; it was estimated that the primary analysis had 54% power and the network meta-analysis had 64% power (the intended power was 80%). The difficulty with recruitment was partly due to a marked reduction in the use of Hickman during the course of the trial, coupled with a large expansion of nurse-led PICC services across UK oncology sites. Approximately half of the patients in both groups reported at least one complication; however, we found a higher complication rate per catheter week associated with PICCs. The dominant complication for Hickman was infection whereas for PICCs it was mechanical failure. The presence of a cuff and subcutaneous tunnel with a Hickman is thought to reduce the risk of both mechanical problems and infections. Although we found a much lower risk of mechanical complications with Hickman, the risk of infection was nearly three times that of PICCs. Venous thrombosis was similar between the two devices (5% with Hickman *vs* 6% with PICCs), as were most of the other complications. PICCs were associated with substantially lower total costs (difference in costs £1553). Allowing for the longer dwell time of Hickman still made them more expensive at an extra £126 per catheter week.

There was a significant difference favouring PICCs over PORTs in the index EQ-5D value. Otherwise there were no other significant differences in QOL based on the EQ-5D and the EORTC QLQ-30 in any comparison. It appears these instruments are not sensitive to the device but more influenced by the underlying disease state and treatment. By contrast, the device-specific questionnaire showed many aspects of QOL to be significantly better with a PORT than a Hickman or a PICC. This issue, and in particular the potential limitation of EQ-5D in this context, will be discussed in a forthcoming health economics paper.

This preference was further reinforced by the findings of our qualitative study, which sought to explore the acceptability of the three devices among patients and staff.[20] Although all three devices were well accepted by patients and preferable to peripheral cannulation, PORTs were perceived to offer unique psychological benefits, including a greater sense of freedom and less intrusion in the context of personal relationships.[19] The practical benefits associated with their absence of external lines (ie, less visible, easier maintenance) meant that PORTs were less psychologically burdensome; participants with PORTs repeatedly stressed that it was easy for them to almost forget about their device. Despite considering PORTs more challenging from a clinical and management perspective, staff also favoured them because they were seen as better for patients. Indeed, staff were very well attuned to patient experiences and cited the same practical conveniences of PORTs, as well as the emotional and psychological benefits of a less conspicuous or obtrusive device that patients themselves raised.[19,20]

The median dwell time of PORTs (more than 350 days) was much greater than Hickman (around 160 days) and PICCs (around 120 days). This difference can be partly explained by the lower incidence of device removal as a result of a complication than the other two devices. PORTs are the most complex to place and remove, PICCs are the easiest, and Hickman are inbetween. Therefore, it is highly probable that the threshold for removal due to complication was lowest with a PICC and highest with a PORT. Another factor likely to influence device removal and hence dwell time would be a treatment break; PICCs and Hickman are more likely to be removed whereas PORTs would be left in situ in these circumstances. Extended periods of PORT placement are likely to represent a period of so-called rest for the PORT and the patient, with only periodic flushes, absence of SACT, and overall lower risks of introducing infection.

Peri-procedural or immediate technical complications were rare across all devices. In particular there were no instances of pneumothorax or mediastinal damage. We believe concerns regarding complications of a jugular or subclavian vein puncture are rare and largely historical. Provided there is adequate training and the use of ultrasound guidance, jugular or subclavian vein puncture (Hickman and PORT) should be no more risky than cannulating an arm vein for a PICC.

CAVA's strengths lie in its size, the inclusion of all three CVADs, QOL assessment, and full economic evaluation. The inclusion of all cancer types also makes the findings more generalisable. A 2020 randomised controlled trial only included patients with breast cancer.[8] CAVA, unlike most other similar trials, also included patients with haematological cancer although the numbers were very small (89 [8%] patients). A very high infection rate with PORTs was observed in this group, which warrants further research. Due to small numbers of haematological

malignancies in CAVA, we cannot make any suggestions as to the preferred device in this patient group.

A further strength is that our primary endpoint consisted of an exhaustive list of complications, including some that other studies had excluded such as suspected infection and inability to aspirate blood, all of which directly affect clinical care. We also included other complications to ensure that no relevant data were missed. This clarification of the primary endpoint included in the published protocol as "a composite of infection (suspected or confirmed) and/or mechanical failure" resulted from the initial discussions surrounding data capture for the study and ensured that all individual component complications were recorded for all patients from the first randomisation. A limitation of the study is that this clarification was not specifically noted in the protocol; however, it was supported by the CAVA independent data monitoring committee, which reviewed the emerging study data annually.

Further limitations of the trial included a reduction in power of two of the comparisons after 18 months. All comparisons were initially designed with 90% power; however, a protocol-mandated review of recruitment at this time allowed adjustments to be made on the basis of actual recruitment to each comparison and the results of the pilot study. As a result, the power for both Hickman versus PICCs and PICCs versus PORTs was reduced to 80%. By contrast, the power for Hickman versus PORTs was increased to 95%. Unfortunately, recruitment to the PICC versus Hickman comparison was not completed, and the final analysis was underpowered. This situation was due to a change in landscape with regards to clinical practice over the duration of CAVA. PICCs were becoming the preferred option to Hickman as PICC nurse-led teams expanded. However, the suggested superiority of PORTs over both the other two devices makes the PICCs versus Hickman comparison less relevant in clinical practice.

A further weakness was that we did not capture any further device insertion data after removal of the index device. Had we done so, it is probable that the cost of both Hickman and PICCs would be higher given the potential need for more re-insertions.

Although most of our patients had either colorectal or breast cancer, we feel the results are generalisable to patients with solid tumour cancers requiring a CVAD. It is probable (although untested) that the results of CAVA could be generalisable to other patients needing these devices for other conditions (eg, parenteral nutrition and antibiotics). However, there is a small group of patients such as those with needle phobia and fear of a more invasive procedure who might prefer other devices.

Finally, we had a mix of different staff groups placing the devices reflecting international practice, and in general, PICCs were placed by nurses and Hickman and PORTs by interventional radiologists or anaesthetists. However, there were some centres in which nurse-led teams placed all three and this arrangement could be a model for the future to bring down costs and provide a more responsive service. It is possible that larger numbers of PORT procedures could further reduce complication rates as experience grew and different designs of PORTs could increase the ease of insertions and removals—eg, by not requiring use of full theatre or imaging suite capabilities—further increasing the cost-effectiveness of PORTs over the other CVADs.

CAVA has expanded the knowledge base on these CVADs and the case for a PORT-dominant strategy has been strengthened. These findings should prove useful for updating national and international guidelines to recommend the adoption of PORT-delivered services for relevant patient groups.

Contributors

JGM, OW, and EMcC led the conception, design, and management of the study. ARB, RA, TFM, BLJ, and SH contributed to the conception, design, and management of the study. EMcC designed and performed the statistical analyses. EG was responsible for the qualitative components of the study. OW designed and RH did the health economic evaluation. JD-H and ES managed the trial. SD was responsible for data collection. EMcC and RH verified the data. All authors read and approved or commented on the final publication. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

JGM is paid a personal fee to run PORT training courses for Smith Medical and received PORTs free of charge from four manufacturers. OW is deputy chair of NIHR HTA general funding board (2020 onwards) and was a committee member of NIHR HTA general funding board 2016–19. BLJ receives payment for lectures from Merck Sharp and Dohme and Pfizer; attendance at advisory board for Menarini; owns shares in Novartis and Gilead Sciences; and is a member of the Scottish Medicines Consortium. All other authors declare no competing interests

Data sharing

The CAVA investigators are committed to furthering cancer research by sharing de-identified individual patient data from CAVA with others in the field, who wish to use the data for high-quality peer-reviewed research. We are happy to consider proposals from researchers and will share individual-patient data to the maximum extent, subject to individual study constraints relating to: (1) ethical approval and informed consent; (2) contractual and legal obligations, including a data sharing agreement; and (3) publication timelines (data will not normally be shared before publication of the primary results). All proposals will be reviewed for their scientific merit by the trial management group. Only data relevant to the objectives of a particular proposal will be provided. If you wish to have an initial discussion about accessing data from clinical trial unit studies please contact JGM (chief investigator) at jonathan.moss@glasgow.ac.uk.

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manufacturers, in which local barriers existed to prevent normal NHS purchasing.

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