CAVA

Cancer **A**nd **V**enous **A**ccess (**CAVA**) – A randomised controlled trial with associated qualitative research of venous access devices for the delivery of long-term chemotherapy

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(Partner of Cancer Clinical Trials Unit Scotland (CaCTUS))

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Study Summary

Title:	**C**ancer **A**nd **V**enous **A**ccess (**CAVA**) – A randomised controlled trial with associated qualitative research of venous access devices for the delivery of long-term chemotherapy.
Design:	A randomised controlled trial incorporating pre and post trial qualitative research.
Aims:	To determine which venous access device – subcutaneously tunnelled central catheters (Hickman type device), peripherally inserted central catheters (PICC) or implantable chest wall ports (Port), offers the best outcome from safety, clinical effectiveness and cost effectiveness perspectives.
Outcome Measures:	The primary outcome for the randomised trial is complication rate, a composite of infection associated with the device (suspected or confirmed) and/or mechanical failure. Secondary outcomes include catheter related venous thrombosis, need for device removal/replacement, number of days of interruption to chemotherapy delivery and quality of life.
Population:	Patients receiving chemotherapy
Eligibility:	Long-term anti-cancer therapy (≥12 weeks) where a central venous access device is needed for safe and effective treatment delivery.
Treatment:	Any long term anti-cancer therapy using a central venous access device.
Duration of Trial Participation:	Participation in the trial will continue for as long as the device remains in situ for up to a period of 12 months.

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1 INTRODUCTION

Cancer requiring chemotherapy is common. The National Chemotherapy Advisory Group estimated approximately 65,000 programmes per year and Hospital Activity Data for England reported 425,000 deliveries of chemotherapy for cancer in the year 2009-2010.

When chemotherapy has to be administered by the intravenous route it can either be given through a peripheral cannula into an arm vein or through one of the three central venous access devices: subcutaneously tunnelled central catheters (Hickman type device), peripheral inserted central catheters (PICC) or implantable chest wall ports (Port). Unlike the peripheral cannula these all deliver the drug into a large high flow central vein (superior vena cava), which drains directly into the right atrium of the heart. This avoids local problems from the irritant nature of many chemotherapeutic drugs which damage and rapidly occlude small peripheral arm veins. In addition these three central venous devices are intended to remain in place until the course of treatment has been completed. For patients receiving chemotherapy over several months any one of these devices is regarded as normal practice.

The dominant strategy at present is a Hickman type device, followed by PICC with Ports being used infrequently. There is a gradual shift away from Hickman type devices towards PICC in some centres which may be due to evolving nurse-led delivery. Ports offer many potential advantages which include fewer complications, less maintenance, reduced treatment interruption, improved quality of life and patient satisfaction. However Ports are the most expensive device and their cost effectiveness is unknown. It is likely that the initial cost and the slightly more complex insertion procedure is limiting usage. In the private healthcare sector ports are increasingly the dominant strategy.

The decision-making processes behind choice of device is poorly understood and varies from centre to centre. In addition to clinical factors the views of the oncologist, nurse or radiologist, the availability of staff, cost pressures and who places the device all play an unknown role. Currently there is no evidence-based guidance to help choose between them. Venous access services are evolving and there is increasing input from dedicated nurse specialists. In some of the more proactive centres these nurses will discuss the options with a patient and then place the device. This nurse driven service is usually under the supervision of either anaesthetists or interventional radiologists. Surgeons have less involvement in this area expect for paediatrics.

1.1. Existing research and pilot studies

Systematic review (Hickman type versus Port)

We conducted a systematic review[1] to evaluate the risk of complications associated with Hickman type devices compared with Ports in patients receiving chemotherapy for the management of solid or haematological malignancies. Five randomised controlled trials (RCTs) [2, 3, 4, 5, 6] and 24 observational studies were included in the review; only one study was conducted in the UK.

Of the five RCTs included in the review, two were terminated prematurely. One trial randomised solid and haematological oncology patients (≤21 years) to prophylactic urokinase and heparin, stratified by Hickman lines and Ports. This trial was terminated at 18 months (intended trial duration of three years) following urokinase being withdrawn by the US Food and Drug Administration Association[3]. The other trial randomised patients (>15 years) with acute leukaemia to Hickman lines or Ports; the trial terminated prematurely due to high bleeding rate in the Port arm[4]. The remaining three trials, albeit small in sample size provided some data on the risk of complications (device failure leading to removal, infection and mechanical problems) when comparing Hickman lines and Ports in adult oncology patients (one study included adults and paediatrics[5]).

Overall, the systematic review included studies covering a diverse patient population (children and adults) with a mixture of cancer types (solid tumours and haematological malignancies).

The quality of the studies varied. Major limitations include: partially reported demographic characteristics and patient selection criteria, inadequate sample size and lack of definition of the complications evaluated.

The majority of the studies were in general agreement that Hickman type devices are associated with an increased risk of infection, ranging from a non-statistically significant increase in risk (OR 2.19; 0.78 to 6.14) to as much as a five-fold increase (OR 5.81; 1.44 to 23.36) in RCTs, and OR 1.28 (0.44 to 3.76) to OR 12.01 (6.58 to 21.93) in observational studies. Only one retrospective cohort study reported a reduction in risk of infection with Hickman type devices (OR 0.82; 0.24 to 2.77). Similar trends were reported in the risk of device removal, ranging from OR 1.00 (0.38 to 2.61) to OR 8.81 (2.40 to 32.41) in RCTs and OR 1.03 (0.39 to 2.70) to OR 12.32 (2.84 to 53.40) in observational studies. Due to the substantial heterogeneity within the evidence base, the true magnitude of these risks cannot be established. For instance, despite sharing similar study objectives in assessing the complications, the definition of complications vary wide in these studies (e.g. infection may be defined as exit-site infection, tunnel infection, bacteraemia, or combinations of the three, based on clinical inspection or blood cultures), bringing into question the generalisability of the findings of these studies. Furthermore, other important factors such as patient reported quality of life and cost effectiveness are also unknown.

Glasgow Feasibility Study 2011-2013 (Hickman versus Port)

This feasibility study comparing Hickman lines and Ports is ongoing. It aims to collect and refine outcome measures, assess quality of life, test a device-specific questionnaire, gather healthcare resource use data and conduct a pre-trial economic evaluation. To date, all 100 patients have been recruited and the study is in follow up. It has been specifically designed to provide information to help optimise the design of this larger study. The final results are expected early in 2014.

PICC trials

To our knowledge, the rate of complications between Hickman type devices and PICCs in patients receiving chemotherapy has not been previously assessed. A literature search found two RCTs comparing PICC with the other devices:

• In one trial (n=102), patients receiving total parenteral nutrition were randomised to PICC or subclavian tunnelled central lines. The primary outcome was any complication mandating device removal. This outcome was significantly better with the central line arm (33%) compared with the PICC arm (56%) ($p<0.05$). The infection rate was 4.9 per 1000 catheter days and was similar for each catheter type. PICCs were associated with higher rates of clinically evident thrombophlebitis ($P<0.01$), difficult insertion attempts ($P<0.05$), and malposition on insertion ($P<0.05$) [7].

• In another trial (n=68), patients receiving chemotherapy were randomised to either PICC or Ports. The overall complication rate was higher in the PICC (45%) than the Port arm (10%). Similarly, major complications were higher in the PICC (26%) than the Port arm (3%). Central venous thrombosis was observed in four patients in the PICC arm, but none in the Port arm[8].

Evidence of cost-effectiveness

There is a substantial difference in the cost of implanting these devices. For instance the cost of the individual devices alone are approximately £60 for PICC, £80 for Hickman type device and £300 for a chest wall port, although these costs can vary significantly at different NHS sites due to local discounting deals etc.

To date, only one study has attempted to investigate the costs and health benefits associated with central venous catheters in the delivery of chemotherapy[9]. In a retrospective cohort study (n= 30 Hickman and 22 Ports), the complication rates and the costs associated with implanting Hickman lines were compared with Ports in patients with solid tumours. The total costs took into

account costs associated with the device purchase, insertion, treatment of complications and catheter removal and reinsertion. Despite the substantial difference in the purchase costs of the two devices, the estimated total costs were £1512 per Hickman catheter compared with £1483 per Port-a-cath. This study suggested that Ports may be safer and less costly than Hickman lines in the delivery of chemotherapy.

2 STUDY OBJECTIVES

The primary objective is to compare the clinical and cost effectiveness of three central venous access devices in routine use for the delivery of chemotherapy: PICCs, Hickman type devices and chest wall ports

The specific research questions are:

- Are PICCs non-inferior to Hickman type devices in terms of complication rate?
- Are PICCs cost-effective compared with Hickman type devices?
- Are chest wall ports superior to Hickman type devices or PICCs in terms of complication rate?
- Are chest wall ports cost-effective compared with Hickman type devices or PICCs?
- What is the most cost-effective device with acceptable complication rates for delivering long-term chemotherapy?
- Are these devices acceptable to clinical staff and patients?

3 STUDY DESIGN

This main study focus is an open multicentre randomised controlled trial between the three devices. The first 9 months will involve qualitative research followed by patient recruitment over the next 48 months with the final 18 months to include follow up, data cleaning, analysis and an end of trial qualitative study on acceptability (see Gantt chart, appendix 4). The total trial duration is 75 months and the aim is to randomise approximately 1300 patients.

There are four randomisation options for each eligible patient:

1 Hickman type device versus PICC versus chest wall port
2 PICC versus chest wall port
3 PICC verses Hickman Type device
4 Chest wall port versus Hickman type device (This arm closed to randomisation on the 30th November 2015)

Clinicians may choose any of the open randomisations depending on the individual patient and the practice at their individual site. Treatment allocations will be obtained by contacting the CRUK CTU Glasgow (see section 5.2)

The primary endpoint for the randomised study is complication rate, a composite of infection associated with the device (suspected or confirmed) and/or mechanical failure (for full definitions please refer to Appendices I and II). Secondary outcomes include venous thrombosis (superficial or deep), re-intervention rates (device removal and replacement), interruptions to chemotherapy delivery and quality of life. Health-related quality of life will be measured using the EQ5D and EORTC QLQ-C30 as well as a device-specific quality of life questionnaire.

In order to fully address the research questions, the proposed work consists of mixed methodologies of qualitative research, randomised controlled trial and economic evaluation (see flow diagram appendix III).

Setting
This trial will be carried out in several regional UK cancer units including:

- Beatson West of Scotland Cancer Centre, Glasgow (lead centre)
- Queen Elizabeth Hospital, Birmingham
- St. James' Hospital, Leeds
- The Christie Hospital, Manchester
- Freeman Hospital, Newcastle
- Durham and Darlington NHS Trust
- Northampton General Hospital
- Weston Park Hospital
- Imperial College Healthcare NHS Trust
- Royal United Hospital Bath
- Forth Valley Royal Hospital
- Cumberland Infirmary
- Kent and Canterbury Hospital
- Royal Cornwall Hospital
- Mid Essex NHS Foundation Trust

There are some additional units in reserve and the final number of active centres will be guided by the results of the qualitative research.

4 QUALITATIVE STUDY

In order to facilitate recruitment to the study and to explore the attitudes of clinical staff and patients towards the three venous access devices and to facilitate recruitment to the study, the following qualitative work is planned:

4.1 Pre-trial Qualitative Study

Approximately two thirds of trials fail to reach their recruitment targets or have to extend their recruitment period (Watson and Torgerson, 2006; McDonald et al, 2006). This is especially the case for multi-centre trials, in which recruitment may also be uneven. Low and uneven recruitment may result in reduced statistical power, inconvenience to staff and participants, increased costs, the abandonment of important questions and potentially the introduction of bias (Donovan et al. 2009:29). Qualitative research methods have been shown to be successful in refining the presentation of study information and in increasing rates of randomisation[10]. For example, the ProtecT feasibility study for PSA testing for prostate cancer (Donovan et al, 2002) resulted in the proportion of the eligible patient population consenting to randomisation increasing from 49% to 70%. The research team achieved this by interviewing eligible patients and by feeding these findings into recruitment strategies (e.g. by refining the presentation of study information). As such, in order to facilitate recruitment to the study, qualitative research will be carried out prior to the commencement of the CAVA Study. This nested qualitative study will explore the attitudes of clinical staff and patients to issues likely to influence recruitment into the trial and willingness to randomise/be randomised, with a particular focus on uncertainty (equipoise), acceptance of randomisation (with a focus on the relatively complex nature of the CAVA study) and attitudes toward long-term venous access devices. The pre-trial qualitative study will comprise two components:

- Focus group with patients
- Interviews with clinical staff

This pre-trial qualitative study is designed to deliver tailored recruitment strategies and materials for the target population.

Methods:
We plan to carry out one focus group discussion with patients (involving approximately 6-10 patients) and approximately 20 one-to-one semi-structured interviews with clinical staff (nurses, oncologists, radiologists, anaesthetists and surgeons, as relevant). The focus group schedule will

examine attitudes towards the three venous access devices, views on trial participation and acceptance of randomisation, as well as responses to recruitment and study documentation (Appendix 6). The interview schedule will explore attitudes towards the three long-term venous access devices, interest and motivation in participating in the trial, attitudes regarding equipoise, reasons they believe or do not believe they'll have difficulty accruing patients, perceptions of the key benefits and deterrents of participation, and potential negative and positive impacts of the trial on their professional activities, as well as views on recruitment and study documentation (Appendix 6).

Sampling and recruitment:
It is anticipated that there will be variations in attitudes regarding equipoise across specialities/roles and differences in local practice (due to the availability of staff, cost pressures, who places the device etc.) which may act as facilitators and barriers to randomisation. As such, all clinical staff (nurses, oncologists, radiologists, anaesthetists and surgeons, as relevant) from across the six centres will be invited to attend (n=35; of which we will aim to interview 20) with the aim of recruiting from all six centres and achieving a sample comprising a range of relevant roles. They will be recruited and consented by the researcher (who will make initial contact with the relevant individuals via the local principle investigator at each site).

It is anticipated that the attitudes of patients toward the three venous access devices and towards trial participation will be similar across the six regional cancer units. As such, only patients receiving care at the lead centre (Beatson West of Scotland Cancer Centre, Glasgow) who are eligible for recruitment to the CAVA trial (i.e. patients receiving long-term chemotherapy (12 weeks or more) where a central venous access device is needed for safe and effective drug administration) will be invited to take part. Patients will be sampled purposively to include newly diagnosed and metastatic patients, patients with solid malignancies and patients with haematological malignancies with the aim to also get a reasonable balance between women and men. Eligibility will be judged by the oncologist or oncology nurse at the outpatient clinic appointment or by the vascular access nurse. Patients will be given an information sheet detailing the qualitative study by the oncologist or oncology nurse at their outpatient clinic appointment or by the vascular access nurse. Those interested in being involved in the study will be asked to sign a form consenting to their details being passed onto the researcher. The researcher will be copied into the clinic letter or notified by the vascular access team and will follow up the initial contact by telephone to recruit patients.

All procedures regarding data collection, data management and qualitative analysis are described below; as they are identical for both pre-trial and post-trial studies.

Expected results and impact:
The findings from the pre-trial study will be used to develop recruitment materials and processes (including addressing any logistical issues), to provide initiation training for clinical staff on recruitment procedures and the findings will be fed back to clinical staff at a launch meeting as the trial commences.

The overall aim will be to ensure recruitment processes are feasible at each setting, to ensure staff are highly motivated and to ensure study information is presented similarly across all of the centres. Additionally, the qualitative researchers will provide regular training updates for all staff and individual feedback as required.

4.2 Qualitative study on acceptability on completion of the trial

In order to address the acceptability of the devices and to explore (through a number of focus group discussions and interviews) patients and clinical staff attitudes toward long-term venous access devices post trial qualitative research will be undertaken. In addition, we will use this as an opportunity to explore patients and clinical staff experiences of participating in the CAVA study. There is a wide literature on attitudes toward participation in trials, but less on the experiences and perspectives of actual trial participants. Obtaining the views of patients who

have had a device in place should put clinicians in a better position to support future patients with more robust evidence based information prior to device selection, as well as how best to support patients during anti-cancer treatment via venous access. These data may also support the development of a specific quality of life measure for patients who use inserted devices.

The post-trial qualitative study will comprise two components:

- Focus groups with patients
- Interviews with clinical staff

Methods:
We plan to carry out three focus group discussions with patients (each involving 6-10 participants) and approximately 20 one-to-one semi-structured interviews with clinical staff (nurses, oncologists, radiologists, anaesthetists and surgeons, as relevant). The focus group schedule will examine attitudes towards the three venous access devices and experiences of taking part in the RCT (Appendix 7). The interview schedule will also explore attitudes toward the three devices and experiences of taking part in the RCT from a staff perspective (Appendix 7).

Sampling:
Clinical staff (nurses, oncologists, radiologists, anaesthetists and surgeons, as relevant) from across the sites will be invited to attend (n=35; of which we will aim to interview 20) with the aim of recruiting from all six centres and achieving a sample comprising a range of relevant roles. They will be recruited and consented by the researcher (who will make initial contact with the relevant individuals via the local principle investigator at each site).

Patients who were eligible for, and took part in, the CAVA trial will be invited to take part in the post-trial qualitative study. Patients will be sampled purposively to include participants receiving all three devices from all four randomisation options (and if relevant, from centres where recruitment was particularly high or low). We will include newly diagnosed and metastatic patients and patients with solid malignancies and patients with haematological malignancies. We will also aim to include patients that suffered venous access device complications during their time in the trial. Demographic data will also be available (from CRF records) and we will aim to get a balance between women and men.

Recruitment of patients:
During the patient's next visit to their CAVA trial centre, a treating clinical team member will mention that a focus group study is taking place and ask if the patient is interested in participating. They will hand interested patients a patient information sheet about the qualitative study. The qualitative researcher team will only approach those patients who have indicated to the treating clinical team their willingness to consider participating in a focus group. Interested patients will be asked to sign a consent form found at the end of patient information sheet to consent to their contact information being passed to the qualitative researcher. The researcher will make regular (weekly) telephone contact with the local principal investigator in each participating site to receive contact details of interested patients. Those patients will then be contacted by the qualitative researcher by telephone or email (whichever contact information the patient provides) and given an opportunity to ask further questions about the study and their participation, and arrangements for attendance at a focus group discussed. The researcher will take steps to ensure the patient is still alive and has not had a cancer recurrence prior to contacting them.

Expected results and impact:
This qualitative evaluation of the trial will supplement the quantitative outcomes data collected. The in-depth information on participants' experiences and insight into the acceptability of the devices for both patients and clinical staff, will be analysed in the context of the findings from the effectiveness and cost-effectiveness elements of the trial. In addition, the study will be able to enhance the literature on acceptability of participation in an RCT.

4.3 Focus group procedures:

Patients will provide informed written consent at the start of the focus group. It will be emphasised to patients that the focus groups will be facilitated by members of the research team who have no access to their records or involvement in their care. Each focus group will comprise six to ten participants and will take place in a quiet room (at the relevant centre). The focus groups will be no longer than one hour.

4.4 Interview procedures:

The semi-structured interviews with clinical staff will taken place in a suitable location at each of the six centres (the researcher will travel to all six locations on one or repeated visits). If face-to-face interviews are not feasible in all instances (due to competing demands on time) interviews will be carried out over the telephone. Interviews will be no longer than 30 minutes. Participants will provide informed written consent at the start of the interview or verbal consent at the start of the telephone interview.

4.5 Data management:

All interviews and focus groups will be digitally recorded (including telephone interviews). Recordings will be transcribed verbatim, anonymised and uploaded to the QSR NVivo 9.2 qualitative software programme for efficient data management. All qualitative data (recordings and transcripts) will be held along with case record files (CRF) at the CRUK CTU Glasgow. Participants will be asked to consent to the use of their anonymised extracts of talk in the study report and future publications.

4.6 Qualitative Analysis:

The data will be thematically analysed[11]; a process which involves coding participants' talk into categories that summarise and systemise the content of the data. The QSR NVivo 9.2 software programme will be used in order to facilitate the analysis. First, initial codes will be identified, based on careful reading and re-reading of the data by two members of the research team independently (Dr Shaw and the researcher). These codes will then be sorted into potential themes. Finally, the themes will be refined through repeated investigation both of similar and anomalous examples.

5 RANDOMISED CONTROLLED TRIAL

5.1 Participant Entry

5.1.1 Inclusion Criteria

I. Aged ≥ 18 years
II. Receiving or to receive anti-cancer intravenous therapy
III. Duration of anti-cancer intravenous therapy ≥ 12 weeks
IV. Intended duration of continual device placement ≥ 12 weeks with no temporary removal for surgery
V. Clinical team uncertain as to which device is optimal for this indication
VI. Solid or haematological malignancy
VII. Suitable upper extremity vein for all the access devices to which the patient may be randomised
VIII. Able to provide written informed consent

5.1.2 Exclusion Criteria

I. Life or treatment expectancy <3 months
II. Previous venous access device removed due to complication within last 2 weeks.

III. Patient has any evidence of active infection
IV. Requirement for high volume (apheresis) line
V. Need for catheter to be placed in a non upper extremity vein
VI. Patient previously randomised into the CAVA trial

5.2 Patient Randomisation

There are four randomisation options for each eligible patient:

1 Hickman type device versus PICC versus chest wall port
2 PICC versus chest wall port
3 PICC verses Hickman Type device
4 Chest wall port versus Hickman type device (This randomisation option closed to recruitment 30th November 2015)

Clinicians may choose any of the four randomisations depending on the individual patient and the practice at their individual site. Treatment allocations will be obtained by contacting the CRUK CTU Glasgow.

The three-way randomisation will initially be set up with a 2:2:1 (Hickman type device: PICC: chest wall port) ratio in order to over recruit to the arms involved in the non-inferiority comparison which requires more patients. The number of patients assigned to each treatment group in the three-way and two-way randomisations will be monitored at six-monthly intervals and adjustments may be made to the three-way randomisation ratio as appropriate.

The randomisations detailed above will be performed using a minimisation algorithm incorporating a random component.

The stratification factors used in the minimisation will be:

- Centre
- Body mass index: <20, 20-<30, 30-<40, ≥40[12]
- Device history: patients with no prior devices fitted, patients having previously had at least one device fitted more than 3 months prior to the study, patients having had devices fitted within 3 months of the study.
- Type of disease: haematological malignancies, solid tumours
- Planned treatment mode: in-patient, out-patient

Patients will not be able to be randomised to the study until all appropriate regulatory requirements have been completed.

Prior to inserting the access device and when the patient's eligibility has been confirmed, consent forms and registration forms have been completed, the CRUK CTU, Glasgow must be contacted to randomise the patient to the study. Randomisation to the study can be done by either telephone or fax on the following numbers:

Randomisation Telephone Number: 0141 301 7952
Randomisation Fax Number*: 0141 301 7228

Randomisation Service: Monday- Thursday 08.30-17.00, Friday 08.30-16.30. Fax 24 hours.
*(Faxes received outside office hours will be dealt with the next working day)

All patients must be randomised onto the study prior to insertion of the venous access device.

Each patient randomised will be allocated a unique sequential patient ID number for the randomisation arm together with an allocated study arm.

5.3 Withdrawal Criteria

Patients will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. The investigator also has the right to withdraw patients from the study if they develop a medical or psychiatric condition that would contra-indicate continued study participation.

Full details of the reasons for withdrawal should be recorded on the relevant Case Report Form (CRF) and patient's medical record.

If a patient withdraws from treatment and withdraws their consent for follow-up, a Consent Withdrawal Form must be completed and retained at the study site. A Consent Withdrawal Notification Form must also be completed and submitted to the Cancer Research UK Clinical Trials Unit, Glasgow.

By completing the Consent Withdrawal form these patients withdraw consent for the use of any data gathered on or after the date of withdrawal and therefore no subsequent follow up data will be collected. The patient may also choose to withdraw consent for any previously collected data to be used.

6 INTERVENTION ARMS

Subcutaneously tunnelled central catheter (Hickman type device)
Introduced in 1979, these lines commonly known as Hickman lines consist of a thin plastic tube inserted into a central vein in the neck or upper chest region. It is "tunnelled" under the skin for a few centimetres and has a Dacron cuff to improve stability and minimise the risk of infection. Generally, the purchasing costs of these devices are slightly more than PICC. These catheters are usually inserted by nurse specialists, interventional radiologists or anaesthetists in a procedures room away from the ward. Similar to PICC, caring for these catheters involves regular dressing change and weekly line flushing with heparin. The cuff needs a minor surgical procedure to release it allowing the line to be removed when no longer required.

Peripherally inserted central catheters (PICC)
Introduced in 1975, a PICC line is a thin plastic tube inserted into a peripheral vein in the upper arm. It is the cheapest and simplest device to place. These catheters are commonly inserted by nurse specialists sometimes at the bedside but more commonly in a procedures room. Caring for PICCs catheters involve regular dressing change and weekly line flushing with heparin. Removal of the line is straightforward when no longer required.

Implantable Chest Wall Ports (Ports)
Introduced in 1981, a chest wall port is a small, coin-sized device with a silicone membrane buried just under the skin in a subcutaneous pocket. It connects to a thin plastic tube similar to the other two devices. The entire device is completely implanted with no tubes hanging out through the skin. Therefore the chest wall port has to be punctured through the skin and membrane with a needle when used. This is the most expensive device to purchase (up to six times the cost of a PICC). Chest wall ports are most frequently placed by interventional radiologists in an interventional theatre, but anaesthetists, surgeons and more recently nurse specialists are increasingly involved. As chest wall ports are totally implanted there is no dressing requirement and flushing is only needed monthly with heparin. A minor surgical procedure is needed to remove the chest wall port when no longer required.

These three devices are all in current clinical practice in the U.K. There will be no restriction on the manufacturer of any of the devices, the choices being left up to local practice. Ultrasound is increasingly used during the placement of all three devices

7 SAFETY REPORTING

7.1 Adverse Event

7.1.1 Definition of an Adverse Event

An adverse event (AE) is any untoward medical occurrence that a patient experiences whilst participating in the trial. This includes occurrences which are not necessarily caused by or related to the trial intervention.

7.1.2 Adverse Event Reporting

Adverse Events (AEs) must be recorded as they are reported, whether spontaneously volunteered or in response to questioning about well being at trial visits. The questioning about adverse events will cover the current visit as well as the period of time between the previous and the current visit. All adverse events must be documented in the patient's medical records.

All AEs related to Hickman type device, PICC line or chest wall port complications, must be recorded in the patient's case notes and the Study Case Report Forms (CRFs). All AEs must be followed until resolution, or for at least 30 days after the trial intervention, whichever comes first or until the adverse event has resolved to baseline or until the adverse event is considered to be irreversible.

An exacerbation of a pre-existing condition is an AE.

7.2 Serious Adverse Events

Serious Adverse Events (SAEs) do not require reporting for the CAVA trial. Details of any hospital admissions and medically significant events must be recorded in the patient notes and the appropriate sections of trial CRFs.

7.3 Reporting to the Medicines and Healthcare Products Regulatory Agency (MHRA)

The CAVA trial is a Non-CTIMP trial and therefore does not fall under the requirements of the Medicines for Human Use (Clinical Trials) Regulations. However the treating oncologist is responsible for reporting any serious and unexpected reactions to chemotherapy for trial patients recruited from their site, using the standard yellow card system. PIs are required to report any unexpected events that are related to the administration device, to the MHRA. Such reports are as reported using the MHRA's on-line reporting procedure for devices. Please refer to the MHRA's website for guidance on on-line and yellow card reporting. If a yellow card or on-line device report of an unexpected reaction or event is made, please inform Pharmacovigilance at the CTU. By submitting an email with details of the report to:

Email: mvls-ctu-pv@glasgow.ac.uk

If any advice about the requirements for reporting events is needed, please contact the Pharmacovigilance at the, CR-UK CTU, Glasgow

Fax no: +44 (0) 141 301 7213

Tel no: +44 (0) 141 301 7209/7211/7212

7.4 Procedure for Identifying Serious and Unexpected Events

There is a requirement that, any serious and unexpected events that relate to using either a Hickman type device, a PICC or chest wall ports are reported to the Main Research Ethics Committee.

Expected events include pneumothorax, arterial puncture, air embolus, haemorrhage, kinking of catheter, and separation of catheter from device, suspected or proven catheter related infection and occlusion of, or inability to, aspirate from the device.

For any reports of unexpected events related to either a Hickman type device, PICC or chest wall port device, the Chief Investigator (CI) will be contacted to confirm the event requires expedited reporting to the Main REC.

7.5 Expedited Reporting

Reports of related and unexpected events will be submitted within 15 days of the CI becoming aware of the event, using the 'report of serious adverse event form' for non-CTIMPs published by the National Research Ethics Service (NRES).

Related events will be any event that is considered possibly, probably or definitely related to the chest wall port, PICC or Hickman type device. See table below for all definitions of the relationship to protocol treatment.

Relationship	Description
Unrelated	There is no evidence of any causal relationship
Possible	There is some evidence to suggest a causal relationship However the influence of other factors may have been contributed to the event (e.g. the patient's clinical condition, other concomitant treatments)
Probable	There is evidence to suggest a causal relationship and the influence of other factors in unlikely.
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

7.6 Annual Progress Report

An annual progress report including information on any unexpected reactions to anti-cancer treatments or unexpected events which are related to the devices, will be produced by the project manager and submitted to the REC.

8 ASSESSMENT, FOLLOW-UP & DATA COLLECTION

The routine standard procedures at each site will be followed for the insertion and care management of all three access devices. All sites subscribe to the EPIC[13] guidelines for the use of access devices and any new sites that enter the study will be asked to adhere to these guidelines.

Patients' pre-treatment evaluation, treatment and assessments during treatment, will be unaffected by participation in this study and will be the standard management for these patients.

8.1 Data Collection

All patients will be registered at the CRUK CTU, Beatson West of Scotland Cancer Centre, Glasgow.

The following data will be recorded:

(a) Demographic data (all patients) including patient's initials, age, sex, date of birth, ethnic origin, the referring hospital and clinician as well as any significant medical history e.g. history of DVT or uncorrected coagulopathy pre procedure or previous problems with central venous access

(b) Tumour details: including anatomical location of the primary, tumour stage, histological type and grade of differentiation, and the sites of any metastases should also be recorded;

(c) Treatment details: including the chemotherapy regimen or other systemic therapy administered, the number of courses and the dates administered

(d) Device details: manufacturer, model no, catheter lumen diameter and number, type of coating, if the device has capability for high pressure injection, whether the catheter is open or closed ended (Groshong Valve)

(e) Procedure details: operator status, environment, anaesthesia, use of imaging, access vein, line tip position, number of needle passes, anchorage device used and type of dressing applied

(f) Complication data: infection and mechanical failure (see Appendix I and II for definitions). Procedural complications and technical failure

(g) Re-interventions: device replacement, thrombolysis, line stripping and device manipulations

(h) Quality of life: EQ-5D, EORTC QLQ-C30 and the device-specific questionnaire will be collected at baseline and monthly thereafter until line removal (on average dwell time is 8 months) (please note device specific questionnaire is not required at baseline)

In addition the following data on healthcare resource use in each of the three arms will be collected alongside the trial, these include:

- Details of the placement procedure including the type and number of clinical staff involved and the duration of the procedure
- Number of clinic, outpatient and emergency department visits
- Total length of stay in hospital
- Details of treatment associated with complications
- Details of the removal procedure including the type and number of clinical staff involved and the duration of the procedure

These data will be collected prospectively during monthly patient follow-up visits, using a case report form (CRF)

CRFs will be supplied by the CRUK CTU, Glasgow. These forms should be completed in accordance with the CRF completion guidelines issued for the study. Queries should be handled as described in the study data-flow section of the CRF completion guidelines. Specific questions about data management should be addressed to the Clinical Trial Co-ordinator (CTC) for the study.

All CRFs must be returned to the CRUK CTU, Glasgow for data entry and ultimately, statistical analysis.

CRFs from the study will be stored in line with current regulatory requirements, that is, until 5 years after completion of the study or as long after this as is agreed between the sponsor and investigators. Other essential documents, including source data, consent forms, and regulatory

documents, will be archived by or for the Investigator in an appropriate archive in line with current regulatory requirements and made available for monitoring, audit and regulatory inspection.

8.2 Follow-Up and End of Trial

Patients will be followed up for up to 12 months post trial entry or until the device is removed, whichever comes first. The end of trial will be defined as last patient last visit

9 STUDY MANAGEMENT

9.1 Trial Management Group (TMG)

A TMG will oversee the running of the trial. Members of the TMG will include the Chief Investigator, Co-Investigators, Project Manager, Clinical Trial Co-ordinator, Trial Statistician, IT Staff, Quality Assurance Manager and Clinical Trial Monitor.

The TMG will meet every 2 months or as required, meetings may be by teleconference.

9.2 Trial Steering Committee (TSC)

A TSC will provide overall supervision for the trial. The TSC will be responsible for monitoring the progress of the trial towards its interim and overall objectives, focusing on adherence to the protocol, Good Clinical Practice (GCP), and patient safety. The TSC will include independent members who are not directly involved in other aspects of the trial.

9.3 Data Monitoring and Ethics Committee (DMEC)

A DMEC will be established for the trial. The DMEC will assess at intervals (approximately annually) the progress of the trial, the safety data, the critical efficacy endpoints, and will make any recommendations to the Sponsor and TMG whether to continue, modify or stop the trial.

10 STATISTICS AND DATA ANALYSIS

10.1 Sample Size

The sample size is based on the three hypotheses of interest:

Hypothesis 1: PICCs are non-inferior to Hickman type devices in terms of complication rate
Based on the assumption that the Hickman type device complication rate is 55%, PICCs will be considered non-inferior if their complication rate is no more than 10% higher, i.e. 65%. To rule out this difference with 90% power, 1-sided, significance level 2.5% requires 778 patients in total using a 1:1 randomisation.

Hypothesis 2: Chest wall ports have a lower complication rate and are more cost-effective than Hickman type devices
The minimum requirement here is to demonstrate that chest wall ports have a lower complication rate than Hickman type devices. Based on the assumption that the Hickman complication rate is 55%, we aim to detect at least a 15% reduction with chest wall ports. To detect this reduction with 95% power, 2-sided, significance level 5% requires 550 patients in total using a 1:1 randomisation.

Hypothesis 3: Chest wall ports have a lower complication rate and are more cost-effective than PICCs

The minimum requirement here is to demonstrate that chest wall ports have a lower complication rate than PICCs. Based on the assumption that the PICC complication rate is 55%, we aim to detect at least a 15% reduction with chest wall ports. To detect this reduction with 80% power, 2-sided, significance level 5% requires 341 patients in total using a 1:1 randomisation.

The overall size required for the study is complicated by the proportion of patients who enter via the three-way randomisation but we estimate 1300 patients in total will be required.

The Glasgow feasibility study indicated that 241 patients/arm would be sufficient to show a difference between the Hickman and Port arms in terms of net monetary benefit based on cost and QALYs.

10.2 Analysis Plan

The analysis will be performed separately for the three pairwise comparisons of interest, with the same endpoints and the same statistical techniques used throughout.

A "per-protocol" sensitivity analysis will be undertaken for the non-inferiority comparison excluding patients who do not get the device allocated by the randomisation (it is thought the percentage of such patients will be extremely low, certainly <1%). All other analyses will based on the "intention-to-treat" population (however note that the complication rate is only defined as the period the device is in place, so this analysis will almost directly correspond to a "per-protocol" analysis).

Primary Endpoint

The primary outcome for the randomised trial is complication rate, a composite of infection (suspected or confirmed) and/or mechanical failure (for definitions please see Appendices I and II). This will be analysed using logistic regression including terms for treatment group and randomisation stratification factors.

Secondary Endpoints

An analysis will also be conducted based on complication event rate data[13]. This analysis will estimate the effect of the access devices on the individual component complications (infections and mechanical failure) and will allow an assessment of the similarity of these effects via a likelihood ratio test. The incidence of venous thrombosis will be compared using logistic regression and also as an event rate. The frequency of the various complications will be assessed. The total duration of treatment interruptions will be summarised and compared using a Mann Whitney U-test.

A further descriptive analysis will present the study results in terms of complications (both overall and the individual components) per catheter days.

Scores for the five dimensions of the EQ-5D (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and the visual analogue score for health will be summarised and the EQ-5D curves will be compared between treatment groups using an area under curve (AUC) approach standardised for the period on study and using the baseline value as a covariate.

Scores for the 5 functional scales (physical, role, emotional, cognitive, social) and 9 symptom scales (fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, financial difficulties) of the EORTC QLQ-C30 will be calculated according to standard EORTC conventions, as will global health status score. These scores will be summarised and analysed as EQ-5D.

The results from the device-specific questionnaire will be summarised only.

Economic Evaluation

A probabilistic decision model will be constructed to simulate the clinical pathways associated with the two interventions, according to the guidance set out by NICE. The basic model structure will consist of three arms, replicating the clinical consequences of patients implanted with the individual devices. The main data source relating to the key parameters of the model will be provided by the feasibility study.

In the final analysis of the data, the mean costs and quality adjusted life years associated with the devices will be calculated for the modelling periods. Cost-utility analysis will also be carried out and incremental cost per quality adjusted life years gained will be calculated. Particular consideration will be given to the potential for cost effectiveness to vary by patient risk groups and treatment duration where suggested by the literature.

Probabilistic sensitivity analysis will be used to characterise uncertainty in parameters of the model, following the recent recommendations by NICE, and presented using cost-effectiveness acceptability curves. Standard univariate sensitivity analysis will be carried out to explore areas of structural uncertainty in the analysis. Finally a value of information analysis on the expected value of perfect information will also be carried out to quantify the potential value of further research based on the difference between the expected net benefit with perfect information and the existing information.

10.3 Interim Analysis

An independent data monitoring committee will be set-up to review the study data approximately annually.

For the non-inferiority comparison of Hickman type devices and PICC lines, conditional power methods[14] will be used to aid the committee in reaching decisions about recommending study continuation; this recommendation will also take into account any impact on the health economic assessment.

For the superiority comparisons of Hickman type devices versus chest wall ports and PICCs versus chest wall ports, interim analyses would not be expected to lead to early closure of either randomisation on safety or efficacy grounds. These are interventions in routine use in the NHS and in addition, the aim would be to maximise the data ultimately available for health economic analysis.

10.4 Internal Pilot Period

The first 18 months of the recruitment period compromised the internal pilot period. At this point the independent Trials Steering Committee (TSC) formally assessed the study progress against the following criteria:-

- At least 35% of the target recruitment met (individually for each of the three two-way comparisons)

If this milestone is not met for a particular comparison the TSC would have considered stopping recruitment to that comparison, this was not the case at the end of the pilot period.

Note that prior to this assessment health economic data from our Glasgow feasibility study will be available and this will have been used to refine the target sample size estimates for the chest wall port v PICC and chest wall port v Hickman type device comparison.

11 REGULATORY ISSUES

11.1 Ethics Approval

All patients will give written informed consent on entering the study. The protocol will require a favourable opinion by a coordinating Research Ethics Committee, and approval by NHS Greater Glasgow and Clyde Research and Development Department.

The study will be carried out in accordance with the Research Governance Framework and the World Medical Association Declaration of Helsinki (1964) and its revisions (Tokyo 1978, Venice 1983, Hong Kong 1989, South Africa 1996, Edinburgh 2000 and Seoul 2008).

11.2 Consent

Consent to enter the study must be sought from each participant only after full explanation has been given, an information sheet offered and time allowed for consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the trial the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the best interests of the participant, but the reasons for doing so must be recorded. In these cases the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

11.3 Confidentiality

Participants' identification data will be required for the registration process. The CRUK CTU will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

11.4 Indemnity

NHS employed researchers will be covered for negligent harm through CNORIS (Clinical Negligence and Other Risks Indemnity Scheme)

11.5 Sponsor

NHS Greater Glasgow and Clyde will act as the main sponsor for this study. Delegated responsibilities will be assigned to the CR-UK CTU and NHS Trusts/Boards taking part in this study. Details of responsibilities will be outlined in the clinical trial agreement that should be signed prior to site initiation.

11.6 Funding

This study is funded by the HIHR Health Technology Assessment programme (project reference 11/67/01).

11.7 Audits and Inspections

The study may be subject to inspection and audit by NHS Greater Glasgow and Clyde under their remit as Sponsor, the CRUK CTU and other regulatory bodies to ensure adherence to GCP.

12 QUALITY ASSURANCE

Trial investigators and site staff must ensure that the trial is conducted in compliance with the protocol, Research Governance Framework 2006 (as amended) and the principles of Good Clinical Practice and the applicable regulatory requirements.

Telephone monitoring will be performed by the Sponsor. This will be in the form of telephone monitoring calls by the Clinical Trial Monitor at predetermined time points during the trial. The Sponsor reserves the right to conduct a for-cause monitoring visit or an audit in the event that non-compliance is suspected or confirmed. Central monitoring of trial data will be performed by the Study Statistician and the CTC.

The CTU will control data consistency and data quality by entering trial data onto the CTU trial database. Computerised and manual consistency checks will be performed and queries issued in cases of inconsistency or missing information. A full audit trail of any changes to the database will be maintained.

13 PUBLICATION POLICY

It is anticipated that manuscripts will be prepared from the results of this study and that these will be submitted for publication, with authorship according to the requirements for manuscripts in the Vancouver Statements. No data will be published without prior approval of the Trial Management Group,

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15 APPENDICES

APPENDIX I: DEFINITION OF INFECTIVE EPISODES

Exit site infection

Local inflammation (>1 cm redness and/or purulent exudate) at exit site, tunnel or pocket.

(i) Requires antibiotic therapy, or
(ii) Delays line use
(at physicians's discretion)

Laboratory-confirmed all-cause blood stream infection (BSI)

There are two definitions to be used for LBSI. Either qualifies

For either definition the device must have been in place for ≥48 hours to qualify

Definition 1
Patient has a recognised pathogen cultured from ≥1 blood cultures and the organism isolated from blood is not related to an infection at another site

Isolation of same pathogen within 14 days represents the same episode.

Examples of pathogens are: Staphylococcus aureus, E. coli, Klebsiella spp., Pseudomonas spp, Enterococci

Definition 2
Patient has at least one of the following signs and symptoms: fever (>38°C), chills* or hypotension* (*with no other recognized cause)
and
a common commensal is cultured from ≥2 blood cultures drawn on separate occasions within 24h.

Examples of commensals are: Diphtheroids, Bacillus spp. Propionibacterium spp., Aerococcus spp., and Micrococcus spp, (coagulase negative staphylococci, viridans group streptococci)

Possible Catheter Related Blood Stream Infection (CRBSI) (negative blood cultures)

1. Fever, chills, rigors, hypotension associated with line use.

2. Systemic symptoms of unknown cause but thought to be related to presence of line

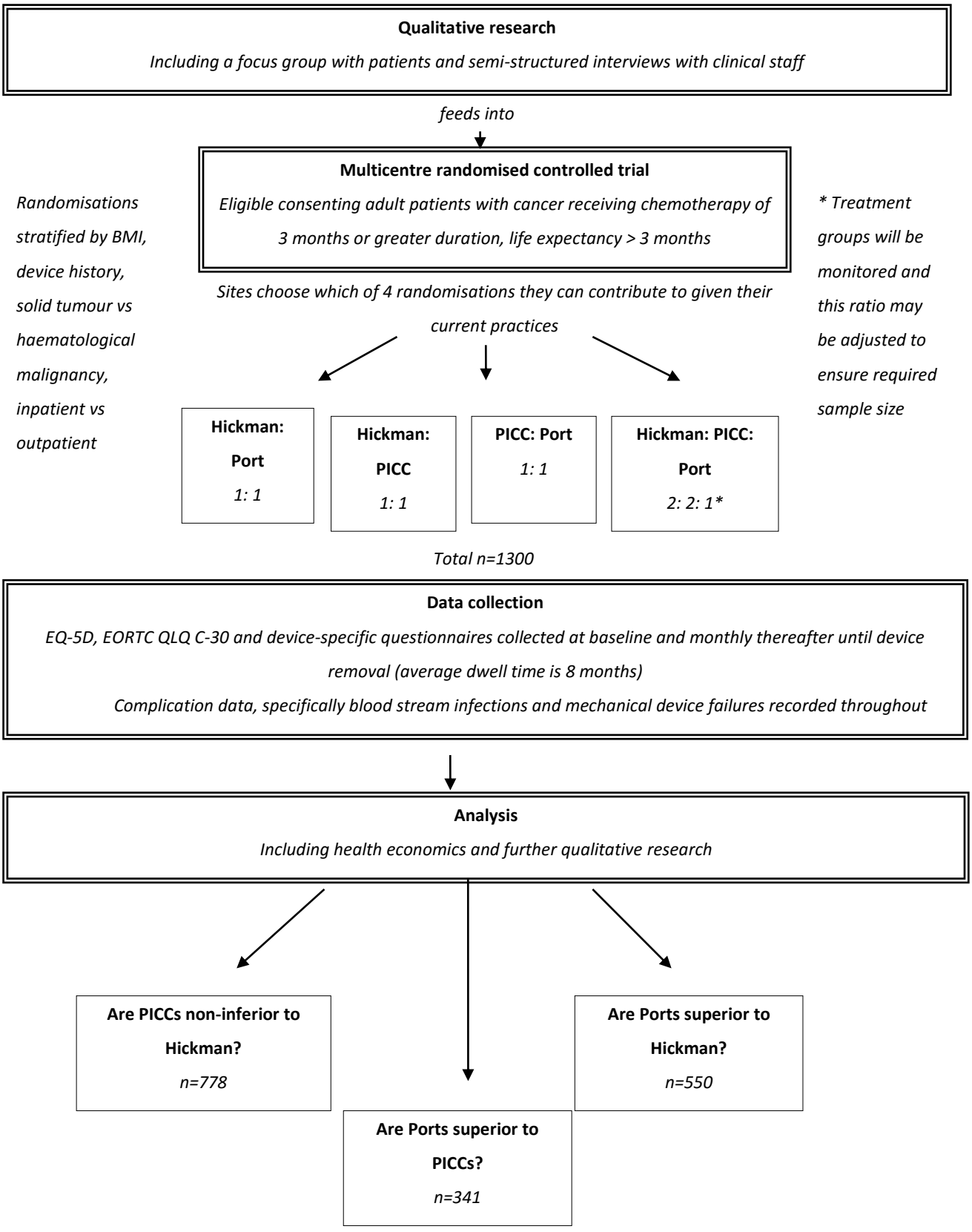
(i) Requires antibiotic therapy, or
(ii) Delays line use.
(at physician's discretion)

APPENDIX 2: DEFINITION OF MECHANICAL FAILURE

Mechanical failure includes ANY of the following:

- Line occluded (either for aspiration or infusion)
- Line fracture
- Line separation from chest wall port
- Exposure of line cuff
- Exposure of chest wall port or breakdown of wound
- Chest wall port flip
- Line fallen out
- Line migration requiring intervention

APPENDIX III – Study Flow Chart



Appendix IV – Gantt Chart

Year		Year 1				Year 2				Year 3				Year 4				Year 5				Year 6				7
Month	Pre-trial	1-3	4-6	7-9	10-12	13-15	16-18	19-21	22-24	25-27	28-30	31-33	34-36	37-39	40-42	43-45	46-48	49-51	52-54	55-57	58-60	61-63	64-66	67-69	70-72	73-75
Study set-up: Including Staff recruitment, protocol development, ethics and sponsor approval, database development																										
Pre-Trial Qualitative Research																										
Recruitment																										
Follow-up period																										
Interim analysis																										
Data cleaning and analysis																										
Economic evaluation																										
End of trial qualitative study on acceptability																										
Final Report																										
TSC Meeting																										
DMC Meeting																										

APPENDIX V – QoL Measurements

Venous access device quality of life questionnaire

We are trying to assess how much your Hickman type device, PICC or chest wall port interferes with your life. Please take a couple of minutes to answer these questions. Please indicate your answer by circling the number that best applies to you. Thank you for your assistance.

Subject Trial Number: _____ Date of completion_____

Type of device: _____

Does the access device reduce your ability to carry out the following day to day activities?

	Not At all	A Little	Quite a bit	Very much
Driving a car?	**1**	**2**	**3**	**4**
Getting in or out of a car?	**1**	**2**	**3**	**4**
Using public transport?	**1**	**2**	**3**	**4**
Going out shopping?	**1**	**2**	**3**	**4**

Does the access device affect you ability to carry out normal day to day activities such as:

Eating	**1**	**2**	**3**	**4**
Hygiene - washing, bathing, showering, hair brushing, drying yourself etc.	**1**	**2**	**3**	**4**
Sleeping	**1**	**2**	**3**	**4**
Mobility or movement	**1**	**2**	**3**	**4**
Normal work activity	**1**	**2**	**3**	**4**
Exercise - swimming etc.	**1**	**2**	**3**	**4**
Hobbies - gardening etc.	**1**	**2**	**3**	**4**
Does the access device make you self conscious?	**1**	**2**	**3**	**4**
Has it affected your socialising?	**1**	**2**	**3**	**4**
Do you feel at risk of infecting the access device?	**1**	**2**	**3**	**4**
Do you feel at risk of damaging the access device?	**1**	**2**	**3**	**4**
To what extent has the presence of the access device had a negative impact on your quality of life ?	**1**	**2**	**3**	**4**

EQ5D quality of life questionnaire

Please place a tick in ONE box for each of the five groups below which best describe your own health state today.

Mobility

I have no problems in walking about ☐

I have some problems in walking about ☐

I am confined to bed ☐

Self-care

I have no problems with self care ☐

I have some problems washing or dressing myself ☐

I am unable to wash or dress myself ☐

Usual Activities (e.g. work, study, housework, family or leisure activities)

I have no problems with performing my usual activities ☐

I have some problems with performing my usual activities ☐

I am unable to perform my usual activities ☐

Pain/Discomfort

I have no pain or discomfort ☐

I have moderate pain or discomfort ☐

I have extreme pain or discomfort ☐

Anxiety/Depression

I am not anxious or depressed ☐

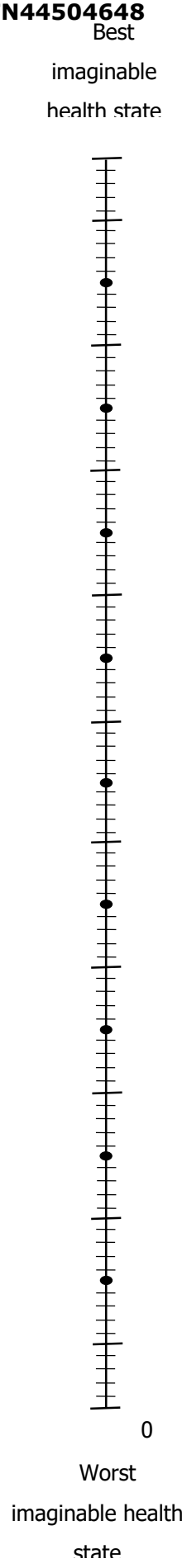
I am moderately anxious or depressed ☐

I am extremely anxious or depressed ☐

Any other comments:

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0

Your own health state today



APPENDIX VI – Qualitative Research Pre Trial

Pre-trial Focus Group with Patients

Resources:
PIS for CAVA; photos of the three devices; actual devices

Introduction:

We have received funding to study three different venous access devices for the delivery of long term chemotherapy.

This will be a large multi-centre study comparing subcutaneously tunnelled central catheters (Hickman type device), a peripherally inserted central catheters (PICC) and totally implanted devices (chest wall port). It's expected to start in the Autumn of 2013. In preparation for this, we'd like to ask you some questions before we start recruitment and get your feedback on our recruitment materials.

There are no right or wrong answers and everyone is entitled to voice their opinion. The discussion will last about an hour. We will be tape recording the conversation. After today's session the tape will be transcribed anonymously and kept in a locked cabinet at the University of Glasgow. Your name will not appear in any of the transcripts or findings.

1) Attitudes toward the three devices (the researcher will describe the three devices – with photos and actual devices and then ask questions)

There are three different long term venous access devices available to patients receiving chemotherapy; a subcutaneously tunnelled central catheter (Hickman type device), a peripherally inserted central catheter (PICC) and a totally implanted device (chest wall port).

They are all generally placed using local anaesthesia although sometimes, if you wish, additional sedation can be given. Ultrasound is commonly used to identify a suitable vein and the procedure carried out in either a small procedures room or a theatre.

<u>Hickman Type Device</u>
A Hickman type device is a thin, flexible tube which is inserted into the jugular vein in your neck. One end of the line lies in the large vein running to your heart. The other end of the tube is tunnelled, or buried under your skin and comes out somewhere on your chest through a small (3-4mm) incision. This end of the line will be held in place by a special "cuff" which allows tissue to grow around it fixing the line in place and reducing the chance of infection and dislodgement. The end of a Hickman device hangs out of the small skin incision at all times whether it is being used or not. When your treatment needs to be given the nurse simply connects the infusion pump onto the end of the Hickman type device.

<u>Chest wall port</u>
A chest wall port is a small chamber or reservoir that sits under your skin in a small pocket. An incision (2.5cm) is made on your chest in order to bury the port which is then stitched in place. One end of the line lies in the large vein running to your heart. The chest wall port is connected to the line which is placed in exactly the same manner as a Hickman line. The main difference is that there is nothing hanging out as everything is buried under the skin. You can feel the chest wall port, but unless you are very thin you cannot usually see it. When you need treatment, your nurse puts a needle through the skin into the chest wall port and connects up the infusion pump. The needle is removed once the infusion is completed.

<u>PICC</u>

A PICC line is a thin flexible tube which is inserted into one of the veins in your arm. One end of the line lies in the large vein running to your heart. The other end hangs out of the small skin incision at all times whether it is being used or not. When your treatment needs to be given the nurse simply connects the infusion pump onto the end of the PICC line.

A photo of a PICC is shown below

Question 1: How do you feel about the three long-term venous access devices?

Prompt: Do you have an opinion as to which device you might prefer?
Prompt: Do you or a relative or friend have experience of any of them?

2) Views on trial participation and acceptance of randomisation (the researcher will explain the study and then ask questions)

As I said at the beginning, we've received funding to study these three different venous access devices.

The purpose of this study is to assess the overall health, cost and quality of life for patients who receive Hickman type devices versus those who receive chest wall ports versus those who receive PICCs.

The best way of determining which of the three treatment options is more effective is by carrying out a randomised controlled study.

To do this we put people randomly into groups and give each group a different treatment (referred to as a treatment 'arm'). A computer allocates which treatment each patient receives randomly. Neither they nor their doctor can choose the treatment received. The results are compared to see if one treatment is better than the other.

Question 2: Does the study make sense to you?

Prompt: How would you feel about the possibility of receiving any one of three devices?
Prompt: Do you have an opinion as to which device you might prefer?
Prompt: Were there any aspects of the study that you are uncertain about?

Question 3: Are you clear how it would be decided which device you'd get if you were taking part?
Prompt: Why was it decided like this?
Prompt: What is this study trying to find out?
Prompt: Do you think you'd be more likely to get one particular device rather than another? Why?
Prompt: How do you feel about this way of deciding which device you should have? Is there a better way?

Question 4: Do you think that patients should be asked to take part in medical research?
Prompt: Would you be prepared to take part in a study comparing devices?
Prompt: Would you be prepared to take part in a study where treatment was chosen at random?
Prompt: In a random choice study, if the treatment you were receiving did not suit you for any reason you could always leave the study. Your doctor would then give you whatever other treatment might be appropriate for you.
Did you know that?
Prompt: Would that encourage you to take part?

2) Study documentation (researcher will explain protocol and distribute PIS to feedback on – focus on complex nature of CAVA).

If a patient decides to take part they will be allocated a Hickman type device or PICC or chest wall port at random and asked to complete a short questionnaire. They would then be asked to complete this questionnaire every month during the time they have an access device in place.

Although it would be ideal to place all patients into a single randomisation arm (A) which compares all three devices this may not be appropriate for everyone. For example a patient may not be suitable for one of the devices e.g. if they had no open arm veins then a PICC line is not possible. To allow for this but still include as many patients as possible we have three additional trial arms available (groups B, C & D) and these will only compare one device with another excluding the third option.

There are four trial arms:

A. PICC or Hickman or Port – i.e. a patient is suitable for any of the three devices.

B. PICC or Hickman – i.e. a patient is **NOT** suitable for a Port

C. PICC or Port – i.e. a patient is **NOT** suitable for a Hickman

D. Hickman or Port – i.e. a patient is **NOT** suitable for a PICC.

We are aiming to include approximately 2000 patients in this study. They will be mainly coming from 6 large cancer units in the U.K. It is anticipated the study will take 5 years to recruit and follow up all the patients.

Question 5: Are there any questions about this?

Question 6: Could I ask you to look at the information sheet and feedback on it

Question 7: Is there anything else you'd like to add?

Thank you very much for your time.

Pre-trial Interview Clinical Staff
(Oncologist/Nurse/Radiologist/Anaesthetist/Surgeon)

Introduction:

We have received funding from the Health Technology Assessment arm of the National Institute of Health Research in the UK to run a phase III trial of three different long term venous access devices available to patients receiving chemotherapy. This will be a large multi-centre study comparing subcutaneously tunnelled central catheters (Hickman type device), a peripherally inserted central catheter (PICC) and a totally implanted device (chest wall port) and your hospital is taking part.

In preparation for this, we'd like to ask you some questions before we start recruitment and get your feedback on our recruitment materials. In order to do this, we would like you to take part in an interview. This interview will take no more than 30 minutes of your time. We will audio-record the interview for our records, but transcripts will be anonymised and your name will not appear in any of the findings.

Question 1: Are you familiar with Hickman type devices, PICCs and chest wall ports?

Question 2: Clinical trials are undertaken when there is uncertainty about which treatment is the best for patients - do you feel that there is uncertainty about these three options (equipoise)?

Prompt: Which of these 3 options do you use in your practice? Which most often? Why?
Prompt: Are there particular situations when you would chose to use one of them in preference to the others? Why?
Prompt: Would you be willing to use the others?
Prompt: Do you have a preference for one of the options? Why?
Prompt: Do you feel confident that the most effective device is unknown?
Prompt: That all patients who meet the criteria are eligible?
Prompt: That a trial is needed?
Prompt: That randomisation is a plausible way of reaching a decision?

Question 3: Would you be willing to recruit patients to a randomised study of these 3 options?

Prompt: How do you feeling about discussing the uncertainty around these three devices with patients?
Prompt: How do you feel about discussing the process of randomisation with patients (e.g. the four options)?

Question 4: We plan to [explain process of recruitment at Beatson]. Would that work at your centre?

Prompt: Are there any factors which you think might hinder participation in the trial?
Prompt: Are there any factors which you think might facilitate participation in the trial?

Question 5: Are there any potential negative or positive impacts of the trial on your professional activities?

Question 5: Finally, could I ask you to look at the information sheet and feedback on it.

Question 6: Is there anything else you'd like to add?

Thank you very much for your time

APPENDIX VII – Qualitative Research Post Trial

Post-trial Focus Group with Patients

Resources: photos for the three devices; actual devices

Introduction:
As you are aware we have been running a trial of venous access devices for the delivery of long term chemotherapy therapy funded by the Health Technology Assessment arm of the National Institute of Health Research in the UK.

This large multi-centre study is comparing Hickman Type devices, PICCs and chest wall ports. As you have taken part in this trial, we'd like to now ask you some questions about your experience of your device. We would also like to discuss your experiences of being a trial participant.

There are no right or wrong answers. The discussion will take around an hour. It will be audio-recorded for our records. All information will be anonymous and your name will not appear on any transcripts.

Question 1: What factors did you take into account when considering and deciding to participate in this trial?
Prompt: Was there enough information?
Prompt: Did you have any doubts?
Prompt: What discussion did you have with you clinician/family etc.?

Question 2: What knowledge or experience of venous access did you have before you had your device inserted? [Researcher will have devices/photos available as prompts]
Prompt: Did you have a preference for any particular device prior to being randomised in the trial?
Prompt: Do you think you received enough information prior to device insertion?

Question 3: What were the positive / negative aspects of your device?

Question 4: How did your device affect your everyday life?
Prompt: Did you experience any problems with your device?
Prompt: What problems?
Prompt: Did you discuss these with your clinician? How did they handle these problems?
Prompt: Would you have preferred a different device, why?

Question 5: What aspects of care related to (a) insertion and (b) aftercare could be improved upon?

Question 6: We would like to know about your experience of the trial itself.
Prompt: How did you feel about being randomised?
Prompt: What were your impressions of the QOL questionnaire?
Prompt: Timing of questionnaire/did the content of the items relate well to you?/find them easy to answer
Prompt: Would you consider taking part in trials if asked again?

Question 7: Is there anything else you would like to tell us about your device?

Post-trial Interview with Clinical Staff
(Oncologist/Nurse/Radiologist/Anaesthetist/Surgeon)

Introduction:
We've completed the phase III trial of venous access devices for the delivery of long term chemotherapy. Thank you very much for taking part.

We'd like to ask you some questions about your participation in this trial.

This interview will take no more than 30 minutes of your time. We will audio-record the call for our records, transcripts will be anonymised and your name will not appear in any of the findings.

Question 1: Were you familiar with Hickman type devices, PICCs and chest wall ports?

Question 2: Clinical trials are undertaken when there is uncertainty about which treatment is the best for patients - Did you feel that there was uncertainty about these three options (equipoise)?

Prompt: Which of these 3 options do you use in your practice? Which most often? Why?
Prompt: Are there particular situations when you would chose to use one of them in preference to the others? Why?
Prompt: Would you be willing to use the others?
Prompt: Do you have a preference for one of the options? Why?
Prompt: Did you feel confident that the most effective device is unknown?
Prompt: That all patients who met the criteria were eligible?
Prompt: That a trial was needed?
Prompt: That randomisation was a plausible way of reaching a decision?

Question 3: What factors, if any, hindered participation in the trial?

Question 4: What factors, if any, facilitated participation in the trial?

Question 5: How did you feeling about discussing the uncertainty around these three devices with patients?

Question 5: Were there any negative or positive impacts of the trial on your professional activities?

Question 6: Is there anything else you'd like to add?

Thank you very much for your time