**Comparing traditional *P*lacement *W*ith electroc*A*rdiography for central *V*ascular access d*E*vices trial (P-WAVE Trial)**

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1. **SYNOPSIS**

**BACKGROUND:**

The insertion and use of Central Venous Access Devices (CVADs) has progressively become the mainstay for patients requiring extended intravenous therapy rather than the regular insertion of peripheral intravenous catheters (PIVCs) which are limited by factors such as duration of dwell, limitations on medications that can be infused, as well as high failure rates[1-3](#_ENREF_1). CVADs are hollow thin catheters that are inserted in to the major veins of the upper arm, chest or neck. These CVADs follow the path of the major veins and terminate above the heart in the superior vena cava (SVC)[4](#_ENREF_4),[5](#_ENREF_5)The incorrect placement of CVADs can have serious adverse effects and have contributed to patient fatality. Recent coronial findings of patient deaths from incorrect CVAD placement has prompted a need to innovate more efficient, safer and simple CVAD placement procedures[5-7](#_ENREF_5). There is a great need to also reduce repositioning the catheter post insertion as dressing disruption can lead to increased hospital acquired infection and delay in vital treatment[8](#_ENREF_8). The correct CVAD insertion depth is typically guided by anthropometric measurement[9](#_ENREF_9),[10](#_ENREF_10) and international standard practice for the correct confirmation of the CVAD tip for bedside placement is the chest x-ray. Although chest x-ray confirmation is a widely accepted procedure, it is subject to limitations; including variation in clinician experience with x-ray film interpretation to confirm catheter placement and the time delay (sometimes hours) between CVAD insertion and when the chest x-ray is performed. A simpler alternative procedure with CVAD insertion is the use of intra-cavitary electrocardiographic (ECG) based insertion that has high success rates[11](#_ENREF_11). ECG based insertion is safe, radiation-free and allows precise, real-time placement verification of the catheter allowing for immediate device use and treatment as well as reducing the need for post procedural repositioning[9](#_ENREF_9).

Recently, the Central Venous Access Service (CVAS) at Liverpool Hospital has been using the ECG-guided insertion technique for the majority of CVAD insertions, in conjunction with chest x-ray to confirm correct placement of CVADs with great success and precision (greater than 95% success rate). The ECG method is accepted practice across the world and locally has been endorsed as a method for catheter tip verification by professional safety bodies such as the New South Wales Clinical Excellence Commission.

**OBJECTIVES:**

The main objectives of this randomised control trial (RCT) are to assess and compare CVAD tip location between two insertion methods; 1) anthropometric landmark placement (chest X-ray confirmation) and 2) ECG guided placement. The investigators will also compare any cost difference between the two insertion methods as well as differences in procedural time and malposition rates. This study will examine the feasibility of replacing current CVAD placement with ECG-guided placement to reduce the requirement for chest X-ray.

**STUDY PLAN:**

This is a single centre, randomised control trial comparing standard anthropometric practice for CVAD placement where distal tip of the CVAD is confirmed by chest X-ray post insertion, against the ECG-guided CVAD placement method where confirmation of correct placement is confirmed by ECG during the procedure. Both groups will have CVAD tip confirmation with chest X-ray at the end of the procedure, as is current standard practice within Liverpool Hospital. Adult patients at Liverpool Hospital referred to the Central Venous Access Service for catheter placement will be screened for eligibility.

1. **RATIONALE / BACKGROUND:**

In Australia, it is estimated that over 2 million CVADs are inserted in hospitalised patients every year[12](#_ENREF_12). Traditionally, final anatomical CVAD position has been confirmed either in the radiological setting using fluoroscopic guidance or for bedside insertion, by anthropometric measurement and post procedure chest X-ray[13-15](#_ENREF_13). Confirmation of correct CVAD placement is required before commencement of therapy to minimise catheter related complications[10](#_ENREF_10).

One of the major risks with CVAD tip malposition is venous thrombosis, in particular if the catheter tip has terminated in the middle third to upper third of the superior vena cava (SVC), in the brachiocephalic vein, in the internal jugular vein (IJV) or in the subclavian vein[8](#_ENREF_8),[9](#_ENREF_9),[16](#_ENREF_16). Malpositioned CVADs can also lead to arrhythmias, heart wall erosion and tricuspid valve dysfunction[9](#_ENREF_9). Radiological studies have shown that PICCs are associated with a higher risk of malposition than standard centrally inserted central catheters (CICCs) where the catheter tip can move up to 3cm with inspiration and up to 5cm with movement of the arm chosen for insertion[6](#_ENREF_6) which further exemplifies the importance of correct positioning.

The chest X-ray is the current international standard for bedside confirmation of correct CVAD placement. Chest X-rays however, have some limitations in clinical practice for CVAD insertion. These include time delay from insertion to CVAD use, which delays treatment and increases hospitalisation, as well as exposure to radiation[9](#_ENREF_9). The interpretation of the chest x-ray can also be subjective, and accuracy is determined by the level of training and experience of the clinician interpreting the film[9](#_ENREF_9),[15](#_ENREF_15).

Typically, if incorrect placement of the catheter tip is identified by chest x-ray, the CVAD is required to be repositioned or reinserted. This leads to increased costs, increased radiation exposure due to repeated X-rays, time delays, missed medication doses and the potential for further complications, including catheter related bloodstream infection due to the integrity of the dressing being interrupted[10](#_ENREF_10),[17](#_ENREF_17),[18](#_ENREF_18).

ECG guided CVAD placement can provide real-time, accurate tip confirmation during the insertion procedure and can eliminate the requirement for chest X-ray confirmation entirely. The major benefit for ECG guidance is for PICC placement, however with the use of ultrasound, scanning of the lung lining to assess its integrity post insertion of a CICC is just as effective as chest x ray to excluded pneumothorax, as such ECG guidance can be used for both CICC and PICC insertion[19](#_ENREF_19). The incidence rate of pneumothorax (0.1%) and accidental arterial puncture (0.1%) for CICC insertion by the Central Venous Access Service at Liverpool hospital since 2012 is well below published CICC procedural complication rates[20](#_ENREF_20).

The ECG based method for tip location relies on the identification and changing amplitude of the patients native P-wave by making the CVAD an intra-cavitary electrode. This is achieved by attaching a sterile alligator clip to the metal guide wire inside the catheter or by the use of a column of physiological saline solution contained within the catheter[9](#_ENREF_9). The increased amplitude of the P-wave equivalent to the QRS denotes that the catheter is close to the sino-atrial node. Anatomically and intravenously this is the cavo-atrial junction, which is internationally recognised as the best position for a CVAD (other than a dialysis catheter) to terminate[21](#_ENREF_21).

The clinical and cost-effectiveness in comparison to the anthropometric method for determination of correct catheter positioning have yet to be fully assessed by quality randomised trials[22](#_ENREF_22),[23](#_ENREF_23).

This randomised trial will add strong evidence on the clinical effectiveness of ECG guided CVAD placement as an accurate and safe method to identify the final anatomical position of the catheter, and importantly show how this method can reduce cost and intra procedural malposition, as well as reducing operator time. This study will demonstrate the positive clinical and costs benefits for an organisation adopting such technology.

1. **AIMS / OBJECTIVES / HYPOTHESIS:**

The aim of this study is to test the following hypotheses:

1. ECG guided CVAD placement is superior to conventional anthropometric catheter placement for catheter position.
2. ECG guided CVAD placement will improve patient safety by reducing catheter malposition, exposure to radiation and reduce re-manipulation of the catheter post insertion.
3. ECG guided CVAD placement will have cost benefits compared with conventional anthropometric catheter placement due to chest X-ray not being required, reduced procedural time, reduced repeat x-rays and reduced need for consumables.
4. **PARTICIPATING SITES:**

Liverpool Hospital

1. **RESEARCH PLAN / STUDY DESIGN:**

***6.1 Type of Study:***

This study is a pragmatic, single centre, unblinded randomised control trial with two arms: 1) ECG guided CVAD placement method and 2) conventional CVAD placement method. Randomisation will be undertaken using an electronic randomisation program.

* 1. ***Study Procedures:***

The CVAD insertion procedure will be identical for both groups. Routine ultrasound guidance will be used to assess patient vessels for thrombosis, diameter and tortuous pathway prior to insertion as per standard practice. Ultrasound will also be used real time to access the vessel and to scan during the procedure to aid placement as per standard practice. Care and maintenance of the devices in both groups will be based on current hospital guidelines and will not be distinguished.

*Confirmation using Chest X Ray (both groups):*

Post procedure a chest x-ray will be used in both groups for the study. An independent and senior ICU doctor (blinded to the insertion protocol) with extensive experience with chest x-ray film interpretation, will review the CXR to verify the catheter tip location. The portable anterior – posterior chest x-ray will be taken with the patient positioned at a 30 degree angle in the bed. The height of the bed, distance of the machine lens to the patient and the angle of the machine lens will be the same for all films taken to limit shadowing and artefact on the x-ray film. The blinded assessor will use the digital callipers on the computerised x-ray film to measure the CVAD tip position.

The tracheal carina visible on x-ray will be used as a reliable landmark to verify correct catheter tip position[4](#_ENREF_4),[5](#_ENREF_5),[24](#_ENREF_24), with the following zones used as a guide.

1. Zone 1: Lower third of SVC (within first 3cm under the tracheal carina);
2. Zone 2: Cavo-atrial junction (3cm under the tracheal carina);
3. Zone 3: Upper third of the RA (from 3cm to 5cm under the carina).

All three zones will be acceptable for catheter tip location and will not require catheter manipulation. For this study and as per standard practice within Liverpool hospital, the optimal position for the CVAD tip will be between 3cm and 5cm below the tracheal carina (Zone 3). Catheter tips outside the three zones will be deemed as malpositioned.

*Confirmation using ECG:*

Confirmation of catheter tip using ECG (for the ECG-guided CVAD placement group only) will incorporate the following:

1. The catheter will be attached to a sterile ECG electrode. As the catheter is advanced towards the right atrium, the amplitude of the P wave increases until it has maximal amplitude compared to the QRS. This waveform denotes the junction between the right atrium and the distal SVC.
2. An independent and radiologist (blinded to the insertion protocol) with extensive experience with chest x-ray film interpretation, will review the CXR to verify the catheter tip location using the tracheal carina measuring method as described above.

*Confirmation of no pneumothorax* (for the ECG-guided CVAD placement group only and when catheters are placed in the chest or Neck):

1. The inserter will scan the pleural lining with a linear ultrasound probe between the first and second intercostal space on both the insertion side and opposing side (pre and post insertion).
2. The inserter will look for the integrity of the visceral and parietal pleura by noting the sliding of the two surfaces on the ultrasound screen (sliding lung sign)[19](#_ENREF_19).

***6.3 Primary Outcome Measure***

1. CVAD tip placement in the cavo-atrial junction / upper RA measured by within 3-5cm below the tracheal carina.

***6.4 Secondary Outcome Measures***

1. Improvement in service efficiency and safety composite of:

* Number of catheter re- manipulations
* Number of subsequent chest x-rays.

1. Procedural cost composite of:

* Operator time (categorised as start of procedure to when patient is ready to return to ward – in minutes)
* Mobile chest x-ray(s) and radiologist report
* Extra cost of consumables for re-manipulation of CVAD

***6.5 Data sources and collection***

*Data Collection*

Data collection will be undertaken by the Central Venous Access Services (CVAS) nurses during routine placement of CVADs. Data will be entered onto an electronic database. Data collected for the purposes of the study will be re-identifiable to enable researchers to verify accuracy and completeness of information as required. The case report form will be made re−identifiable by assigning a unique number to the participant. All data collected from the participant will then be identified by this number. The study site will keep a log of the enrolled participants which will include the participant’s initials and Medical Record Number and their assigned study number. This log will be stored separately to the patient case report forms. Patient data will be stored on password-protected computers and in locked, secure offices with access only to members of the study team at Liverpool Hospital.

Baseline data will include age, gender, diagnostic group, reason for CVAD insertion, type of CVAD required and anatomical placement. Other data collected will be any procedural complications, procedural time, and any secondary catheter manipulations and subsequent x-rays. Patient follow-up will include catheter dwell, reason for catheter removal, and latent complications of symptomatic thrombosis or catheter related blood stream infection.

***6.6 Population and sample size***

The study will be undertaken by the Intensive Care Unit Central Venous Access Service (CVAS) at Liverpool Hospital, operated by advanced practice nurses credentialed in inserting CVADs. The service is based in the tertiary level intensive care unit situated in South Western Sydney Local Health District. Adult patients requiring the insertion of a CVAD for medical treatment referred to the CVAS will be screened for eligibility.

*Sample size and power study*

Sample size calculation is based on the CVAS current catheter malposition rate. Between June 2013 and June 2015, 1600 CVADs were inserted by the service. A total of 268 catheter tips were malpositioned (composite of any CVAD tip outside of the cavo-atrial junction) for a 16.75% catheter tip malposition rate. Sample size calculation determined that 163 patients are required per group for >90% power to reach statistical significance (*p* = 0.05). With an estimated 5% attrition rate, 172 patients will be randomised in each group (total of 344 patients).

***6.7 Expected duration of study and start times***

Based on current CVAD insertion numbers of approximately 800 devices annually and safety of the study, it is expected that recruitment period will be 12 months.

***6.8 Statistical Analysis***

*Data Analysis*

All outcomes will be analysed using the principles of intention-to-treat. Incident rates of these outcomes, between the ECG guided and non-ECG guided placement groups will be compared as rate ratios (and 95% confidence intervals) using Poisson regression.  The CVAD insertion procedure will be the unit of measurement (patients may require consequent CVADs as part of routine therapy and may be allocated into a separate group). Primary and secondary outcomes will be compared between groups using parametric and non-parametric techniques appropriate to the level of measurement.

*Cost Analysis*

Procedure cost will be measured by assessing the staff time associated with the CVAD insertion procedure, X-ray cost(s) and any extra consumables used. Opportunity costs of CVAS staff time, radiographer and radiologist time will be valued from NSW Ministry of Health wage rates. Cost of equipment (consumables) will be valued based on the hospital contract price with the consumable / device manufacturer.

1. **ETHICAL CONSIDERATIONS:**

***7.1 Recruitment and selection of participants***

*Recruitment and randomisation*

The advanced practice nurses from the CVAS will screen patients daily using a screening log comprised of inclusion and exclusion criteria. Patients will be randomly assigned using randomisation software in a 1:1 ratio, to either anthropometric CVAD placement or ECG guided CVAD placement. Randomisation will be undertaken using a centralised computer randomisation service; allocation group will be concealed until the point of randomisation. Below is the study profile of patient flow:

***7.1.1 Inclusion and exclusion criteria***

*Inclusion Criteria:*

1. Adult patients referred to the CVAS for CVAD placement.
2. Native heart rhythm with an identifiable P wave

*Exclusion Criteria:*

1. Paediatric patients (under 18 years of age):
2. Patients whose native rhythm does not have an easily identifiable P wave (such as patients with atrial fibrillation, atrial flutter and idioventricular rhythms).

***7.2 Informed Consent***

This study will be conducted in accordance with the principles of ICH-GCP and the NHMRC National Statement on Ethical Conduct in Human Research, March 2007. We anticipate that informed consent will not be required as the insertion of CVADs using ECG-guidance is currently being used as standard CVAS practice. Consent is obtained from the patient or their Next of Kin prior to their referral to the CVAS and insertion of their CVAD. All patients will receive care as per standard hospital practice. This study does not require any additional invasive procedures and may, in fact, reduce the necessity for other invasive procedures. The use of ECG technology is non-invasive and carries negligible risk. The majority of data collected for this study is usually collected as part of standard practice by the CVAS. All other data collected will be used for the purposes of this study only.

***7.3 Confidentiality and privacy***

Patient demographic information including gender, age and diagnostic information will be collected. No identifying patient information will be collected. All patient information will remain anonymous. All data will be analysed in a de−identified fashion. No personal information or potentially identifying information will be included in any publication.

***7.4 Data storage and record retention***

Stringent processes will be used to ensure that the data are kept confidential and housed at Liverpool Hospital. Any paper data forms will be stored in a locked filing cabinet in the CVAS office and only be accessible by the principal researchers. Computer data will be stored on a secure computer located in the ICU at Liverpool Hospital. Information will be stored for a mandatory period of fifteen years in accordance with Good Clinical Practice Guidelines. After this period, all electronic records will be deleted and hard copies will be shredded.

1. **OUTCOMES and SIGNIFICANCE:**

This study will provide valuable data for clinicians and hospital administrators internationally and may benefit patients worldwide. The results of this study may present significant cost-savings for the Australian health care system through the elimination of the need for chest X-ray, chest x-ray reporting, as well as clinician time and excess consumables. Patient safety may also be improved with real time navigation of the catheter to reduce catheter malposition, by the ability to use the CVAD earlier and by reduced patient exposure to unnecessary radiation.

1. **TIMELINES and MILESTONES:**

**October 2015:** Ethical application lodged

**December 2016 – December 2017:** Undertake study

**December 2017 – March 2018:** Analyse results and develop peer review publication

1. **PUBLICATION POLICY:**

The study can be expected to be published in peer reviewed clinical journal. All authors have made and will continue to make substantial contributions to the study conception and design, acquisition of data and analysis and interpretation of data. Each author will contribute to the drafting and editing of any manuscript for publication as per the International Committee of Medical Journal Editors Convention. The authors will declare any unrestricted research grants received to assist in undertaking this study.

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