Cedar

Healthcare Technology Research Centre

External assessment centre report:

Sherlock 3CG Tip Confirmation System for placement of peripherally inserted central catheters

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CARDIFF UNIVERSITY PRIFYSGOL CAERDYDD

External Assessment Centre report

The purpose of the External Assessment Centre (EAC) report is to review and critically evaluate the sponsor's clinical and economic evidence and may include additional analysis of the submitted evidence or new clinical and/or economic evidence.

This report was updated on 4th November 2014 with the following amendments to correct inconsistencies and errors.

1. Where the text refers to the sponsor's model using *Blind PICC replacement at the bedside*, this has been changed to *PICC replacement at the bedside using the original insertion methods*. This is to clarify that, in the sponsor's model, if Sherlock 3CG TCS is used for the original insertion, it is also used for a replacement where the option of "adjustment at bedside" is selected.

2. Table 4 contained a typographical error which has been corrected to

Right atrium (upper 2cm)	63	26.4%
Right atrium (lower than 2cm)	39	16.3%

3. An error in the sponsor's model was identified at a late stage, meaning that the model did not include the full cost of reinsertion with Sherlock 3CG TCS, where necessary. This does not impact on the sponsor's base case which assumed reinsertion with fluoroscopy, or on the main EAC scenario, which assumed that there would be no reinsertions using Sherlock 3CG TCS. There is an impact for tables created by the EAC for Sherlock 3CG TCS with x-ray, where some reinsertions were included. This is particularly significant for the scenario using ICU data where the cost saving was reduced from £97.72 to £41.35. The following tables have been amended: Table 23,24, 25,26,28,29 and 30.

Sherlock 3CG Tip Confirmation System for placement of peripherally inserted central catheters

The title should be taken from the NICE scoping document, unless it has been agreed with the Medical Technologies Evaluation Programme (MTEP) that an alternative should be used.

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Declared interests of the authors

Description of any pecuniary relationship with sponsors, both personal and of the EAC. Please refer to NICE's Code of Practice for declaring and dealing with conflicts of interests.
http://www.nice.org.uk/niceMedia/pdf/Guidanceondeclarationsofinterest.pdf

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Rider on responsibility for report

The views expressed in this report are those of the authors and not those of NICE. Any errors are the responsibility of the authors.

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1 Summary

1.1 Scope of the sponsor's submission

The scope of the sponsor's submission agreed in most aspects with that published by NICE. The economic model is based on the population that require PICCs and are also suitable for ECG tip location technology. The original scope included all patients requiring PICCs. The sponsor's clinical evidence did not include comparison with PICC placement under fluoroscopy, as there was no evidence available. PICC placement under fluoroscopy was included as a comparator for the literature search scope, and is also included as an option in the economic model. Although none of the outcomes were excluded from the sponsor's submission, evidence was only available on the number of malpositions, time and cost.

The sponsor restricted the submitted evidence to the current model of the device available in the UK, Sherlock 3CG TCS, as specified by NICE. In the light of the small quantity and low quality of evidence available, the EAC widened the scope to include previous models of the device that included both magnetic tracking and ECG tip confirmation. This resulted in only one additional study reported as a Powerpoint presentation with insufficient detail to assess quality.

1.2 Summary of clinical evidence submitted by the sponsor

The sponsor concluded that Sherlock 3CG TCS reduces the incidence of PICC malpositions and subsequent repositioning, and that it eliminates the need for confirmation of placement by chest x-ray. The sponsor submitted four studies in either abstract or poster format as clinical evidence. In addtion a questionnaire of selected NHS sites using Sherlock 3CG TCS was submitted, although not analysed in the submission.

1.3 Summary critique of clinical evidence submitted by the sponsor

The EAC included one additional paper (Johnston et al. 2014) that was identified by the sponsor but not included as it became available online on the day before the submission date.

The evidence apart from Johnston et al. (2014) was limited to posters or abstracts, giving very little information. Although all the evidence found that use of Sherlock 3CG TCS had reduced the number of malpositions, the lack of information and of peer review means it must be treated with great caution. The only full published paper (Johnston et al. 2014) also found a reduced number of malpositions, but the number of malpositions was much higher than the other evidence, at 20.5 to 56.1% depending on definintion of malposition. The PICCs described in Johsnton et al. (2014) are all placed in an Intensive Care Unit, which may be another source of differences.

The available evidence concentrates on reporting malposition rates judged by chest x-ray after initial placement using Sherlock 3CG TCS tip confirmation. The studies are not comparative, therefore there is no information on the blind PICC placement malposition rates in the same setting. There is no information on what the consequences of the malposition were. We are unable to tell how many of the PICCs were adjusted,

how many of these were a simple pull-back, how many required reinsertion, and by what method. There is no evidence available as to the longer term consequences of inaccurate postioning using Sherlock 3CG TCS.

Several of the sites from the published abstracts (Adams 2013, Stewart 2013, Barton personal communication, Parikh 2013, Symington 2011) report that routine chest x-rays are no longer used to confirm PICC placement. The sponsors report that 9 NHS sites using Sherlock 3CG TCS have had sufficient confidence in the device to remove the requirement for routine chest x-rays to confirm tip location. The EAC were able to confirm 4 of these, however the remaining 5 did not respond to information requests.

1.4 Summary of economic evidence submitted by the sponsor

The sponsor identified two posters with economic content and correctly assessed these as low quality, requiring the creation of a de novo economic model. The sponsor used a wider literature search to find evidence for the model, and in most cases model inputs were well documented, justified and used the best evidence available.

1.5 Summary critique of economic evidence submitted by the sponsor

The economic model produced was mainly appropriate for the NICE scope and evidence available. The model deviated from the population in the scope by including only patients requiring PICC placement who were suitable for Sherlock. It does not consider outcomes of PICC placement past the point of correct placement. Model inputs were well documented and in most cases from the best evidence available. The model assumptions are well documented, although the EAC has noted additional assumptions. There are some pathway assumptions, but most have limited impact on the results. One important issue is the use of different nurse times for treatment with Sherlock 3CG TCS without x-ray, vs blind placement with x-ray, with no valid evidence base. Removing this assumption makes the base case for Sherlock 3CG TCS vs Blind placement no longer cost saving. The sponsor provided extensive one-way, two-way and scenario sensitivity analysis, however the underlying differences in nurse time between branches reduces the utility of these.

1.6 External Assessment Centre commentary on the robustness of evidence submitted by the sponsor

The sponsor identified all available evidence and made some attempt to gather additional information by contacting an expert clinical advisor and NHS sites using the technology.

The evidence available is very limited, both in the quality of the studies and the detail of the reporting. Only one study is fully reported as a peer reviewed paper (Johnston et al. 2014)

There is no comparative evidence available, and none of the studies report on outcomes past the initial identification of PICC tip location. The number of repositions, replacements, complications or adverse events are not reported in any of the evidence.

The economic model is generally well executed given the evidence available, but contains a number of assumptions identified by the EAC which can change the outcomes from cost saving to cost incurring in some circumstances.

1.7 Summary of any additional work carried out by the External Assessment Centre

The EAC conducted an independent search for clinical and economic evidence relevant to the scope. In the light of the small quantity and low quality of evidence available, the EAC widened the scope to include previous models of the device that included both magnetic tracking and ECG tip confirmation. The EAC contacted 5 authors for additional information, and attempted to contact a further 8.

The EAC identified additional assumptions in the submitted economic model and re ran the model with alternative inputs to examine their impact.

THE EAC ran a critical care scenario using results from the Johnston et. al (2013) and Johnston et. al. (2014) papers in the sponsor's model. The scenario was cost saving because of the significant reduction in the rate of malpositioned catheters between the two studies. As the data was all taken from a single centre, there are remaining questions about the generalisability of the findings.

Table 1 Abbreviations

CAJ	Cavo-atrial junction
CVC	Central venous catheter
CXR	Chest X-ray
ECG	Electrocardiogram
FDA	Food and Drug Administration (US regulatory body)
ICU	Intensive care unit
IJ	Internal jugular vein
MAUDE	Manufacturer and User Facility Device Experience, FDA database
MHRA	Medicines and Healthcare Products Regulatory Agency (UK regulatory body)
PICC	Peripherally inserted central catheter
SVC	Superior vena cava
TCS	Tip confirmation system
TLS	Tip location system
TPS	Tip positioning system

2 Background

2.1 Overview and critique of sponsor's description of clinical context

The sponsor's description of the clinical context is appropriate and relevant to the decision problem as described in the NICE scope.

2.1.1 Current clinical management

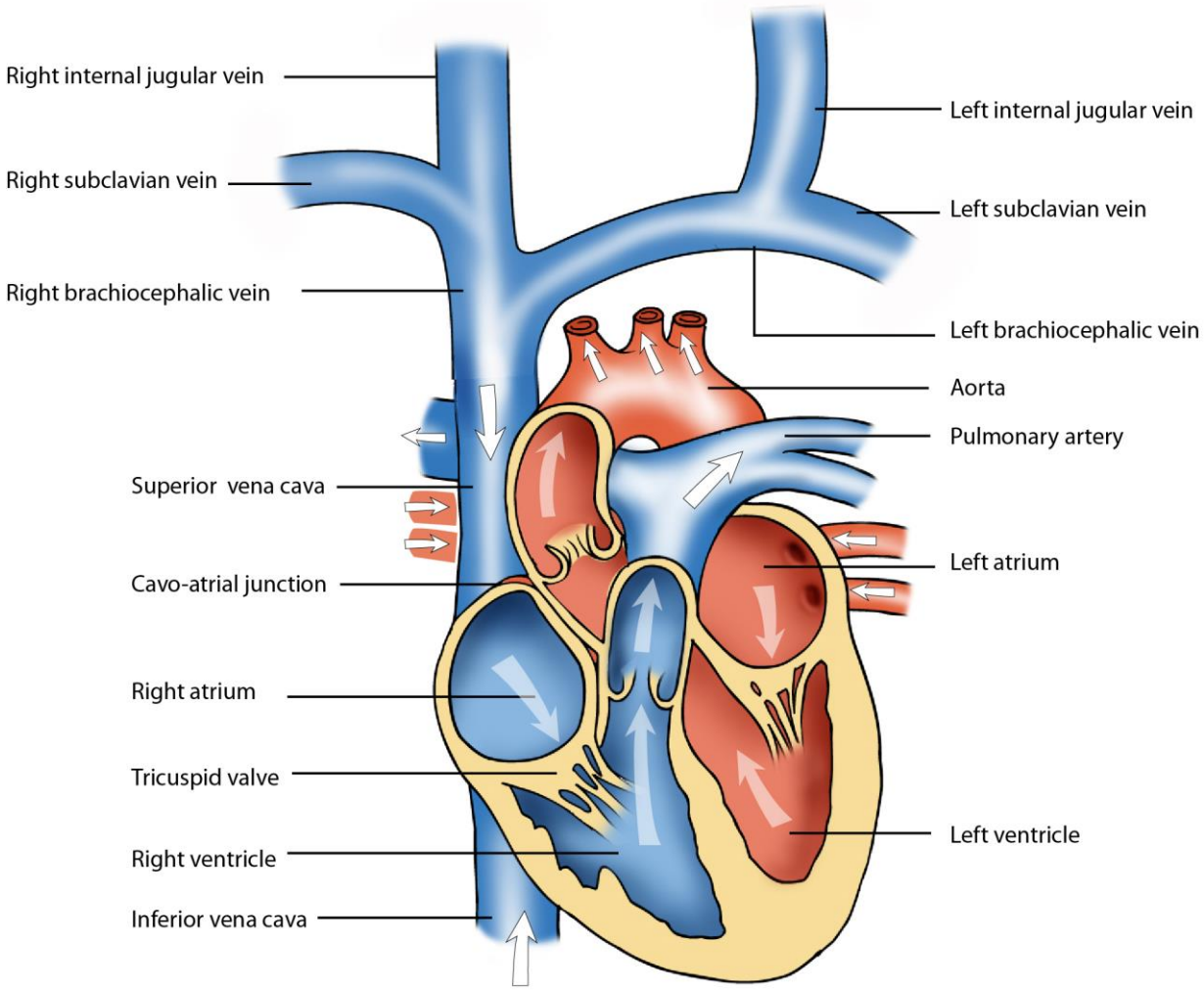
Central Venous Catheters are catheters with the internal tip located at the lower third of the superior vena cava (SVC), just above the junction to the right atrium, or within the higher right atrium (ESPN guidelines, Pittiruti 2009). The precise definition of correct tip location can vary between centres and countries.

Peripherally Inserted Central Catheters (PICCs) are a subset of Central Venous Catheters (CVC) that use a peripheral vein as the insertion site, typically the brachial or cephalic vein in the upper arm. PICCs and other forms of CVC may be used in the following circumstances:

- to take measurements of circulatory or heart functions
- to provide a long term access route for infusions and blood tests
- as a route for delivery of drugs that would damage thinner vessel walls e.g. chemotherapy
- as a route for contrast medium that requires injection directly to this location.

PICCs are inserted using ultrasound guidance into a vein in the arm. The ultrasound is used to ensure that the correct vein is located. The catheter is gently pushed through the vein without visual feedback, aiming to locate the tip in the correct position in the superior vena cava or right atrium. The standard procedure in the UK is to measure the distance from the insertion point to the final tip location desired on the patient using a tape measure and anatomical landmarks. When the catheter has been inserted to the correct length a chest x-ray is used to confirm if tip placement is correct.

Figure 1 Diagram of heart showing venous system used for PICC placement via subclavian vein to access the superior vena cava and right atrium (Cardiff University Media Resources).



Malpositions of the catheter can include diversion upwards into the internal jugular vein, or across into a contralateral vein, rather than downwards towards the right atrium. These would always be considered malpositions.

In addition the catheter may be located slightly too distal or proximal to the intended location. In this case there may be differences of opinion on what is an acceptable tip location. Definitions may include all of the superior vena cava (SVC) and the upper portion of the right atrium, or be confined to the lower SVC and cavo-atrial junction (CAJ).

Ultrasound on the neck can be used to detect malposition in the internal jugular vein, however it may not always be detected by this method.

If the catheter tip is inserted slightly too far, e.g. right atrium, it is a simple procedure to withdraw a small length of catheter and no repeat x-ray is normally required.

For malpositions such as the internal jugular vein it may be possible to move the catheter tip without reinsertion, for instance using patient positioning and flushing the catheter.

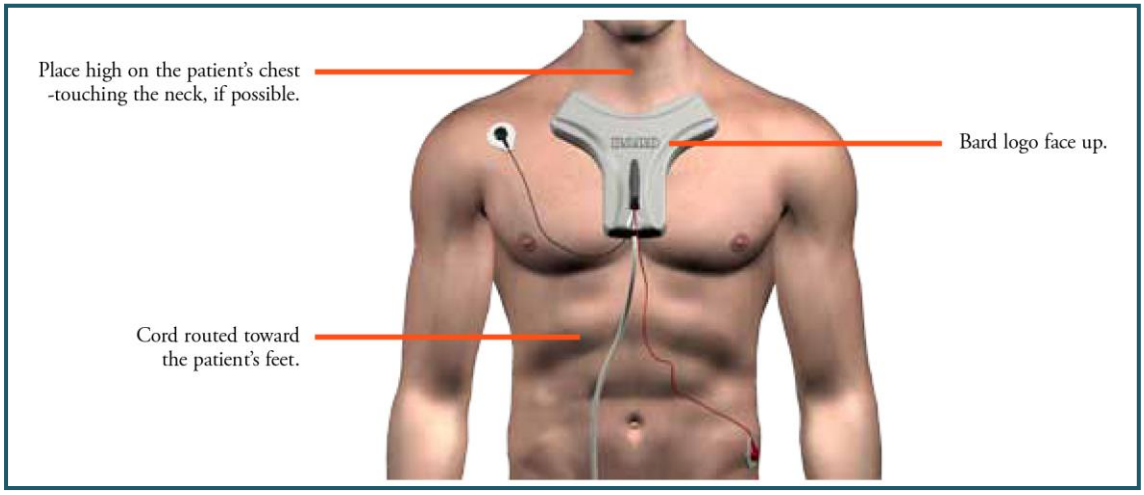
If reinsertion is required, then this may either be attempted by the same method again, or by using fluoroscopy guided insertion. The method used will depend upon local protocol and clinical judgement.

For any PICC, regardless of placement method, it is possible to have movement of the catheter tip after the initial placement.

2.1.2 PICC placement using Sherlock 3CG TCS

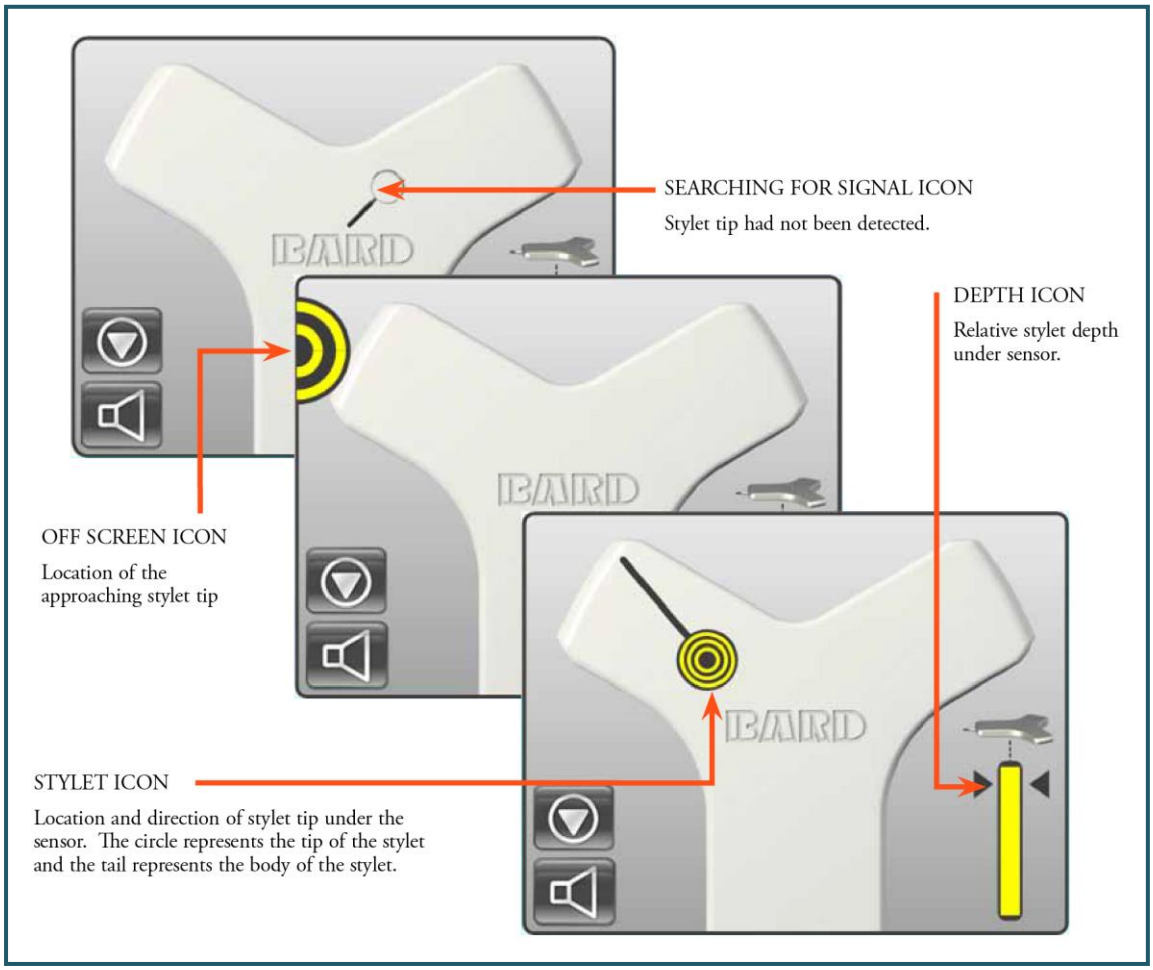
Sherlock 3CG TCS uses a conductive guidewire with a magnetic tip or stylet inside the catheter. The guidewire is inserted into the catheter prior to insertion in the vein, so that the tip is just inside the end of the catheter. The catheter, with the guidewire inside, is then inserted in the same way as a normal PICC procedure.

Figure 2 Sherlock 3CG TCS sensor on patient chest, with ECG electrodes in place. © 2014 C. R. Bard, Inc. Used with permission.



The progress of the magnetic tip is detected by a sensor placed on the patient's chest above the sternum, allowing the operator to see the position of the tip relative to the sensor and the direction of travel. This can indicate for instance a diversion into the internal jugular vein or contra-laterally. A saline column within the catheter is used to transmit the internal ECG signal to the Sherlock 3CG TCS monitor. Two ECG electrodes are also placed externally on the patient for the reference ECG trace.

Figure 3 Screen shots of Sherlock 3CG TCS monitor showing progress of the stylet relative to the external sensor. © 2014 C. R. Bard, Inc. Used with permission.



The internal ECG signal changes due to the relative position of the catheter tip within the electrical depolarisation of the right atrium. As the tip approaches the cavo-atrial junction the p-wave increases in amplitude. If the tip is advanced further the p-wave decreases in amplitude and may become inverted as it enters the right atrium. The operator would then normally withdraw slightly from the position of maximum p-wave amplitude to approximately half the maximum amplitude, positioning the tip at the cavo-atrial junction,. The wire is then withdrawn and the catheter fixed in place.

2.1.3 Clinical setting for PICC placement

The clinical setting and staff for insertion of PICCs varies between different sites. From queries to clinical advisors it is apparent that PICCs may be inserted by nurse-led vascular access teams, or consultant led teams, they may be in theatre or at bedside. For some settings fluoroscopy may be used routinely for most PICCs, for others fluoroscopy would only be used for very complicated cases, or simply not available. Typical arrangements include:

- Nurse-led vascular access teams inserting PICCs at bedside or outpatient clinics using blind insertion and x-ray confirmation.

- Consultant led vascular access in theatres with the option of fluoroscopy.
- Radiologist led service using fluoroscopy.

The options for both initial insertion and subsequent reinsertion will depend on the local arrangements and the patient population normally treated.

2.1.4 UK prevalence for PICC placement

The sponsor reports that UK PICC sales for 2013 were approximately 74, 490 (iData, 2014). The EAC does not have access to this report to comment on the figure, however it appears reasonable in light of data we do have available. Hospital Episode statistics (HES) for England were examined for 2012-13, and for inpatient procedures there were 31,437 procedures recorded (OPCS code L99.7 Percutaneous transluminal peripheral insertion of central catheter). An unknown, but substantial proportion of PICCs are placed in outpatient settings. HES records 1,222 outpatient PICCs being placed, however only the main procedures are recorded, and even these may be incomplete.

In an attempt to look further at the number of PICCs being placed in the UK, a brief informal literature search was carried out. Reports of PICC numbers annually ranged from 40 to 460 for different settings. A summary of papers examined is in Appendix 2.

2.2 Overview of sponsor's description of ongoing studies

There is one ongoing study, clinical trial NCT01969981. The sponsor identified the trial and reported the information as described on the clinicaltrials.gov.uk database. They did not submit any additional information concerning this trial. The EAC have contacted the principal investigator, but have not received any further information. The trial is an observational study in a single centre in France. The primary outcome measures are given as the efficacy and success rate of PICC placement using Sherlock 3CG TCS. Additional outcome measures include the number of repositions and acute complications. Longer term outcomes are not included. The clinicaltrials.gov.uk database states that it is due for completion in April 2014, but it also states its current status as recruiting.

Study NCT01275430 is reported in clinical trials.gov.uk as terminated. This was a two part trial:

- Phase 1: determine the location of the peripherally inserted central catheter (PICC) tip upon observation of maximum p-wave amplitude
- Phase 2: determine the precision of PICC placement in the Sherlock 3CG group versus the standard PICC placement

The study is described as a randomised controlled trial, and one of the secondary outcomes for Phase 2 is to record adverse events for 30 days.

The sponsor informed the EAC that part 1 was completed but has not yet been reported, and that part 2 is going through an approval stage to commence. The study is taking place in the USA, with BARD as the sponsor. No additional information was submitted.

2.3 Critique of sponsor's definition of the decision problem

2.3.1 Population

The scope used by the sponsor matches that issued by NICE. The published evidence submitted by the sponsor has very limited information on the patient population, although they are generally adults suitable for PICC placement with ECG guidance e.g. no atrial fibrillation. In interpreting the evidence attention needs to be given to the population used in any accuracy calculations. For example, where a 95% accuracy is quoted for patients where ECG tip confirmation was carried out, the accuracy for the entire group of patients suitable for PICC is likely to be lower, as some will not have been suitable for ECG tip confirmation and have been excluded.

Johnston et al. 2014 state that their patients are all in ICU, other evidence sources do not give patient details. It is clear from Johnston et al. [2013, 2014] that there are some differences between PICC placements for ICU and non ICU patients. The authors suggest that these may include the presence of ECG artefacts creating difficulties in tip location, difficulties of positioning patients, presence of other central venous catheters and differences in venous flow due to mechanical ventilation.

2.3.2 Intervention

The technology described in the sponsor's submission matches the final scope issued by NICE. The submission was restricted to Sherlock 3CG TCS, the only version of the device that has received CE marking and is sold in the UK. Sherlock 3CG TCS is classified as a Class I Medical Device and obtained a CE mark in December 2011, this covers the sensor and all other parts that are external to the body. The sponsor has provided the EAC with a copy of the declaration of conformity dated December 2011. The Sherlock 3CG TCS magnetic stylet is packaged with the Power PICC SOLO catheters. These are a Class III Medical Device and obtained a CE mark in February 2012, with a declaration of conformity dated May 2012. The sponsor has satisfied the regulatory requirements and supplied the EAC with the necessary documentation. The sponsor states that the technology was launched in the UK in April 2013.

The key mechanisms for the Sherlock 3CG TCS are

- the use of a magnetic tracking system to visually follow the progress of the catheter and stylet (relative to the sensor placed on the patient's chest) into the superior vena cava and towards the right atrium
- the use of ECG to confirm correct positioning of the catheter at the cavo-atrial junction.

There are several different versions of the device that were FDA approved and available in the USA prior to Sherlock 3CG TCS. The EAC believes that it is reasonable to include evidence that is based on previous devices that use both magnetic tracking and ECG.

Table 2 summarises the previous versions, highlighting which would be similar in concept to Sherlock 3CG TCS.

Table 2 Previous technologies related to Sherlock 3CG TCS

Device Name	First FDA approval date	Magnetic tracking	ECG	Appropriate for inclusion?	Comments
Sherlock Tip Locating System (TLS)	14/4/2006 additional approvals 2/6/2006 and 21/11/2006	Yes	No	No	Some papers refer to Sherlock II, this appears to be covered by the same FDA approval.
Sherlock 3CG Tip Positioning System (TPS)	07/08/2009	Yes	Yes, 3 ECG electrodes (including stylet)	Yes	
Sapiens Tip Confirmation System (TCS)	20/9/2011	No, but can be used together with Sherlock TLS to give magnetic tracking	Yes	No, unless used with Sherlock TLS	Previously Sapiens TLS, manufactured by Romedex International (FDA approved 15/7/2010)
Sherlock 3CG Tip Confirmation system (TCS)	19/3/2012 and 14/03/2014	Yes	Yes, 3 ECG electrodes (including stylet)	Yes	

2.3.3 Comparator(s)

The comparators used by the sponsor match the NICE scope:

- PICC insertion followed by chest x-ray
- Fluoroscopy to guide PICC insertion and confirm tip placement

All evidence was based on the introduction of Sherlock 3CG TCS to a service and initially using chest x-rays for confirmation of tip location in addition to Sherlock 3CG TCS. Comparison was made between these techniques, but there was no evidence that compared blind placement with chest x-ray confirmation to Sherlock 3CG TCS.

No evidence was found that considered the consequences of reported malpositions. This could include number of reinsertions actually performed, or occurrence of adverse events.

The scope specifies the use of fluoroscopy as a comparator, this was also included by the sponsor, however no evidence was available.

The sponsor did consult a clinical expert and also send 7 questionnaires out to NHS sites that use Sherlock 3CG TCS. Details of this are reported in section 3.4.7.

2.3.4 Outcomes

The only clinical outcomes specified in the scope that were reported in any of the published evidence were:

- accuracy of catheter tip placement
- incidence of catheter malposition
- treatment delay following catheter placement
- change in staff time
- requirement for confirmatory chest x-ray

Additional outcomes that were reported included: the number of PICCs successfully placed in an acceptable location using Sherlock 3CG TCS, and the percentage of patients where Sherlock 3CG TCS could be used. In addition some papers reported cost and time savings.)

The final scope listed additional outcomes, which were not reported in any of the published evidence identified. These were:

- need for catheter re-positioning
- impact of malposition-related complications such as infection / thrombosis
- reduced in-hospital stay
- requirement for fluoroscopy to correctly place the PICC tip
- time taken to insert PICC
- PICC failure / re-insertion rates
- patient experience measures
- quality of life
- device-related adverse events

2.3.5 Cost analysis

The economic model is based on the population that require PICCs and are also suitable for ECG tip confirmation. The original scope included all patients requiring PICCs, those who do not use ECG tip confirmation will require a differnent approach and this should be included in the cost. It is likely that this would be either blind insertion and chest x-ray, or PICC insertion using Sherlock 3CG TCS combined with a chest x-ray for confirmation of tip position. The cost impact of this change would be low where there are small numbers requiring a different pathway and the pathways have similar costs..

2.3.6 Subgroups

No subgroups were identified in the scope, however the evidence (Johnston et al. 2014) does suggest that placement accuracy in ICU may be different from other situations (i.e. limited patient mobility makes the procedure more difficult).

2.3.7 Special considerations, including issues related to equality

No special considerations were identified in the scope.

No equality issues were identified in the scope. Neither the sponsor nor the EAC have identified any further equalities issues.

3 Clinical evidence

3.1 Critique of the sponsor's search strategy

The strategy has been assessed in accordance with the PRESS checklist (Peer Review of Electronic Search Strategies). The search strategy used by the sponsor is comprehensive using a range of Subject Headings and free-text terms together with Boolean and proximity operators. However the sponsor has not mapped the index terms to the various databases e.g. Embase uses the EMTREE thesaurus whereas Medline uses MeSH and these do not necessarily cross-match. It was noted that the sponsor assumed that the brand name would be contained within the title or abstract of relevant literature, lines 17 and 18 of search strategies. The EAC additionally identified Sainathan et al. (2014), albeit using Sherlock II TLS, which did not state the brand name in the title or abstract. Therefore a more general search string should have been incorporated to cover 'electromagnetic devices'.

The sponsor limited the search to 'English language' and to studies published in the year 2000 or later. These are appropriate limits in that studies identified would be applicable to patients in England and cover the periods when the technology was launched.

The sponsor searched the following Ovid databases:

- MEDLINE 1946 to present
- EMBASE 1988 to 2014 July 09
- EBM Reviews – ACP Journal Club 1991 to June 2014
- EBM Reviews - NHS Economic Evaluation Database 2nd Quarter 2014
- EBM Reviews - Cochrane Central Register of Controlled Trials June 2014,
- EBM Reviews - Cochrane Database of Systematic Reviews 2005 to May 2014,
- EBM Reviews – Cochrane Methodology Register 3rd Quarter 2012,
- EBM Reviews - Database of Abstracts of Reviews of Effects 2nd Quarter 2014,
- EBM Reviews - Health Technology Assessment 2nd Quarter 2014

The report indicates that Medline In-Process was searched although this is not clear and a strategy was not included for this database, it is likely that this database was searched simultaneously with Medline. The sources searched provide reasonable coverage of likely published evidence. Although conference abstracts were identified for this report a specific search of a conference proceedings database (e.g. Web of Science Conference Proceedings Science Citation Index) was not performed.

The sponsor contacted NHS clinicians who were known to be using the technology as well as authors of identified relevant conference presentations. The sponsor searched the MHRA website and FDA (MAUD) database for adverse events.

Although the sponsor has identified the only ongoing trial it was not stated if a search of the WHO International Clinical Trials Registry Platform or ClinicalTrials.gov for ongoing studies was performed. The sources searched provide reasonable coverage of likely unpublished evidence however a search of the two clinical trials platforms together with a specific search of a conference proceedings database would have made the search for unpublished evidence more rigorous. The sponsor did not identify any unpublished studies.

A flow diagram of study selection was clearly presented in the sponsor's submission.

We believe that the sponsor has identified all the relevant literature for this technology at the time of writing their report. They also identified relevant abstracts from grey literature that were not identified in the EAC search.

3.2 Critique of the sponsor's study selection

The selection criteria were as specified by NICE in the published scope and these were appropriate. There was no selection based on study quality, and the EAC agree with this decision based on the very limited amount of evidence available.

The sponsor restricted the submitted evidence to the current model of the device available in the UK, Sherlock 3CG TCS, as specified in the scope. In the light of the small quantity and low quality of evidence available, the EAC widened the scope to include previous models of the device that included both magnetic tracking and ECG tip confirmation. This only resulted in one additional presentation that was of low quality (Symington 2011).

The sponsor also sent questionnaires to selected NHS sites, but omitted to include this information in their submission. The information was provided separately to the EAC, and is summarised in table 7.

A study by Johnston *et al.* 2014 was identified by the sponsor, but no details were included in the submission. This is presumed to be due to the publication of the study on the day before the sponsor's submission. The EAC have included details of this study in the assessment report.

3.3 Included and excluded studies

Studies are described in more detail in section 3.4, including methodology and results. Table 3 summarises the papers that were included by the sponsor, and the additional information included by the EAC. None of the studies included by the sponsor were excluded by the EAC.

Table 3 Studies included by the sponsor and EAC

Study	Patient population	Country	Study design	Technique used previously to study	Number of PICC tips placed using Sherlock ECG TCS
Included by sponsor					
Barton 2014	Adults with no atrial fibrillation	UK (NHS)	Case series	Chest x-ray confirmation	65 in original study 225 in follow up
Adams 2013	Excludes patients without an identifiable p-wave.	USA	Case series	Chest x-ray confirmation	333
Parikh 2013	Excludes patients with atrial fibrillation, atrial flutter, no discernable p-wave and those at increased risk of bleeding	USA	Case series, prospective	Sherlock II TLS (magnetic tracking) plus chest x-ray confirmation	209 in original study 437 in follow up
Stewart 2013	Not stated	Australia	Case series	Chest x-ray confirmation	Unknown. Abstract states "over 65"
Included by EAC					
Johnston 2014	Excludes patients not in sinus rhythm. Setting is ICU.	UK (NHS)	Case series, retrospective	Chest x-ray confirmation	239
Symington 2011	People in whom PICCS are inserted	USA	Case series	Sherlock II TLS (magnetic tracking) plus chest x-ray confirmation	63
NHS Questionnaire	Not stated	UK (NHS)	Questionnaire	Chest x-ray confirmation	unknown

3.4 Overview of all included studies

Only one study had a full published paper, all other evidence is based on conference abstracts and posters. Therefore critical appraisal could only be conducted for Johnston (2014) as the methodologies for the other studies were not sufficiently described.

All of the studies are case series. The studies used a chest x-ray for confirmation of tip position, and the success rate is reported. For some studies it is unclear if the success rate relates to all PICCs placed, cases

where Sherlock 3CG TCS was attempted, cases where placement was ECG guided, or where ECG guidance was attempted.

The definition of successful tip location varies between studies, and in some is not defined at all (Stewart 2013).

3.4.1 Johnston 2014

Methodology

Following the introduction of Sherlock 3CG TCS, a retrospective review of the first 250 patients to have PICCs placed was carried out. The included patients were all in the Intensive Care Unit (ICU), and this was the initial site for introduction of Sherlock 3CG TCS due to the high levels of malposition normally seen. PICCs were placed by the Vascular Access Team at the bedside, and a portable chest x-ray was used to confirm the tip location. If PICCs needed to be withdrawn to correct the location, this was done by the ICU team. If the PICC needed to be reinserted then the Vascular Access Team was used.

From the first 250 patients, 11 were excluded from review because of failed insertions (2 cases), no chest x-rays (2 cases), not possible to determine the tip position on the chest x-ray (2 cases), unable to interpret ECG criteria (4 cases), and catheter not long enough (1 case). For the review, two independent reviewers examined the chest x-rays and recorded the catheter tip location. It was noted that the arm was abducted for tip placement, and adducted for the chest x-ray, which may have caused movement of the catheter tip between placement and x-ray.

Although there is no direct comparator for the intervention in this study, the same authors published a paper the year before Sherlock 3CG TCS was introduced (Johnston et al. 2013). This was a retrospective service evaluation reviewing records for patients both within ICU and non-ICU patients. The PICCs were placed using a blind anthropometric method, and then confirmed by chest x-ray. Data was collected on consecutive patients from ICU and every third non-ICU patient, since there were approximately three times as many non-ICU patients. Chest x-rays were reviewed by at least 2 out of 3 authors (1 of whom also reviewed chest x-rays for Johnston et al. (2014)).The study was at the same hospital with the same type of patient population and the same members of staff as Johnston et al. (2014).

Critical Appraisal

The paper clearly states the aims and methods of the study, patients are recruited consecutively and results are reported fully. There are no explicit exclusion criteria stated prior to the review. There were 11 patients excluded, and the reasons for exclusion given. For patients where malpositions were noted, there is no information about whether subsequent intervention to reposition the catheter was required, or whether a repeat procedure was needed (i.e. starting the process over again). No details of the patients included in the trial is given, other than they required PICC placement while being treated in ICU. No information about

adverse events is given. Declaration of interests is clearly stated – two authors have previously received honoraria from Bard, no external funding for the study or equipment was received.

Results

The abstract reports tip location, as judged by two independent chest x-ray reviews, for each of the 239 PICC placements where ECG was used for tip confirmation. Table 4 shows the number of PICCs placed in each position, together with the results from the period prior to introduction of Sherlock 3CG TCS, taken from Johnston 2013.

Table 4 Results showing catheter tip locations, as defined by chest x-ray, both using Sherlock 3CG TCS and prior to its introduction (Johnston et al 2013, 2014)

Tip position	Using Sherlock 3CG TCS (Johnston 2014)		Prior to Sherlock 3CG TCS (Johnston 2013)			
	ICU		**ICU**		Non ICU	
	(n=239)	%	(n=246)	%	(n=233)	%
Malpositions[a] above the superior vena cava (ipsilateral and contralateral)	1 [c]	0.0% [c]	51 [c]	20.7 [c]	33 [c]	14.2 [c]
High superior vena cava	7	2.9%	27	11	26	11.2
Mid superior vena cava	22	9.2%	42	17.1	25	10.7
Low superior vena cava	58	24.3%	36	14.6	70	30
Caval-atrial junction	47	19.7%	23	9.3	23	9.9
Right atrium (upper 2cm)	63	26.4%	20	8.1	18	7.7
Right atrium (lower than 2cm)	39	16.3%	35[c]	14.2 [c]	28 [c]	12.0 [c]
Malpositions[b] below the right atrium	1 [c]	0.0% [c]	5 [c]	2.0 [c]	5 [c]	2.1 [c]
Others	1	0.4%	7	2.8	5	2.1

[a] Malpositions include ipsilateral and contralateral positioning in the axillary vein, internal jugular vein, subclavian vein and brachiocephalic vein.

[b] Malpositions include the right ventricle and inferior vena cava

[c] These figures were calculated by EAC from papers due to different presentations of figures between the two papers.

The authors used two alternative definitions of acceptable placement to summarise the data. Criteria 1 is the low superior vena cava and cavo-atrial junction, reflecting the definition typically used in the USA. Criteria 2 is the mid and lower superior vena cava, cavo-atrial junction and the high right atrium, which is in line with

European guidelines (Pittiruti et al, 2009). Table 5 shows the results for prior and post the introduction of Sherlock 3CG TCS.

Table 5 Number of catheter placements defined as malpositioned using two different criteria, both using Sherlock 3CG TCS and prior to its introduction (Johnston et al 2013, 2014)

Definition of adequate tip position	Using Sherlock 3CG TCS (Johnston 2014)		Prior to Sherlock 3CG TCS (Johnston 2013)			
	ICU		ICU		Non-ICU	
	(n=239)	% and 95% CI	(n=246)	%	(n=233)	%
Criteria 1: Low SVC / CAJ	134	56.1% (50-62%)	187	76.0%	140	60.1%
Criteria 2: Mid and low SVC / CAJ / high RA (upper 2cm)	49	20.5% (16-26%)	125	50.8%	97	41.6%

Johnston et al. (2014) also calculate malposition rates using different definitions of the acceptable portion of the right atrium. They show that the malposition rate would be as low as 4.2% (10/239) using Sherlock 3CG TCS if any position in the right atrium were considered acceptable.

The malposition rate using Sherlock 3CG TCS is significantly lower than blind anthropometric placement for both criteria ($p<0.0001$), although caution is needed as the studies are not directly comparing identical populations. The malposition rate using Sherlock 3CG TCS is noticeably higher than that reported in the other studies (Pittiruti et al. 2012, Schweickert et al. 2009). Johnston et al. 2014) suggest several reasons for this. They noted that it was sometimes difficult to determine the exact point of a maximum p-wave or biphasic p-wave, particularly with patients in ICU as they are likely to have ECG artefacts due to co-morbidities. They also note the possibility that the catheter tip moves with arm movement since the PICC is placed with the arm abducted, and the chest x-ray with the arm adducted. In an earlier paper Johnston et al. (2013) also show differences between ICU and non ICU for blind PICC placements with X-ray and suggest that factors could include the difficulty of patient positioning during catheter insertion, presence of other central venous catheters and differences in venous flow due to mechanical ventilation.

The authors conclude that if a broader definition of an adequate tip position is considered acceptable, then Sherlock 3CG TCS can be used for tip confirmation without a routine chest x-ray. However if a narrower definition of tip position (low SVC / CAJ only) is required, then Sherlock 3CG TCS is inadequate without chest x-ray.

3.4.2 Barton 2014

Methodology

An abstract for an oral presentation from the World Congress Vascular Access 2014 reports on the introduction of Sherlock 3CG TCS to a nurse led PICC service at Frimley Park Hospital. Sherlock 3CG TCS was used for PICC placement in 65 patients, all adults with no atrial fibrillation. All patients had chest X-rays to

confirm the tip location. Following this first trial, an application to amend local protocol and remove mandatory chest x-ray following PICC placement was made, and during the application process a further 160 PICCs were placed using Sherlock 3CG TCS and position confirmed using chest x-ray, giving a total of 225 reported patients. The definition of acceptable tip position was the lower third of the SVC, or CAJ. Positioning in the right atrium would have been clinically unproblematic and may not be clearly distinguished using the chest x-ray (personal communication 2014).

Critical Analysis

Only a short abstract is available and therefore critical analysis is not possible. The information has not been peer reviewed. The author was contacted and added information on the acceptable tip position used and the number of patients where Sherlock 3CG TCS could not be used.

The abstract reports the success rate of tip positioning in only those patients in whom the magnetic tip position plus ECG tip confirmation could be used. This did not account for cases where Sherlock 3CG TCS was not suitable, or where there was a failure of the ECG system, however the author has subsequently provided this information.

Review of chest x-rays was by an independent physician. No declaration of interests was stated.

Results

Chest x-rays confirmed that the tip position was acceptable in 100% of the cases reported. The author reports that during the trial period only 2 patients were not suitable for Sherlock 3CG TCS and had PICCs placed with fluoroscopy. Since the introduction of Sherlock 3CG TCS to the hospital, 11 patients have required chest x-rays due to failure of the ECG system to provide tip confirmation. Of these, 5 cases were due to atrial fibrillation, and 6 cases were due to a failure of the electrode connections. Frimley Park Hospital has gone on to remove the requirement for routine chest x-ray

3.4.3 Parikh 2013

Methodology

A poster from the Radiological Society of North America 2012 for a prospective case series, from October 2011 to April 2012, reports on 247 PICCs that were placed in 221 patients, mean age of 62 (range 15-100). Sherlock 3CG TCS was used for tip placement and confirmation, except for patients with atrial fibrillation, atrial flutter, no discernable p-wave and those at increased risk of bleeding (38/247). The tip position was confirmed by chest x-ray evaluated by 2 independent observers. A satisfactory tip placement was defined as the superior vena cava or cavo-atrial junction.

The study was carried out in 2 phases:

Phase 1 – Voluntary training consisting of a 1 hour PICC refresher, 3 hour online course, 1 hour taught course and 1:1 training with Bard nurse trainer (completed by 4 out of 7 nurses).

Phase 2– Mandatory completion of Phase 1 training plus performing 5 PICCs with observation by a Bard nurse trainer.

Following the completion of the study, from November 2012 to May 2013, 567 further PICCs were placed, 437 using Sherlock 3CG TCS.

Critical Appraisal

Only a poster is available, however it is quite detailed and contains sufficient information for some critical analysis. The patient population was clearly defined, as was the acceptable tip placement. Assessment of the tip position was by 2 independent observers who had not seen the clinical reports. Patients excluded are clearly stated, with reasons. The information has not been peer reviewed.

No declaration of interests was stated.

Results

For Phase 1, 95.4% (62/65) of PICCs were placed using Sherlock 3CG TCS, 4.6% (3/65) were excluded from the results in line with the criteria. Successful tip placement was 83% (n=62) for those using Sherlock 3CG TCS.

For Phase 2, 80.8% (147/182) of PICCs were placed using Sherlock 3CG TCS, 19.2% (35/182) were excluded from the results in line with the criteria. Successful tip placement was 96% (n=147) for those using Sherlock 3CG TCS.

Between November 2012 to May 2013, 567 PICCs were placed, of which 437 used Sherlock 3CG TCS for tip placement and confirmation. Of the 437 PICCs that used Sherlock 3CG TCS, 24.9% (109/437) still used chest x-ray for confirmation. Reasons given included unclear baseline cardiac rhythm and difficult or complicated PICC placements. It is unknown if the PICCs that did not use Sherlock 3CG TCS required chest x-ray, however this is probable.

The study highlights the need for thorough training in using the ECG tip confirmation technology.

3.4.4 Adams 2013

Methodology

A poster from the Association of Vascular Access annual meeting 2013 reports on the introduction and evaluation of Sherlock 3CG TCS to the Eden Medical Centre, USA, prior to removing routine chest x-rays from the standard local protocol. Sherlock 3CG TCS was used over a 9 month period, to place PICCs in 333 patients, who all subsequently had a chest x-ray assessed by two radiologists. Correct placement was interpreted as the distal SVC or CAJ.

Critical Analysis

Only a short abstract and poster are available and therefore full critical analysis is not possible. The information has not been peer reviewed. The poster reported the number of occasions where Sherlock 3CG

TCS was used to confirm tip position, and the success rate of accurate tip position for these as reported separately by two radiologists. The poster also reports changes in waiting time and costs.

No declaration of interests was stated.

Results

Sherlock 3CG TCS was used to confirm tip position in 83.5% of patients (278/333). In 16.5% (55/333) the ECG system could not be used to confirm tip position because of an abnormal p-wave, loose connections, poor electrode placement or similar. Abnormal p-wave accounted for 12.9% (43/333) of patients.

Where Sherlock 3CG TCS was used to confirm tip position, the first radiologist found that 96.4% (268/278) were placed accurately and 3.6% (10/278) were malpositioned. The second radiologist found that 98.2% (273/278) were placed accurately and 1.8% (5/278) were malpositioned.

Previous tip location had used Sherlock Tip Location System, with magnetic tracking and a confirmatory chest x-ray. Rates of malposition in 2011 were reported as 14%, it is unknown if these required a simple pull back of the catheter, or more intensive intervention such as a replacement catheter procedure.

The poster reports that the PICC line was ready for infusion 61 minutes earlier when using Sherlock 3CG TCS than using chest x-ray and radiologist report for tip position confirmation. There is no information available on how this was measured, or if this resulted in infusions being given earlier, or if any gain in time was carried through to subsequent treatment.

Cost savings are reported, however there are very few details provided. This is discussed in the economic evidence section 4.1.

Chest x-rays are no longer mandatory for PICCs placed using Sherlock 3CG TCS at this health facility.

3.4.5 Stewart 2013

Methodology

This abstract and poster from the Association of Vascular Access annual meeting, 2013, provided very little methodological information. The abstract states that between “Nov 2012-March 2013 we recruited over 65 patients”. The PICCs were placed using Sherlock 3CG TCS and tip position confirmed using chest X-ray. No information is given on what tip positions were deemed acceptable, or who reported on the chest x-ray.

Critical Appraisal

Only a short abstract and poster are available and give minimal information. No critical analysis is possible. The information has not been peer reviewed. Information should be treated very cautiously since even the number of patients recruited is not accurately reported.

No declaration of interests was stated.

Results

The abstract reports that 100% of malpositions were corrected at the time of placement, 96% of ECG guided tip locations were within the CAJ, with 4% being within the right atrium. Discrepancies between locations reported by ECG and x-ray were noted, though these were resolved as experience with Sherlock was gained.

A saving of the time between PICC and results of chest x-ray of 1 hour 51 minutes was noted. There is no information available on how this was measured, if this led to earlier treatment, or if any gain in time was carried through to subsequent treatments.

Cost savings are reported, however there are very few details provided. This is discussed in the economic evidence section.

3.4.6 Symington 2011

Methodology

A presentation is available, from the Association of Vascular Access annual meeting, 2011. Sherlock TLS and Sapiens TCS were used together at two sites and the results reported for the first 63 patients where the technology was technically successful.

Critical Appraisal

Only a presentation is available with minimal information on the trial, full critical analysis is not possible. The information has not been peer reviewed.

The author is a paid presenter for Bard Access Systems, and this is clearly stated in the slides. The EAC contacted the author who confirmed that the system used was Sapiens TCS for ECG monitoring, and Sherlock TLS for magnetic tracking. These are earlier versions whose technologies were subsequently combined to give the Sherlock 3CG TCS.

Results

The presentation reports that approximately 5% of patients were not “technically successful”. The reasons given were quoted as:“ could not cannulate vein; could not advance catheter; would not go down with Sherlock II detector; too short; occluded veins”. These patients were excluded from the 63 reported results, where 62/63 were within the accepted tip location. Only 1 was reported as being too short due to a pseudo or accessory SA node.

At the time of the presentation Symington reports a total of 604 PICC placements having been completed using Sherlock TLS / Sapiens TCS, and that routine chest x-rays were no longer required if ECG tip confirmation was used.

3.4.7 NHS Questionnaire 2014

Methodology

For the purposes of this evaluation, the sponsor sent questionnaires to 8 centres (2 centres covered by 1 contact) in the UK that currently use Sherlock 3CG TCS, 6 questionnaires were completed.

Critical Appraisal

Not all the questions were clearly worded, and they have been answered in different formats by different centres making any summation of the numerical results difficult. The information has not been peer reviewed. The sponsor states that the questionnaire was sent to the sites that had been fully trained in the use of Sherlock and that had considerable experience of using the device. Sherlock 3CGTCS is currently used in 14 sites in NHS England and 2 sites in the NHS in Northern Ireland. There was a risk of bias in the responses since not all sites were surveyed, and those with the most positive views may be those with the most experience of using the device. To investigate this, the EAC sent a brief set of questions to the 7 of the remaining 8 sites (one did not have a co-ordinator in post) plus the site who had not responded to the sponsor. The 6 responses received are summarised in table 9.

The sponsor reports that 9 sites have discontinued the routine use of chest x-ray confirmation, where Sherlock ECG TCS is used for PICC placement. The EAC was only able to confirm 6 of these from the sponsor questionnaires and EAC questions due to missing data.

Results

The results are presented in full in table 10. Due to different interpretations of the questions and the variation in services and protocols it is not meaningful to aggregate the responses, however they do highlight the wide variety of different practices that occur across the UK. Actual variation will be even greater since the responses are from services that are already set up in such a way that utilising Sherlock 3CG TCS fits into their practice.

All 6 responses had nurse-led PICC placement services and previously used chest x-ray to confirm PICC tip location. When asked the number of malpositions prevented by using Sherlock 3CG TCS 5/6 gave a positive number, 1/6 did not respond. The numbers cannot be interpreted with confidence since the question is not clear if these should be reported on a per week basis, or since starting to use Sherlock 3CG TCS.

For repositioning if the tip is too long (judged by chest x-ray) 5/6 sites said they pulled back the PICC to the correct length, 1/6 did not respond. 2/6 said that they would carry out a repeat chest x-ray, 2/6 did not mention using a repeat chest x-ray and 1/6 would sometimes x-ray again.

When the tip is malpositioned in the internal jugular vein, contralateral vein, or above the SVC , 3/6 would remove and replace the PICC, 2/6 would wait overnight if the malposition was IJ, and 1/6 would pull the PICC back and use as a midline catheter. Only 1/6 said they would immediately use the fluoroscopy suite (if available)

Table 6 Responses to sponsor questionnaire survey part 1

1. Practice before the introduction of Sherlock 3CG TCS					
Centre 1	**Centre 2**	**Centre 3**	**Centre 4**	**Centre 5**	**Centre 6**
1.1 How is your PICC service currently set up (Nurse/Radiographer/Radiologist/Anaesthetist let, location of PICC service, days you offer service, day case/inpatient)?					
Nurse- led service	Nurse-led with 4 PICC placers	The PICC service runs 5 days a week from 8-4pm. It is a Nurse led service with 99% of all PICCs being inserted by the Clinical Nurse Specialist for Vascular Access. The Consultant Interventional Radiologists provide supportive clinical guidance and assistance should a complication occur. The most common complication was malposition, although in the last 6 months they have not had to reposition any PICCs placed with Sherlock 3CG. The Nurse led PICC service covers every department of the Trust including outpatients, ITU, Oncology, haematology, Parenteral nutrition etc.	Nurse led/ Medical Day Unit's and Minor Procedure Suite/ service Monday to Friday/day case and inpatients	Nurse led 3 days per week both day case and inpatient.	Nurse Led , non-emergency service, 5 days a week
1.2 What was the current method of PICC placement (devices used to aid placement etc)?					
Ultrasound	Ultrasound and micro-introducer	Prior to using Sherlock 3CG PICC lines were placed at the bed side using the site rite and asking the patient to perform placement manoeuvres, tucking chin to the left or right etc. Placement was confirm via a chest x-ray, If the PICC was malpositioned in the IJ or contra laterally then the PICC would be repositioned or reinserted in interventional radiology with fluoroscopy by the CNS for vascular access or by an Interventional radiologist.	Siterite5 Ultrasound and MI kit for upper arm placement	Currently using Sherlock 3CG	Upper arm placement using Ultrasound
1.3 What was the current method of PICC tip confirmation?					
Chest X-ray	CXR	CXR	CXR	CXR	CXR

1.4 How many patients in last 12 months prior to Sherlock 3CG TCS had delay in their treatment waiting for a confirmation X-ray?					
1.4a Number of patients					
All patients had PICC insertion prior to admission for Rx	As we place next to the x ray department this is difficult to estimate as our CXR's are done quickly. We do get a regular delay of an hour wait each Monday as we place just prior to lunch which frequently means that x ray is closed over lunch. Patients are booked closely together which means that we have to wait for the CXR before starting the next patient this can be an additional 15minutes on each PICC placement	425	30	N/A as still training, however no overwire changes or re CXR required. still able to use Sherlock 3cg with patients that have cardiological morbidity e.g. atrial flutter pacemaker.	none
1.4b Average wait time (hours)					
No response	No response	1 hour	2	Sending pts to x-ray knowing tip is down	No response given
1.4c minimum wait time hours					
No response	No response	20 mins	0.5	Sending pts to x-ray knowing tip is down	No response given
1.4d maximum wait time hours					
No response	No response	48 hours	6	Sending pts to x-ray knowing tip is down	No response given
1.5 What was your procedure for PICC malposition (malposition defined as PICC in IJ / contra lateral vein / above SVC)?					

Removal of the PICC and a new line placed	We bring the patient back into the PICC room and try and reposition the picc then do a second cxr. If the picc is still in the incorrect position for instance IJ then we would pull the PICC and go to the opposite arm or refer for a tunnelled line under fluoroscopy.	The PICC would be adjusted or re-inserted in the Fluoroscopy suite if one was available. If Fluoroscopy not available, the PICC would be left unused for up to 12hours and re-x-rayed, if the PICC was still in the wrong place an fluoroscopy suite would be sought again and the PICC reinserted, if fluoroscopy unavailable still, the PICC would be removed and re-insertion rescheduled with fluoroscopy.	IJ- leave in overnight and check X-Ray the next day. Contralateral- remove and replace. Above SVC- over guidewire exchange.	Await 24hours and re xray if IJ, alternatively overwire change, new procedure, then cxray if still misplaced referred skin tunnelled line.	Pull back PICC to use as midline
1.6 Please indicate the number of patients (or %) with the following					
1.6a PICC in IJ					
2%	40% including poor position in SVC and PICC in IJ	10%	7	15	4
1.6b PICC in contralateral vein					
0.50%	No response	1%	1	0	No response
1.6c PICC above SVJ					
10%	40% including poor position in SVC and PICC in IJ	5%	3	2	no response
1.7 What was your procedure for PICC repositioning when Chest X-ray confirms PICC tip is too long?					
Pull back the line and re-X-ray	We are able to measure on the CXR and pull back the amount needed. If over 5cm then we do a second CXR	The PICC would be measured on the X-RAY and pulled back accordingly, this would be documented and them the PICC could be used.	Pulled back to suggested length, sometimes re-x-rayed	67	Ward nurses pull back PICC
1.8 What patient demographic do you place PICC for (disease area only)?					
Malignant and non-malignant Haematology as well as oncology	Oncology and Haematology	Oncology, Breast CA, Haematology, Respiratory, Gastroenterology, ITU (single and multi-organ failure), CFU, Paediatrics, ambulatory care, orthopaedic bone infections, surgical site infections, Parenteral Nutrition, All patients who require vascular access and fulfils the criteria for PICC insertion.	Cancer	Oncology haematology, parenteral nutrition, long term iv antibiotics.	Oncology , haematology , antibiotics, access
1.9 What was your hospital policy for PICC confirmation? Please attach a copy or paste a link below, if appropriate					

No response	We aim to place picc in the low svc	The picc line was considered safe to use if the tip of the picc was placed in the lower 3rd of the svc, or 5cm below the carina.	Patients must not be discharged back to the ward until a post-procedure check cxr has been reviewed by the individual who performed the procedure. The tip of a cvad should be verified on chest x-ray prior to use and the exact location of the tip documented in the medical notes.	Cxr	Vascular access nurses check tip placement after achieving competencies, and irmer course

Table 7 Response to sponsor questionnaire survey part 2

2. Placing PICCs without Sherlock						
	Centre 1	**Centre 2**	**Centre 3**	**Centre 4**	**Centre 5**	**Centre 6**
2.1 Average number of PICCs placed (BEFORE Sherlock 3CG; Quantity per week)	4	650 PICCs per year	9 PICCs per week between April12 and April13	12	296 per annum	21.9
2.2 Malpositions (quantity in 12 months)*	30	Estimated total of 40%				No response
2.2a PICC in IJ	No response	No response	42/425	7	15	No response
2.2b PICC in contralateral vein	No response	No response	4/425	1	0	No response
2.2c PICC above SVC	No response	No response	21/425	3	2	No response
2.2d PICC length too long	No response	No response	62/425	28	67	No response

2.3Average wait time for confirmation X-ray in hours	1	We have a minimal wait for CXR as PICC room placed next to CXR	1 hour	30-60 mins	1-4 hours	No response
2.4 Repositioning tip position after X-ray (quantity in 12 months)	20	No response	108/425	28	82	No response

* these questions were also asked in section 1.6, and answered by more respondents

Table 8 Response to sponsor questionnaire survey part 3

3. Placing PICCs with Sherlock 3CG						
	Centre 1	**Centre 2**	**Centre 3**	**Centre 4**	**Centre 5**	**Centre 6**
3.1 a Quantity of PICCs placed to date with Sherlock3CG	25	100+	217	460	50	56
3.1b PICC placement using Sherlock - no per week	5 to 6	10 to 15	10	15	12	1.5
3.1c Malpositions quantity	No response	No response		16		No response
3.1d PICC in IJ	No response	None	None	4	0	No response
3.1e PICC.in contralateral vein	No response	None	None	1	0	No response
3.1f PICC above SVC	No response	None	None	0	0	No response
3.1f PICC length too long	1 (p wave not consistent, so wasn't appropriate for Sherlock)	None	None	4	0	No response
3.1g Quantity of malpositions prevented with Sherlock 3CG? (Number)	9	20 (see additional data)	217	16	10	No response
3.1h Repositioning after chest X-ray (Number)	1 (see 3.1f)	None	None	4	0	No response

3.1j After how many piccs placed with Sherlock 3CG did you stop using confirmation X-ray?	Not happened yet	Still using CXR	The first 100 x-rays have been used to verify Sherlock 3CG.	330	Currently still using both during training	No response
3.1k If you are still using confirmation x-ray after how many PICC placements do you plan to stop? (Number)	35	Yes (number not provided)	Waiting for the final sign off of the first 100.	N/A	100	No response

Table 9 Reponses to EAC questions

Brief questions sent by EAC to NHS sites using Sherlock 3CG TCS who had not received sponsor questionnaire					
Centre A	**Centre B**	**Centre C**	**Centre D**	**Centre E**	**Centre F**
1. How long has Sherlock 3CG TCS been used at your site?					
Since 01/04/14.	Since 10th March 2014.	Since April 2013	Since March 2014.	Since April 2013	Since Jan 2014
2. Has training been completed yet for staff who use Sherlock 3CG TCS?					
5 staff have now reached competency and practicing without supervision.	Yes training has been completed with the exception of one staff member who was off on leave but will have training completed by September.	Training completed within 2 weeks of commencing use although all our placers were already very experienced	There are 2 nurses who are now competent in using the SHERLOCK and 1 who will be soon.	Training has been completed for all 6 staff in the department who use Sherlock 3CG TCS	Yes
3. Approximately how many PICC procedures (in-patient and out-patient) have been carried out at your site using Sherlock 3CG TCS?					
235 lines have been placed in our outpatient oncology service and 150 lines in our inpatient service using the Sherlock 3CG TCS. Both are nurse led services.	81 PICC procedures have been carried out to date.	1185	Approximately 150 since March 2014.	1359 PICC procedures (in-patient and out-patient) have been carried out at our site using Sherlock 3CG TCS	Approx 35

4. Are chest x-rays routinely used with Sherlock 3CG TCS to confirm PICC placement at your site?					
No. We only perform CXR to confirm Tip position on those patients that have AF or if there is any query/concern that the tip may not be in the correct position.	Currently an audit is being carried out with chest x-rays being used with Sherlock 3CG to confirm tip placement but it is hoped that we will stop using chest x rays in the near future.	Yes	We used chest x-rays for the first 40 to ensure the nurses were competent in placing with the ECG. We use x-rays if we are uncertain of the tip position but this is minimal.	Chest x-rays are not routinely used with Sherlock 3CG TCS to confirm PICC placement at our site. A chest x-ray will only be performed if a P wave is not evident.	Yes
5. Do you have any comments to make about Sherlock 3CG TCS and your experience of using it?					

We believe that the Sherlock 3CG TCS is a reliable way of confirming a PICCs position within the SVC. It enables the inserter to visually direct the line using the magnetic navigation system and then double check this by utilizing the ECG confirmation system. However what is essential is that the inserter is properly trained in the use of the system and recognises its limitation and is fully aware of when a chest X-ray is required for confirmation. Bard do offer a comprehensive training program and work very closely with each individual trainee to ensure that competency is achieved. I strongly believe that this training is equally as important as the technological advancement that this system offers.	Absolutely love the new technology and look forward to learning more and becoming more confident in using this latest piece of equipment.	Our thoughts about it are covered in the discussion of our Anaesthesia paper (Johnston et al, 2014)	The use of SHERLOCK enables a relatively comfortable procedure as many are done at the bedside, family can stay with them. A comment from a patient was “Why does it take a doctor and 2 nurses in Interventional radiology and you manage on your own?” Clinic patients (usually oncology) are relieved they don’t have to go for x-rays as there can be a wait involved.	Our experience to date about Sherlock 3CG TCS has been very positive. It is a very accurate system that streamlines the PICC insertion process	The only issue I would have is that you have to switch off all the plugs around the site to stop electrical interference. That is the only issue I have.

3.5 Overview and critique of the sponsor's critical appraisal

The sponsor only included four conference abstracts for the clinical evidence submission. The sponsor attempted to perform a critical appraisal of each conference abstract, in accordance with the submission template, using an adapted Critical Appraisal Skills Programme (CASP) checklist. Critical appraisal of conference abstracts cannot be undertaken if insufficient detail is reported within abstracts.

3.6 Results summary

The results from section 3.4 are summarised in table 10 for each study.

Table 10 Key outcomes from studies

Study	Country	Review of PICC	Number of PICCs placed using ECG	Acceptable position stated	Number of PICCs placed using ECG that were in acceptable position judged by x-ray	Number of PICCs placed with Sherlock that could obtain ECG placement
Included by Sponsor						
Barton 2014, abstract + additional information from author	UK	x-ray with review by independent consultant chest physician	65 assessed in initial study period and 225 in total before x-ray was discontinued	Lower 1/3 of SVG or CAJ	100%	During trial 2 patients required fluoroscopy for placement.
Adams 2013, abstract and poster	USA	Review of x-ray by a second radiologist	333	Distal SVC or CAJ	96.4% on 1st review 98.2% on 2nd review	16.5% were not able to confirm tip placement using Sherlock
Stewart 2013 abstract and poster	Australia	Unknown	"over 65"	Unknown	96% within CAJ, 4% within RA	Not reported
Parikh 2013 abstract and poster	USA	Chest radiograph assessed by 2 independent assessors	247 PICCs, 221 Patients Phase 1: 62 included, 3 excluded Phase 2: 147 included, 35 excluded	SVC or CAJ	Phase 1: 83% correct Phase 2: 96%	2012-2013: 567 PICCs placed 437 using Sherlock 3CG TCS 109/437 required x-ray (25%)

Study	Country	Review of PICC	Number of PICCs placed using ECG	Acceptable position stated	Number of PICCs placed using ECG that were in acceptable position judged by x-ray	Number of PICCs placed with Sherlock that could obtain ECG placement
Additionally included by EAC						
Johnston 2014 peer reviewed paper	UK	Chest x-ray reviewed by two independent assessors	239 PICCs. From initial 250, 11 excluded:	C1: low SVC or CAJ (based on American practice) C2: mid/low SVC, CAJ or high RA (based on preferred UK practice)	Criteria 1: 134 catheters (56.1%; 95% CI 50–62%) were malpositioned. Criteria 2: 49 catheters (20.5%; 95% CI 16–26%) were malpositioned.	250 PICCs reviewed, 11 excluded: • failed insertions (2); • no chest radiograph after procedure (2); • not possible to determine tip position chest radiograph (2); • unable to interpret ECG criteria(4); • and catheter not long enough for adequate insertion length (1).
NHS Questionnaire from sponsor	UK	Chest x-ray, reviewers unknown	Various	Not stated	Various,	
Symington 2011	USA	By author	63 during study	Sweet Spot, as defined by author	98.4% (62/63)	reported that about 5% of attempts were not successful

3.7 Description of the adverse events reported by the sponsor

The sponsor found no adverse events reported in any studies, or in the publically available search of the MHRA website, and the EAC agree with this finding.

The sponsor searched FDA (MAUDE) using the search terms Sherlock 3CG or Sapiens and retrieved 51 records. The sponsor did not provide details of these records, but commented that they were not necessarily device-related complications or adverse events.

The EAC replicated the search, but using the terms Sherlock AND Bard or Sapiens AND Bard. We retrieved a total of 100 records. The EAC did not carry out any search for other types of PICC insertions and therefore the comparable rate of adverse events for blind PICC insertion with chest x-ray is unknown. The adverse events reported may be common to all types of PICC insertion.

The FDA (MAUDE) data base details reports of device adverse events as they are submitted, in some cases the manufacturer will respond to the report. There is no mechanism for verifying reports, or ensuring details are entered correctly and that they are not duplicated.

There were a number of event types that appeared repeatedly, and the EAC has attempted to summarise these in table 11. The events are summarised based on the descriptions submitted to FDA (MAUDE) and have not been verified in any way, they may be events that are common to other types of PICC line insertion.

There were 29 occasions reporting the wire tip or stylet being broken or damaged during use. Sherlock 3CG TCS instructions for use state that the stylet should be positioned just inside the tip of the catheter to avoid damage to it.

On 23 occasions adverse patient reactions were noted, these were usually during the insertion process and resolved with minimal intervention and a small delay to allow patient recovery. Typical symptoms appeared to be shortness of breath and a flushed face. Treatments included administration of oxygen or anti-histamine.

There were 18 cases of catheter malfunction reported. These included 14 reported leaks, splits or holes plus one blockage, one insertion failure and two cases of knots in the PICC.

Malposition of the PICC tip was reported in 14 cases. It appears that some of these may be problems during initial positioning, and some may have either been detected subsequently or have occurred subsequently due to PICC movement. There is not enough information reported to draw any further conclusions.

Table 11 Adverse events related to versions of Sherlock, reported in MAUDE

Description of reported adverse events	Number of records
Wire tip or stylet broken or deformed during use, no long term complications reported.	29, of which 21 stated that intervention was required.
Patient reaction, no long term complications reported.	23
Catheter malfunction	18, of which 1 event resulted in a patient developing sepsis
Malposition	14
Packaging	1
Unclear	3
Repeat reporting	11
Irrelevant report	1
Total	100

3.8 Description and critique of evidence synthesis and meta-analysis carried out by the sponsor

No evidence synthesis or meta-analysis was carried out. This was appropriate for the evidence available.

3.9 Additional work carried out by the External Assessment Centre in relation to clinical evidence

EAC literature search

The EAC conducted an independent search for clinical and economic evidence relevant to the scope. The methods are presented in Appendix 1. Briefly, we searched the following sources: Medline, Medline In-Process, Embase, The Cochrane Library, HEED, EconLit, Web of Science, National Technical Information Service database, NHS Evidence, Pubmed, Cost Effectiveness Analysis registry, EconPapers, International Clinical Trials Registry Platform, Clinicaltrials.gov, MAUDE, MHRA and EMA. In addition, citation tracking of relevant studies was performed in either Web of Science or Google Scholar and the reference lists were checked for other relevant publications. Both these steps were also carried out for the sponsor's included studies. Figure 4 shows the EAC's study selection process.

In the light of the small quantity and low quality of evidence available, the EAC widened the scope to include previous models of the device that included both magnetic tracking and ECG tip confirmation.

The EAC included:

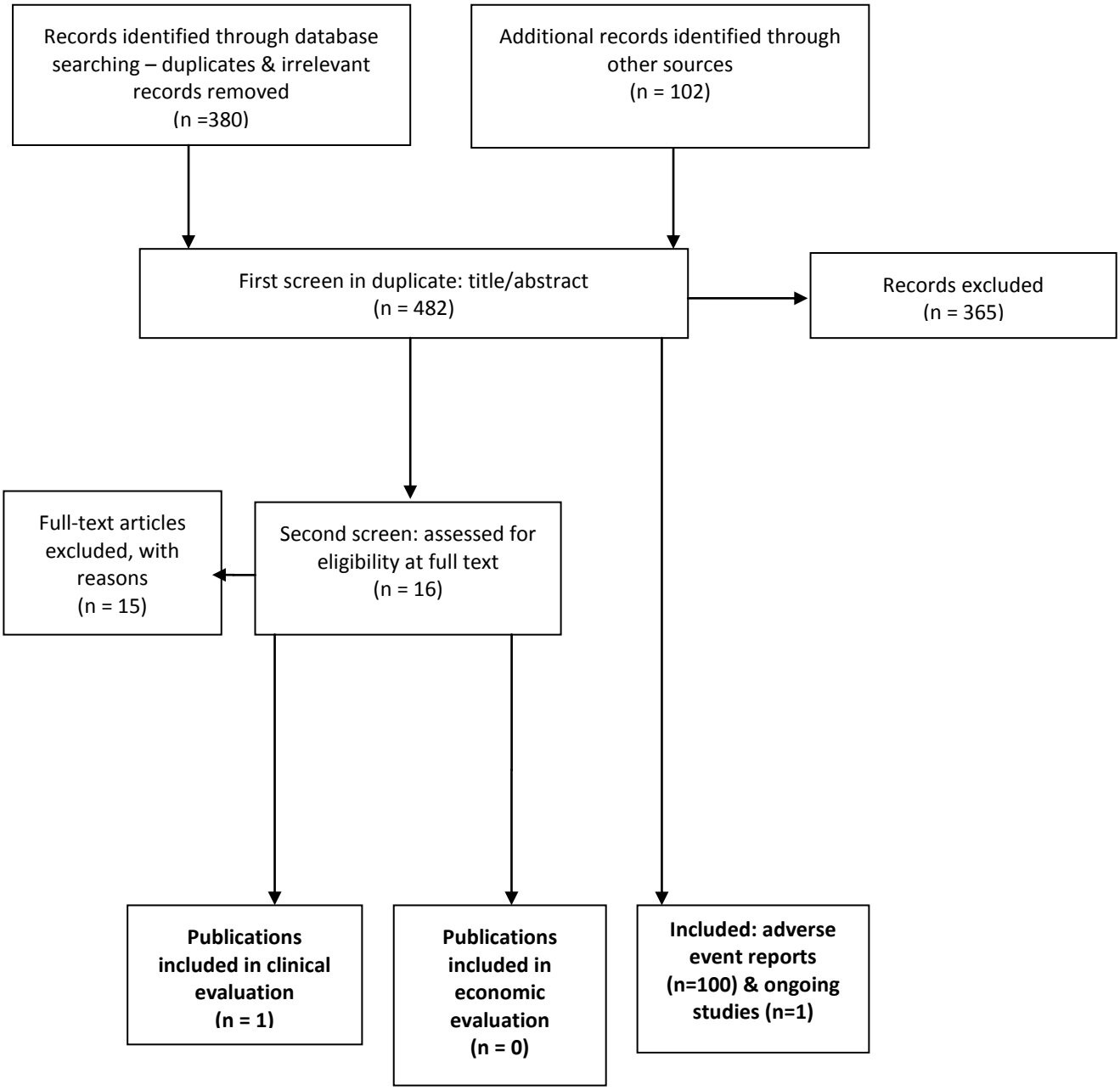
- 5 clinical studies: Adams 2013, Barton 2014, Johnston 2014, Parikh 2012, Stewart 2013, Symington 2011
- NHS Questionnaire
- 100 adverse incident reports
- 1 ongoing study

The EAC contacted authors Barton, Johnston and Symington for additional information. In addition the EAC attempted to contact authors of abstracts identified by the EAC literature search as possibly relevant, however this was not successful.

The EAC requested information from NHS sites using Sherlock 3CG TCS and compiled responses.

The EAC requested information from the sponsor concerning the claim on their website of "In a clinical study, 99.1% of 114 PICCs were placed at the CAJ or within +/- 1 cm using Bard® Tip Confirmation Technology". This was based on a paper by Pittiruti et al (2012) which looked at a number of devices to confirm PICC tip location using ECG, including Sapiens TCS. The sponsors had analysed the subset of patients where Sapiens TCS was used to obtain this result. Sapiens TCS does not include a magnetic tracking component, and Sherlock II TLS (or equivalent) was not used with Sapiens TCS, therefore information from this study was not included. The EAC have not carried out any critical analysis of either the paper by Pittiruti et al. (2012), or the information from Bard taken from this study. The study was not included in the manufacturer submission.

Figure 4 EAC's study selection flowchart



3.10 Conclusions on the clinical evidence

3.10.1 Completeness of sponsor's submission

The sponsor identified and included all relevant evidence, however there were no details of the one full peer-reviewed paper (Johnston et al, 2014) due to its availability the day prior to the sponsor's submission.

The sponsor sent 7 questionnaires to NHS sites that use Sherlock 3CG TCS, however the variability of service provision between the sites makes it impossible to draw any conclusions from the data. The questionnaire and subsequent correspondence with additional sites shows that several sites have now proceeded to use Sherlock 3CG TCS without requiring routine chest x-rays to confirm tip placement.

The only available evidence is from case studies reporting the accuracy of PICC placement judged by chest x-ray for PICCs that were placed using Sherlock 3CG TCS. There is no comparative evidence for either blind PICC placement using chest x-ray or PICC placement using fluoroscopy.

None of the available evidence looks at the consequences of malpositioning, either in terms of necessary interventions to correct it, or adverse events. There is no follow up of patients reported after tip position confirmation by chest x-ray.

3.10.2 Sponsor interpretation of clinical evidence

The sponsor reported that the studies found that Sherlock 3CG TCS is an accurate method of placing PICCs and confirming the final tip position; that it is time saving compared to the use of chest x-ray; safe to use and not associated with any adverse effects or complications.

Although the sponsor looked at all available evidence, the quality was extremely poor and it is impossible to draw a strong evidence based conclusion. All evidence submitted was broadly in favour of Sherlock 3CG TCS improving tip location accuracy, as were the NHS sites contacted by both the sponsor and the EAC. The lack of comparative evidence, and the poor reporting of existing studies means that we cannot tell the extent of the improvement in PICC positioning that is due to use of Sherlock 3CG TCS.

4 Economic evidence

4.1 Published economic evidence

4.1.1 Critique of the sponsor's search strategy

The strategy has been assessed in accordance with the PRESS checklist (Peer Review of Electronic Search Strategies). The search strategy used by the sponsor is comprehensive using a range of Subject Headings and free-text terms together with Boolean and proximity operators. The free text terms cover instances where specific device names have been reported in the title and abstract as well as those instances where the technology is not specified. The index terms have been mapped to the various databases. The sponsor limited the search to 'English language' and to studies published in the year 2000 or later. These are appropriate limits in that studies identified would be applicable to patients in England and cover the periods when the technology was launched.

The following databases and websites were searched:

- MEDLINE (1946 to present) and MEDLINE In-Process via OvidSP
- EMBASE (1974 to 2014 July 02) via OvidSP
- Econlit (1886 to May 2014) via OvidSP
- NHS Economic Evaluation Database (Issue 2 of 4, Apr 2014) via Cochrane Library/Wiley Interscience
- Health Technology Assessment Database (Issue 2 of 4, Apr 2014) via Cochrane Library/Wiley Interscience
- Health Economic Evaluations Database via EBSCOhost
- CEA (Cost-Effectiveness Analysis) Registry via https://research.tufts-nemc.org/cear4/Home.aspx
- ClinicalTrials.gov via https://clinicaltrials.gov/ct2/home
- International Clinical Trials Registry Platform (ICTRP) via http://apps.who.int/trialsearch/
- metaRegister of Controlled Trials (mRCT) via http://www.controlled-trials.com/mrct/
- Conference Proceedings Citation Index- Science (CPCI-S) - 1990-present via Web of Science

The sources searched provide good coverage of likely published and unpublished evidence and included searches for conference abstracts, via Conference Proceedings Citation Index and websites of key conferences, and ongoing trials. In addition, websites of key relevant organisations, a search of Google and communication with Bard were also conducted.

4.1.2 Critique of the sponsors study selection

A flow diagram of study selection was clearly presented in the sponsor's submission, and the EAC believes that this was appropriate.

4.1.3 Included and excluded studies

The sponsor's search identified 13 records for full text scrutiny, but 11 of these were excluded and reasons given.

The EAC did not find any additional economic studies that should have been included by the sponsor.

4.1.4 Overview of methodologies of all included economic studies

Two economic studies (Adams 2013 and Stewart 2013) were included by the sponsor. Both were poster and abstract and included simple cost comparisons between ECG tip location and blind insertion with x-ray confirmation.

The Adams (2013) study was set in the USA and included 333 PICC placements. Sherlock 3CG was used in 83.5% of these and in the remainder there was either unusable ECG (12.9%) or the Radiologist said the PICC was improperly placed (1.8%) or the radiology decision was reversed after review by a second radiologist (1.8%). The costs included PICC insertion kits, X-ray including radiologist time, capital cost of Sherlock 3CG and the costs of repositioning mal-positioned PICCs. The analysis showed a cost saving for Sherlock 3CG of US$82.57 per PICC (=£54.50)(www.oanda.com rate for July 1 2013).

The Stewart (2013) study was set in Australia. The authors reported that 'at least 65 patients were included' and that 96% of ECG guided placements were successfully positioned within the cavo-atrial junction based on chest x-ray, while 4% were placed in the right atrium. The costs included the PICC placement pack, x-rays including radiologist time to read the x-ray, time to correct malpositioned PICCs. The analysis showed a cost saving for 800 PICCs per year of AUS$314,400 (= £188,640) or AUS$393 per PICC (=£235.80) (www.oanda.com rate for July 1 2013). This cost saving is heavily influenced by the assumption that 50% of the PICCs placed without Sherlock 3CG TCS would need a second x-ray and this would lead to an additional day in hospital. Without this assumption the cost saving would be AUS$93 (=£55.80)

4.1.5 Overview and critique of the sponsor's critical appraisal for each study

The sponsor completed a quality assessment on the selected poster and abstract publications and found that both studies were low quality cost-comparison studies based outside the UK. The sponsor concluded that the studies were of limited relevance and had methodological limitations making them unsuitable for the decision problem. The EAC agrees with the sponsor that there is limited value in the studies.

4.1.6 Does the sponsor's review of economic evidence draw conclusions from the data available?

The sponsor proposed that a de novo model is required because only low quality published studies from non-UK settings were identified. The EAC supports this decision.

4.2 De novo cost analysis

4.2.1 Patients

The population defined in the scope is 'adult patients undergoing PICC insertion'. The sponsor has included in the de novo model 'adults undergoing PICC insertion who do not have medical conditions that contraindicate them for insertion with Sherlock 3CG TCS'. This is a deviation from the scope, and patients not suitable for Sherlock 3CG TCS will still need to have the PICC inserted by some other means. This is inconsistent with the scope in the sponsor's clinical evidence submission. An economic model from the perspective of the NHS and PSS should include all patients undergoing PICC insertion. For the Sherlock 3CG TCS pathway, patients not suitable for insertion guided by Sherlock 3CG TCS should be included by adding costs of standard insertion for the proportion of the cohort not suitable for Sherlock 3CG TCS.

4.2.2 Technology

The technology in the scope is 'Sherlock 3CG TCS tip confirmation system' and the sponsor has developed the model in accordance with this.

4.2.3 Comparator(s)

The sponsor's model is based upon two comparators as given in the scope

- Blind bedside placement with confirmation x-ray and
- Fluoroscopy to guide PICC insertion and confirm tip placement.

The sponsor did not present any evidence in the clinical section of the submission in which Sherlock 3CG TCS was used in place of fluoroscopy guided PICC placement.

4.2.4 Model structure

The model is a decision tree with four main branches:

1) bedside PICC placement with Sherlock 3CG TCS with confirmation x-ray

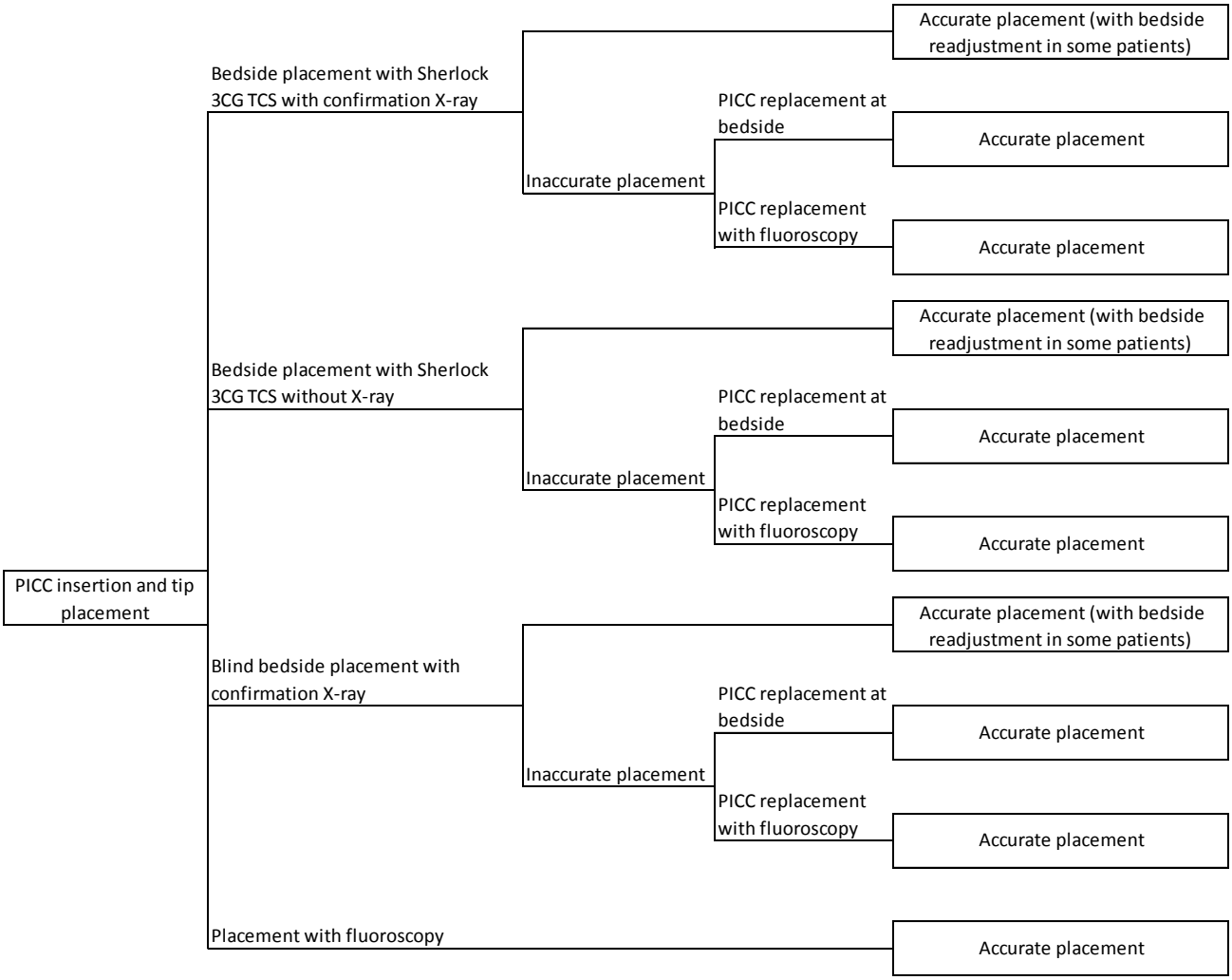
2) bedside PICC placement with Sherlock 3CG TCS without x-ray

3) blind bedside placement with x-ray

4) placement with fluoroscopy

The decision tree is illustrated in figure 5 taken from the sponsor's submission.

Figure 5 Decision tree for the sponsor's model



Placement with fluoroscopy is assumed to be accurate. In each of the other options the PICC is either placed accurately (with re-adjustment in some patients) or for inaccurate placement there are two options for re-placement of the PICC

- PICC replacement at the bedside using the original insertion method
- PICC replacement with fluoroscopy (base case).

All patients are assumed to complete the model with an accurately placed PICC.

For patients in the Sherlock 3CG TCS without x-ray branch it is not logical to include misplacement in the sponsor model which has a short time horizon up to the point of PICC placement. If the ECG confirms correct placement, there is no additional process to confirm tip location and the centres would assume accurate

positioning. The sponsor has included this based upon the published abstract data in which there was a comparison with the chest x-ray, usually while the technology was being introduced to the service.

If ECG confirmation is not possible while using Sherlock 3CG TCS, then the PICC would be placed using magnetic tracking and anatomical landmarks, and a chest x-ray used for tip confirmation.

The PICC re-placement with fluoroscopy may not be appropriate as a base case, since the sponsor's clinical adviser indicated that the normal re-placement procedure would be standard PICC insertion with x-ray confirmation. However there appears to be diversity of practice and fluoroscopy may be used for replacement PICCs in some areas. The sponsor stated that fluoroscopy as the re-placement method is conservative, but this is incorrect since the model requires a greater number of re-placements for the comparator technologies and fluoroscopy is the most expensive option. The sponsor has included an option in the model for re-placement at the bedside using the original insertion method, with x-ray.

4.2.5 Clinical parameters and variables

The time horizon used in the model was the period up until accurate PICC placement was achieved. It would have been better to have longer term follow up of patients to include actual numbers of repositioning or replacement, consequences of inaccurate placement or adverse events, but no evidence or data was available for this. Because of the short time horizon discounting is not applied and this is appropriate.

Clinical data was taken from four published studies Adams (2013), Barton (2014), Parikh (2012) and Stewart (201), but data from Johnston et al. (2014) was not included in the model. The sponsor stated this was because 'the proportion of patients specifically requiring reinsertion was not reported'. This is not a good reason to exclude the only full peer-reviewed paper available and the included abstracts and posters do not clearly report the proportion of patients specifically requiring reinsertion. The sponsor points out that in the Johnston et al. (2014) paper all patients were critically ill in intensive care units and included all patients who required PICC insertion, regardless of whether they were suitable for insertion using Sherlock 3CG TCS. The EAC considers that the critical care group is an important group and could be treated as a sub-group or included in sensitivity or scenario analysis based upon the data from the Johnston et al. (2014) paper. Patients receiving chemotherapy could also be considered as an important subgroup were evidence available.

Only intermediate clinical outcomes (accurate placement based on chest x-ray) were used in the model because no studies reported final clinical outcomes. The outcomes used in the model were determined retrospectively in the publications by reading chest x-rays taken after placement. None of the studies followed patients up and determined what actually happened to the patients, so it is not known how many of the misplaced catheters identified on x-ray were adjusted, removed and replaced or left in place, nor whether there were any clinical sequelae.

4.2.6 Model assumptions

In the submission the sponsor has listed 15 assumptions of the model. These are listed in table 12 below with accompanying EAC comments.

Table 12 Assumptions listed by the sponsor with EAC comments

Assumption listed by sponsor in submission	EAC comments	Impact on model
The time taken to achieve successful placement with Sherlock 3CG TCS is equal to the time for successful placement at the bedside without the technology.	The EAC agrees with this assumption, but this does not match the inputs in the model. The same nurse times were used for Sherlock with x-ray and blind placement, but a shorter time was used for Sherlock without x-ray. The staff time taken for the x-ray is accounted for separately.	Significant impact Model inputs favour Sherlock 3CG TCS without x-ray.
The sponsor has clarified that the assumption above **should read "The time taken to achieve successful placement with Sherlock 3CG TCS *with x-ray* is equal to the time taken for successful placement at the bedside without the technology."**	This now matches the input in the model, and is a reasonable assumption. However the EAC still believe that there is no valid reason to assign a shorter nurse time to Sherlock 3CG TCS ***without x-ray***. It is plausible that the patient pathway might be shorter, however the time for insertion of the PICC will remain similar. The cost of x-ray (including radiologist time) is costed separately (both in the model and in the data source (Walker et al. 2013).	As above
There is no benefit to patients resulting from more rapid PICC line placement with Sherlock 3CG TCS in the scenario where no confirmatory x-ray is required. This is a conservative assumption as there may be benefit to some patients of receiving required drugs sooner.	In a cost-consequences approach the clinical benefits are not included in the cost model. Final clinical outcomes are not included in the time horizon of the model.	Model is appropriate
X-rays are assumed to read with 100% accuracy, meaning that no consequences of misread X-rays are captured in the model. This assumption was made as the clinical evidence did not provide information on the consequence of misread X-rays.	The model is based on intermediate outcomes (accurate PICC placement) and a short time horizon. The clinical consequences of misplaced catheters not identified on x-ray or by ECG confirmation are not considered in any branch of the model.	Model is appropriate, as there is a lack of clinical evidence to do otherwise.
All model inputs are the same for bedside insertion with Sherlock 3CG TCS with X-ray and bedside insertion with Sherlock 3CG TCS without X-ray, with the exception of the initial cost of PICC insertion and tip placement.	There is no rationale for a difference in the initial cost of PICC placement using Sherlock with and without x-rays. The only difference should be the cost of the x-ray and a proportion of re-insertions for the x-ray branch only.	Significant impact, due to different nurse times used. Model inputs favour Sherlock 3CG TCS without x-ray.
Reinsertion of PICC lines following failure with other methods (bedside placement with Sherlock 3CG TCS (with or without X-ray) or	The EAC agrees it would be unreasonable to add an overnight stay for reinsertion by fluoroscopy,	Model is appropriate

blind bedside placement with X-ray) does not involve an additional overnight stay in hospital. This is a conservative assumption as more patients in the bedside placement arm without Sherlock 3CG TCS require reinsertion due to higher failure rates and could therefore incur additional costs due to potential overnight stays.	or any other method. There is no evidence for this.	
Where insertion with Sherlock 3CG TCS is unsuccessful reinsertion is assumed to take place with fluoroscopy. Clinical advice has indicated that in some cases patients may have reinsertion at the bedside (with X-ray), however as the cost of bedside placement is lower than fluoroscopy (and still effective in around 93% of patients at first insertion attempt) using the cost of fluoroscopy insertion in the model is a conservative assumption.	The EAC agrees with the clinical adviser that reinsertion is unlikely to be fluoroscopy-guided for most settings, but there is variation in practice. We disagree with the assertion that using fluoroscopy for re-insertion is conservative because in the model more patients in the comparator (blind x-ray) have re-insertion than in the Sherlock 3CG TCS arms. The sponsor has considered bedside placement for re-insertion in sensitivity analysis but only for the Sherlock 3CG TCS branches of the model.	Significant impact Model favours Sherlock 3CG TCS.
Costs other than those included are assumed to be the same for Sherlock 3CG TCS and the comparators.	There is an underlying assumption that centres have a bedside PICC service in place, as the costs of setting up a new service are not included. If the comparator is fluoroscopy guided PICC insertion this assumption may not be valid. As set-up costs (for example employing new nurses) are specific to local circumstances the EAC has not explored this further.	The existing model may favour Sherlock 3CG TCS compared to fluoroscopy for a short term outlook.
The cost of an X-ray for placement with Sherlock 3CG TCS (table C6) is assumed to consist of the time cost of the radiographer (i.e. no equipment costs) as is the case in the cost analysis conducted by Walker *et al.* The cost for X-ray is not listed within NHS reference costs due to the high volume and low cost nature of the procedure. A NHS Scotland cost for X-ray was identified (£54.79); however this cost includes a number of radiological procedures and is likely to be an overestimation (ISD Scotland, 2013). Therefore, to ensure consistency between the treatment and comparator only the staff cost has been included.	This is a conservative assumption. The EAC has found some alternative costs for a chest x-ray ranging from £13.33 to £49.09 (Khan et.al 2008,Beavan et. al. 2010)and this input was explored by the sponsor in sensitivity analysis.	Model is appropriate
It is assumed in the base case that 3 nurses are trained per Sherlock 3CG TCS device. This is explored in the sensitivity analysis.	This is a reasonable assumption.	Model is appropriate
The cost of an ultrasound scan used in the micro costing all PICC placement (table C6	This is a reasonable assumption.	Model is appropriate

and C7) was assumed to be equivalent to the NHS reference cost for diagnostic imaging cost for anaesthetics (RA23Z: Ultrasound scan, less than 20 minutes). The ultrasound required to locate the vein in PICC placement will be short and of a small area, therefore this cost was judged to be most appropriate.		
Complications occurring post PICC line insertion, such as infection, were not included within the model and are therefore assumed to be equal for each comparator. Walker *et al.* state that infections should not occur if staff and patients are educated on the best ways to minimise infection risk. Therefore, it was judged there are confounding factors influencing infection rates (aside from the method of PICC tip placement).	Complications may be linked to mal-positioning of the PICC resulting in e.g. catheter dysfunction or may be asymptomatic in the short term. Lack of data on the final clinical outcomes is a weakness.	Possible impact, but lack of evidence means the direction is unknown. Not possible to include in model.
Device risks are not included within the model and are therefore assumed to be equal for each comparator. These were not included within the clinical evidence.	Adverse events may be listed on FDA Maude, but this does not give rates of adverse events. There is no reliable data on adverse events to include in the model.	Possible impact, but lack of evidence means the direction is unknown. Not possible to include in model.
Within the model it is assumed that nurses and radiologists are trained in PICC line insertion and additional training required relates to learning how to use Sherlock 3CG TCS only.	The model includes a branch for fluoroscopy guided PICC insertion as a comparator. If a service changed from fluoroscopy guided PICC to Sherlock 3CG TCS at the bedside, there would be additional set-up costs to train the PICC teams. These are not included in the model. As the set-up costs (for example employing more nurses) are site specific the EAC has not explored this further.	The existing model may favour Sherlock 3CG TCS compared to fluoroscopy for a short term outlook
The Sherlock 3CG TCS device is assumed to either be stored within the ward or department where it is used and therefore time is not spent fetching it. Or, in hospitals running a mobile intravenous service the device will be brought to the ward with the specialist nurse using it meaning no additional time is required to fetch the device. This assumption has been made as in current NHS practice the small device is carried around with the nurse responsible for inserting PICC lines.	This is reasonable for centres already operating a bedside PICC insertion service provision, but not for centres who do not have a nurse led PICC team in place.	The existing model may favour Sherlock 3CG TCS compared to units without nurse led PICC teams.
All other assumptions that have been made to populate model input parameters are specified in tables C5, C6 and C7 (of the sponsor submission).		
Assumptions identified by EAC, not listed by Sponsor	**EAC Comment**	**Impact on model**
All PICCs identified as malpositioned by a retrospective chest x-ray were removed	There is no information about what happened to PICCs that were classified	

and replaced	as malpositioned in any of the evidence. Some may have been left in situ, or pulled back slightly.	
A fluoroscopy service can be compared to a bedside PICC placement service	Where both services are in place in one location then this is reasonable. Where there is no bedside PICC placement service existing, then the cost of changing the service should be considered in the short term.	High impact over a short time period (e.g. 1 year) for sites with no bedside PICC service.
83.5% of patients requiring PICCs would be treated using Sherlock 3CG TCS, the remainder would be treated by a different method, no Sherlock 3CG TCS consumables or devices would be used for them, and they are not costed in the Sherlock 3CG TCS route.	The correct interpretation of Adams (2013) is not clear. The EAC believe that 100% of patients may have been treated with Sherlock 3CG TCS, however ECG tip confirmation technology was not successful in 16.5%. In this case all patients would have used the device and consumables and it should be costed appropriately. If the interpretation is as the sponsor believes, then the cost of treating those not appropriate for ECG tip confirmation should be included in the Sherlock 3CG TCs branch of the model.	Impact is very small if the assumption is made that the remaining 16.5% would be treated with blind PICC placement, and the costs are similar to Sherlock 3CG TCS. If the alternative was fluoroscopy the impact would be greater and make Sherlock 3CG TCS more costly.

It is assumed that the study outcomes based on retrospective analysis of chest x-ray to determine whether the PICC was accurately positioned reflect actual interventions in terms of adjustment and re-positioning of PICCs. There was no identified evidence to relate the PICC tip location as determined by chest x-ray to actual repositioning or replacement procedures.

4.2.7 Resource identification, measurement and valuation

The EAC asked expert advisors for information on PICC placement costs and the range of responses are covered in the sponsor's sensitivity analysis. A further source was found from Hughes (2014) who calculated a cost of £250 for blind PICC placement and chest x-ray, this is also included in the range of sensitivity analysis.

Table 13 Sponsor list of resources for Sherlock with x-ray with EAC comment

Items	Value	Source	EAC comment
Price of the technology per PICC line insertion	£6.39	Unit cost of Sherlock 3CG = £9,990 (Bard, 2013). Life span = 4 years (conservative assumption, usually last 8 years) 468 potential uses per year per Sherlock 3CG TCS device (mid-value from survey conducted by Bard). 83.5% of patients requiring PICC lines are suitable for Sherlock 3CG TCS (Adams, 2013). This is known pre-ante,	Agree. Includes assumption that 16.5% of patients are not suitable for Sherlock 3CG TCS and Sherlock 3CG TCS is not used. Impact is negligible.

		so consumables are not wasted on these patients. (£9,990/4)/(468*0.835) = £6.39	
Consumables (if applicable)	£189.91	Pack including PICC, sterile maximum barrier, procedure tray and ECG leads (£175-£200). Mid-point of £187.50 used in base case Printer paper: £120 for 1,000 sheets (12p each and 2 sheets per insertion). Other consumables not included in PICC pack = gloves, lidocaine, saline 10ml, 2 ECG electors and Chloraprep 3ml applicator = £2.17	Agree
Maintenance cost	£1.52	Annual maintenance cost = £595 (Bard, 2013). 468 attempted uses per year (mid-value from survey conducted by Bard). 83.5% of attempted patients are suitable (Adams, 2013) £595/(468*0.835) = £1.52	Agree. Includes assumption that 16.5% of patients are not suitable for Sherlock 3CG TCS and Sherlock 3CG TCS is not used. Impact is negligible.
Training cost	£1.42	Training cost covered by Bard. Requires 4.5 hours of nurse time: £34 per hour of non-face-to-face contact time (PSSRU, 2013) 4.5*41 = £184.50 to train one nurse (in use of Sherlock 3CG TCS). Assumed 3 new nurses trained per year per device = £553.5. 83.5% of 468 PICCs placed per year with Sherlock 3CG TCS. 615/391 = £1.42 per patient to train nurses	Error in calculation. £1.17 used in model is correct. Includes assumption that 16.5% of patients are not suitable for Sherlock 3CG TCS and Sherlock 3CG TCS is not used. Impact is negligible.
Other costs	£111.15	Ultrasound = £18 (NHS reference costs (2012-13). Diagnostic imaging, anaesthetics. RA23Z - ultrasound scan, less than 20 minutes Radiographer time for X-ray = 10 minutes (Walker *et al.*, 2013) multiplied by the cost of radiographer = £34 per hour - Hospital radiologist PSSRU, 2013) = £5.67 Nurse day ward: £84 per hour of face-to-face contact (PSSRU, 2013) multiplied by 62.49 minutes (assumed to be equal to bedside placement time reported by Walker *et al.*, 2013) = £104.15	Ultrasound – agree. Radiographer cost – agree. Nurse cost – should be the same for all of the bedside modalities.
Total cost per insertion	£310.15		

Table 14 Sponsor list of resources for Sherlock without x-ray with EAC comment

Items	Value	Source	EAC comment
Price of the technology per PICC line insertion	£6.39	Unit cost of Sherlock 3CG = £9,990 (Bard, 2013). Life span = 4 years (conservative assumption, usually last 8 years) 468 potential uses per year per Sherlock 3CG TCS device (mid-value from survey conducted by Bard). 83.5% of patients requiring PICC lines are suitable for Sherlock 3CG TCS (Adams, 2013). This is known pre-ante, so consumables are not wasted on these patients. (£9,990/4)/(468*0.835) = £6.39	Agree Includes assumption that 16.5% of patients are not suitable for Sherlock 3CG TCS and Sherlock 3CG TCS is not used. Impact is negligible.
Consumables (if applicable)	£189.91	Pack including PICC, sterile maximum barrier, procedure tray and ECG leads (£175-£200). Mid-point of £187.50 used in base case Printer paper: £120 for 1,000 sheets (12p each and 2 sheets per insertion). Other consumables not included in PICC pack = gloves, lidocaine, saline 10ml, 2 ECG electors and Chloraprep 3ml applicator = £2.17	Agree
Maintenance cost	£1.52	Annual maintenance cost = £595 (Bard, 2013). 468 attempted uses per year (mid-value from survey conducted by Bard). 83.5% of attempted patients are suitable (Adams, 2013) £595/(468*0.835) = £1.52	Agree Includes assumption that 16.5% of patients are not suitable for Sherlock 3CG TCS and Sherlock 3CG TCS is not used. Impact is negligible.
Training cost	£1.42	Training cost covered by Bard. Requires 4.5 hours of nurse time: £34 per hour of non-face-to-face contact time (PSSRU, 2013) 4.5*41 = £184.50 to train one nurse. Assumed 3 nurses trained per year per device = £553.5. 83.5% of 468 PICCs placed per year with Sherlock 3CG TCS. 615/391 = £1.42 per patient to train nurses	£1.17 used in model is correct. Includes assumption that 16.5% of patients are not suitable for Sherlock 3CG TCS and Sherlock 3CG TCS is not used. Impact is negligible.
Other costs	£83.83	Ultrasound = £18 (NHS reference costs (2012-13). Diagnostic imaging, anaesthetics. RA23Z - ultrasound scan, less than 20 minutes Nurse day ward: £84 per hour of face-to-face contact (PSSRU, 2013) multiplied by 39.5 minutes (Adams *et al*., 2013)= £65.83	Ultrasound – agree Nurse cost should be the same as with x-ray.

Total cost per insertion	£272.30		

Table 15 Sponsor list of resources for Blind PICC insertion with EAC comment

Items	Value	Source	EAC comment
Cost of the comparator	N/A		
Consumables (if applicable)	£163.18	Equipment cost for nurses £195.81 (Walker *et al*. 2013) with VAT (at 20% removed) This includes the cost of additional consumables that may be required during adjustment as calculated by Walker *et al*. (2013) for example if a PICC is too long and has to be pulled back and an additional sterile pack may be required.	Agree
Maintenance cost	N/A		
Training cost	N/A		
Other costs	£111.15	Ultrasound = £18 (NHS reference costs (2012-13). Diagnostic imaging, anaesthetics. RA23Z - ultrasound scan, less than 20 minutes Radiographer time for X-ray = 10 minutes (Walker *et al*. 2013) multiplied by the cost of radiographer = £34 per hour - Hospital radiographer PSSRU, 2013) = £5.67 Nurse day ward: £84 per hour of face-to-face contact (PSSRU, 2013) multiplied by 62.49 minutes (Walker *et al*. 2013) = £87.49 It is unclear if this time includes time taken for PICC lines to be pulled back (i.e. adjusted), however as the time taken for PICC placement used to cost successful PICC placement at the bedside and the proportion of successful PICC lines placed we both taken from Walker *et al*. 2013 we can assumed they defined and calculated consistently.	Ultrasound – agree Radiographer – agree Nurse – should be the same for blind PICC and Sherlock 3CG TCS with or without x-ray
Total cost per treatment/ patient	£274.33		

Table 16 Sponsor list of resources for fluoroscopy guided PICC insertion with EAC comment

Items	Value	Source	EAC comment
Cost of the comparator	N/A		
Consumables (if	£217.88	Equipment cost for radiology (Walker *et*	Agree

applicable)		*al*. 2013) with VAT (at 20% removed)	
Maintenance cost	N/A		
Training cost	N/A		
Other costs	£579.05	Radiologist time to insert PICC = 40.13 minutes (Walker *et al*. 2013) multiplied by the cost of radiologist = £99 per hour - Hospital consultant (PSSRU, 2013) = £66.21 Nurse team set up of room: 10 minutes to set up room (Walker *et al*. 2013) multiplied by cost of nurse = £34 per hour – Nurse day ward non face-to-face time (PSSRU, 2013) = £5.67 Theatre cost = £507.18 (Walker *et al*. 2013)	Radiologist – agree Nurse team – this is just for 1 nurse not a team Theatre – cost estimate from Walker 2013 seems very high. EAC propose £101
Total cost per treatment/patient	£814.93		

The sponsor identified time resource needs in relation to PICC positioning and re-positioning as the relevant resource issue and conducted an additional search to identify published studies relevant to this issue. The sponsor's approach of undertaking a pragmatic and focussed search was acceptable. A good range of databases were searched using an appropriate range of Subject Headings and free-text terms together with Boolean and proximity operators. The searches were appropriately limited to the English language.

The sponsor undertook a questionnaire survey of 8 centres currently using Sherlock 3CG TCS. The other 8 of 16 centres were not sent the questionnaire and this selection of centres could have introduced bias into the survey response. The sponsor justified their choice by saying they chose the first seven centres they engaged with to ensure the most complete and extensive data would be included, subsequently the EAC contacted the other centres and the probability of bias appears low (responses in table 9). The survey data was used to inform some of the inputs to the model. Based upon the questionnaire survey, the sponsor identified a mean of 468 attempted uses of Sherlock 3CG TCS per year. The EAC calculates this to be 490 cases from the same data, but the number of PICCs placed per year varies greatly between sites.

The sponsor has assumed Sherlock 3CG TCS was used for PICC insertion in 83.5% of patients based on Adams (2013). It is not clear from the Adams (2013) poster and abstract whether:

- Sherlock 3CG TCS was used for PICC placement, but ECG tip confirmation was not possible, potentially incurring the cost of a chest x-ray, or
- PICC placement was not attempted using Sherlock 3CG TCS because of known problems with ECG tip confirmation for that patient.

The sponsor has assumed placement was not attempted using Sherlock 3CG TCS in 16.5% of patients requiring PICC. A more 'representative of real life' case mix of patients requiring PICC and those who were eligible would

have been ideal. The impact on the existing model structure is minimal since the data was only used to calculate the cost of the device, device maintenance and training. Ideally the possibility of some patients not being able to use Sherlock 3CG TCS would have been reflected in the model structure.

The number of patients treated per year was calculated from these figures and this was used to calculate the equipment costs per patient. However the sponsor did not account for the remaining 16.5% of patients requiring a PICC in the Sherlock 3CG TCS branches of the model. There is lack of clarity in the denominator (population) when calculating percentage rates, in both the published abstracts and in the model. The success rate for PICC placement using Sherlock 3CG TCS is given as 96% in the model, but since 16.5% of patients were deemed unsuitable for Sherlock 3CG TCS this is not the percentage of the total patients requiring PICC placement. The overall success rate for PICC insertion using Sherlock 3CG TCS is 80% of the patients requiring PICCs

The nurse time taken to insert the PICC is from two different sources. For blind insertion at the bedside the time was taken from Walker et. al.(2013), and assumed to be the same for Sherlock 3CG TCS insertion at the bedside with confirmation x-ray. In the study, PICC placement was blind and confirmed by x-ray with nurse time taken for PICC insertion of 62.5 minutes. The 62.5 minutes does not include time taken for x-ray. For insertion using Sherlock without x-ray the nurse time was taken from Adams (2013) and was 39.5 minutes. These differences may be due to different experience of the nurse teams or other institutional differences. There is no clear rationale why there should be a longer time taken to place the PICC using Sherlock 3CG TCS with x-ray compared to without x-ray given that the time taken for the x-ray confirmation is accounted for separately. Communications with expert advisors indicate that times for all three of the bedside placement options are likely to be similar, with varying opinions as to whether Sherlock 3CG TCS or blind insertion is slightly longer. Given the variable times in the publications it would be more sensible to use the same time for PICC insertion by nurse at the bedside with or without Sherlock 3CG TCS.

The results of the model for bedside procedures are strongly driven by the nurse time. Nurse time is included in the sponsor's sensitivity analysis, bundled within total procedure cost, but this does not address the assumption of different times for the procedures.

The sponsor did not include a Tornado chart illustrating the sensitivity analysis results in the submission or in the model outputs, which would have been very useful in identifying the key drivers of the model.

4.2.8 Technology and comparators' costs

The list price for the technology is given by the sponsor as £9,990 excluding VAT. This is a fixed cost for the purchaser i.e. it does not vary with the number of patients treated with Sherlock 3CG TCS. Other fixed costs include the total cost of training 3 staff in the use of Sherlock 3CG TCS of £553.50, and the annual maintenance costs for Sherlock of £595. There are no fixed costs for the blind PICC placement with x-ray confirmation, assuming the hospital already has a bedside PICC placement service. Therefore the sponsor has calculated the

minimum number of patients per year before the Sherlock 3CG TCS with no x-ray becomes cost saving compared with bedside PICC placement with x-ray confirmation to be 103 patients using the base case inputs.

The sponsor assumes a 4 year lifespan for the device and that 468 patients require PICC insertions per year of whom 83.5% are suitable for Sherlock 3CG TCS. There are some small differences in the calculations of costs listed in table C6.1, C6.2 and C7.2 of the sponsor submission and those used in the model. The correct values as intended by the sponsor are used in the model. The only final calculated cost that is different between the submitted tables and the model is nurse training cost per patient, at £1.42 in table C6.1, and the correct value of £1.17 in the model. The cost of a chest x-ray was calculated from radiographer time only by the sponsor as £5.67. This is likely to be an underestimate. The NHS reference costs do not include a cost for a chest x-ray as it is incorporated in general care costs within the relevant codes. The EAC has found a number of estimates for the cost of a chest x-ray between £13.33 and £49.09 (Khan et.al 2008,Beavan et. al. 2010). The sponsor includes cost of a chest x-ray from £3 to £54.79 in sensitivity analysis.

The equipment cost for blind PICC placement of £163.18 was taken from Walker et. al.(2013) with VAT removed and is based on the inventory of equipment actually used by nurse teams. The Walker et. al.(2013) paper is a good source for identifying and quantifying resources, and costing equipment, but possibly less useful for costing staff and theatre time. The sponsor based staff costs on the daily rates from Curtis (2013) which is appropriate.

The equipment cost and staff time for fluoroscopy was also taken from Walker et. al.(2013) with VAT removed. Equipment costs were calculated from an average for 3 consultants based on all items used for the procedure. Staff resources included 40 minutes of Radiologist time and also 10 minutes of nurse time to set up the theatre. Theatre time was costed by Walker et. al.(2013) at £757.10 per hour, which appears very high. The author kindly supplied further details to the EAC. The cost was estimated from a discussion between consultants and the finance team at Raigmore Hospital. As the theatre cost forms a large part of the cost for the fluoroscopy branch of the model it is an important element for this comparator. The National Schedule of Reference Costs 2012-13 gives an average cost for all NHS Trusts and Foundation Trusts for contrast fluoroscopy procedures >40 minutes of £101 (code RA18Z). This code covers a variety of procedures and specialisms and is averaged for 69,778 procedures. It is therefore a more robust value to use and more generalisable to the rest of the UK. The sponsor did submit a scenario which included removing all theatre cost for fluoroscopy (table C13).

4.2.9 Sensitivity analysis

The sponsor has included one-way sensitivity analysis on a number of model inputs. A tornado chart was not provided and this would have been very helpful in identifying the key drivers of the model.

In addition the sponsor has included five two-way scenario-based sensitivity analyses.

4.3 Results of de novo cost analysis

Base-case analysis results

The sponsor base case results are given in tables 17 and 18 below, extracted from table C11 of the sponsor submission:

Table 17 Sponsor's base case results compared with Blind PICC placement

	Total cost	Cost difference compared with Blind PICC insertion with x-ray	EAC comment
Blind PICC insertion with x-ray confirmation	£330.56		
PICC insertion with Sherlock 3CG TCS and no x-ray	£304.90	-£25.67	Due to differences in nurse time, equipment cost and malposition rate
PICC insertion with Sherlock and x-ray confirmation	£342.75	+£12.19	No difference in nurse time compared with Blind PICC placement.

The most valid comparison is Sherlock 3CG TCS (no x-ray) with blind PICC placement and x-ray confirmation. The sponsor's base case shows a small cost saving for Sherlock 3CG TCS.

Table 18 Sponsor's base case compared with fluoroscopy

	Total cost	Cost difference compared with PICC insertion with fluoroscopy	EAC comment
PICC insertion with fluoroscopy	£814.93		
PICC insertion with Sherlock 3CG TCS and no x-ray	£304.90	-£510.03	Substantially due to no theatre cost.
PICC insertion with Sherlock and x-ray confirmation	£342.75	-£472.18	Substantially due to no theatre cost.

In comparing PICC placement using Sherlock 3CG TCS with PICC insertion using fluoroscopy, the sponsor is combining savings made by moving PICC placement from the fluoroscopy suite to the bedside with the cost saving directly attributable to the Sherlock 3CG TCS technology. The majority of the cost saving in the model comes from the change of location and this could also be achieved by changing from fluoroscopy to blind PICC placement with x-ray confirmation. The model does not include the cost of setting up a bedside PICC placement service for hospitals with an existing fluoroscopy service. Costs might include employing, or redeploying staff in the new and old services, training nurses in PICC insertion (in addition to use of Sherlock 3CG TCS, training other staff in the new pathway, managing the service changes etc. Patients having fluoroscopy guided PICC placement may be the more complex cases.

In the model the Sherlock 3CG TCS with x-ray will always cost more than Sherlock 3CG TCS without x-ray because of the additional cost of the x-ray and because the nurse time is set as longer for the with x-ray branch. All other inputs are equal for these 2 branches.

The sponsor provides a breakdown of the cost comparisons in table C12.3 of the sponsor submission. Part of this is reproduced here in table 19 with EAC comments added.

Table 19 Sponsor's base case summary of costs by category per patient for Sherlock 3CG TCS with no x-ray vs blind bedside placement plus x-ray

Item	Blind PICC with x-ray	Sherlock (no x-ray)	Increment (+ if Sherlock costs more)	EAC comment	Impact
Equipment costs	£181.18	£215.82	+£34.64		
Staff costs	£93.15	£56.47	-£36.68	Nurse time for PICC insertion should be equal	If nurse time equal (62.49 min) increment is: -£4.49
Re-insertion costs	£56.23	£32.60	-£23.63	Re-insertion cost should be zero for Sherlock since without x-ray there is no way to know that the catheter is mal-positioned.	If 0% malposition, increment: -£56.23 Note: fluoroscopy being used for reinsertion in comparator arm.
Total	£330.56	£304.90	-£25.67		With both changes implemented: -£26.08

In the sponsor's model, the additional equipment costs for Sherlock 3CG TCS are offset by cost savings from lower staff costs and lower costs for re-insertion. The EAC considers that the nurse time should be set equal. The only difference in staff cost arises from the radiographer time for chest x-ray. For Sherlock 3CG TCS with no x-ray the centre would assume that the catheter was correctly positioned using TPS and ECG guidance. There would be no way to identify any mal-positioned catheters without the x-ray. Therefore there should be no cost for re-positioning in this branch. The re-positioning is assumed to be by fluoroscopy in the base case, but clinical advisers suggest this is often by blind placement with x-ray confirmation. The EAC considers the theatre cost for fluoroscopy to be high. Therefore the additional cost for re-positioning is too high in the base case.

4.3.1 Sensitivity analysis results

One-way sensitivity analysis and threshold diagrams

Variables used in one-way sensitivity analysis are shown in table 20 below with EAC comments.

Table 20 Variables used in the sponsor's one-way sensitivity analysis

Variable	Base-case value	Range of values	Explanation of range used	EAC comment
Bedside insertion with Sherlock 3CG TCS (with or without X-ray)				
Proportion of successful placements	96%	92%-100%	Highest value in literature = 100% (Barton et al. 2014) and lowest = 96% (Parikh et al. 2012 and Stewart et al. 2013) for trained staff. Lower values were considered to represent clinical practice that may be poorer than those in studies.	This excludes the 16.5% of patients deemed not suitable for Sherlock. This is low impact where costs for alternative treatments are similar. Values from the only full paper(Johnston et al. 2014) were not included
Proportion of successful adjustments/ replacements after initial misplacement	0%	0-100%	In base case all go to fluoroscopy after initial failure. Range considers a scenario where all Sherlock 3CG TCS patients with unsuccessful placement have replacement with Sherlock 3CG TCS and cost is £310.15 with X-ray and £272.30 without X-ray.	In many settings, most will go to blind PICC placement at bedside with x-ray. In the model, the comparator is still replaced by fluoroscopy. Consequences are limited due to small numbers affected.
Cost of insertion at bedside (with X-ray)	£310.15	£227.40 - £499.24	In order to calculate the range, each the following inputs have been varied as follows: Number of insertions per year per device: +/-10%; Proportion of patients utilising device: +/- 10 percentage points; Life span of device: 2 to 8 years; Nurses using device: 2 to 8; Hours of training: 4 to 5; Ultrasound cost: £0 to £51; Consumables: £178-203; Time to insert PICC: 30-120 minutes; X-ray cost: £3 - £54.79.	This does not address the structural assumption of different nurse time for insertion with x-ray and without x-ray. There is no explanation of why the range for Ultrasound is £0 to £51 with x-ray, but £18 to 51 without x-ray or blind.
Cost of insertion at bedside (no X-ray)	£272.30	£210.40 - £374.45	In order to calculate the range, each the following inputs have been varied as follows: Number of insertions per year per device: +/-10%; Proportion of patients utilising device: +/- 10 percentage points; Life span of device: 2 to 8 years;	This does not address the structural assumption of different nurse time for insertion with x-ray and without x-ray. A lower range of times has been used for this pathway.

			Nurses using device: 2 to 8; Hours of training: 4 to 5; Ultrasound cost: £18 to £51; Consumables: £178-203 Time to insert PICC: 20-70 minutes.	
Cost of reinsertion with fluoroscopy after initial failure	£814.93	£607.78 - 1,054.67	Range calculated as specified below.	See comments below on fluoroscopy
Blind insertion at bedside with X-ray				
Proportion of successful placements	93.1%	91%-95%	Reported in Walker *et al.*, 2013 introduction.	
Proportion of successful adjustments/replacements after initial misplacement	0%	0-100%	In base case all go to fluoroscopy after initial failure. Range considers scenario where all patients have replacement at bedside and cost is £274.33	May all go to blind PICC placement at bedside with x-ray. There is considerable variation in practice.
Cost of insertion	£274.33	£209.86 - £453.29	In order to calculate the range, each the following inputs have been varied as follows: Equipment cost: +/-10% Time to insert PICC: 30-120 minutes; Ultrasound cost: £18 to £51; X-ray cost: £3 - £54.79.	This does not address the structural assumption of different nurse time for insertion with x-ray and without x-ray.
Cost of reinsertion with fluoroscopy initial failure	£814.93	£607.78 - 1,054.67	Range calculated as specified below.	See note below regarding fluoroscopy
Insertion with fluoroscopy				
Cost of insertion with fluoroscopy	£814.93	£607.78 - 1,054.67	In order to calculate the range, each the following inputs have been varied as follows: Equipment cost: +/-10% Radiologist time: 20-60 minutes; Ultrasound cost: £18 to £51; Theatre cost: +/-30%	EAC considers this cost is too high based on too high theatre cost. Range +/- 30% is too narrow and should go much lower.

The sponsor used the inputs and ranges for the one-way sensitivity analysis to produce a large number of threshold graphs. It is important to remember that the findings only remain true if all the sponsor's assumptions and base values are accepted other than the one being analysed. The numbers given are more useful as an indication of the drivers of the model. An example of this is for PICC placement with Sherlock 3CG TCS (no x-ray). The threshold graph shows that it becomes cost-incurring when Sherlock 3CG TCS has less than 93% successful placements, but also it can become cost incurring if blind placement has more than 96% successful placements. The model depends more on the difference in these success rates and this was

explored in the two-way sensitivity analysis. As the sponsor identifies in their two-way sensitivity analysis the important factor is the increase in accuracy when using Sherlock 3CG TCS.

Two-way sensitivity analysis

For the two-way scenario analyses the sponsor has produced tables of results showing the results for each combination of values, with cost-saving scenarios coloured green and cost incurring scenarios coloured red. This allows the reader to see at a glance the outcomes of the 2-way scenarios. The sponsor has summarised the scenario results in a table and part of this is reproduced in Table 21 below for the comparison of Sherlock 3CG TCS without x-ray and blind PICC placement with x-ray confirmation.

Table 21 Results from sponsor's 2-way scenario analyses

Sherlock 3CG TCS (no X-ray) v. blind bedside placement with X-ray		
	Cost difference (+ve if Sherlock 3CG TCS costs more)	EAC Comment
Costs increased from base case by 25%	-£32.55 per patient	
Costs reduced from base case by 25%	-£19.72 per patient	
Costs relating to Sherlock 3CG TCS increased from base case by 25%	+£50.20 per patient	
Costs relating to Sherlock 3CG TCS reduced from base case by 25%	-£102.12 per patient	
Theatre cost excluded	-£10.96 per patient	
Bedside replacement of PICC line for failed Sherlock 3CG TCS patients	-£45.04 per patient	EAC find this to be -£56.90 as modelled, or -£19.60 if bedside replacement is the route for both arms of the model.
Healthcare professional costs using costs with qualification costs included	-£32.87 per patient	

Sherlock 3CG TCS is cost saving in the scenarios except when the costs relating to Sherlock 3CG TCS are increased by 25%. In the scenario with bedside replacement of PICC line for failed Sherlock 3CG TCS patients, the PICC line replacement for the comparator is using fluoroscopy as in the base case and this favours Sherlock 3CG TCS.

4.3.2 Subgroup analysis

No sub-group analysis was undertaken. The EAC considered that critical care patients could be considered a sub-group and could have been modelled using data from the Johnston (2014) paper.

4.3.3 Model validation

The sponsor states that one economist created the model and a second economist checked it. A third economist quality assessed the economic submission. A clinical expert was consulted on resource assumptions within the model. Published economic evidence was limited but the sponsor reported that Sherlock 3CG TCS was cost saving consistent with the sponsor's model.

4.4 Interpretation of economic evidence

The sponsor reports that the results of the de novo model are consistent with the two selected economic studies, finding cost savings for Sherlock 3CG TCS. The sponsor acknowledges the low methodological quality and limited relevance of the published studies. The sponsor claims to have considered all settings for inpatients and outpatients in scenario and sensitivity analysis. In the sponsor submission the sponsor identified the key strength as the conservative approach to parameter values in the model. Questionnaire responses from some UK centres currently using Sherlock 3CG TCS were used to support this, but the questionnaire survey was selective as only 8 of 16 centres using Sherlock 3CG TCS were invited to take part. This introduces potential bias. Another claimed strength of the submission is the extensive sensitivity analysis and scenario analysis undertaken to overcome limitations in the quality of data available for modelling. The EAC considers that extensive sensitivity analysis was undertaken, but structural assumptions in the model, were not thoroughly investigated. The lack of comparative trial data was identified by the sponsor as a weakness of the submission. The EAC considers this is a major weakness and has made recommendations for research to produce good quality data. Lack of data from outpatient and tertiary centres was also identified as a limitation, mitigated by using clinical advice.

The sponsor identifies the key drivers of their model as the cost of PICC line insertion for each method and the success rate of initial PICC insertion. They state that where the success rate of Sherlock 3CG TCS is above 97.5% it becomes cost saving. Elsewhere in the submission the sponsor's two-way sensitivity analysis indicates that a difference of 4.5% in success rate for Sherlock 3CG with x-ray compared with blind PICC placement was cost saving. This is confirmed by the EAC in the critical care scenario.

In the sponsor's interpretation of economic evidence, the sponsor asserts that 'insertion with Sherlock 3CG TCS (no x-ray) only has to be as effective as blind bedside placement to be cost saving'. This is consistent with the model as submitted, where the cost per PICC insertion is lower for Sherlock 3CG TCS without x-ray than blind PICC insertion. This is due to the shorter nurse time assigned to Sherlock 3CG TCS by the sponsor. Equipment costs for Sherlock 3CG TCS are higher than blind PICC insertion.

4.5 Additional work undertaken by the External Assessment Centre in relation to economic evidence

The EAC has quality checked the sponsor economic model (appendix 3).

Table 22 Model inputs changed by EAC results and impact for Sherlock no x-ray

Input	Sponsor value	EAC value	Sponsor result	EAC result	Impact
Nurse time	62.49 minutes for blind PICC and for Sherlock 3CG TCS with x-ray 39.5 minutes for Sherlock without x-ray	Set all equal to 62.49 minutes	-£25.67	+£ 6.52	+£32.19
Mal-position rate for Sherlock 3CG TCS with no x-ray	4%	0% (since there is no way to identify a mal-positioned PICC)	-£25.67	-£58.26	-£32.59
Re-placement of misplaced PICC	100% Fluoroscopy	100% Bedside PICC placement using original method	-£25.67	-£19.60	+£6.07
Theatre costs for fluoroscopy	£507.18	£101	-£510.04	-£120.10	+£389.94

If nurse time is set equal to 62.5 minutes (or 39.5 minutes) for all bedside procedures then Sherlock 3CG TCS without x-ray becomes cost incurring +£6.52 compared with blind PICC placement and x-ray confirmation

The EAC also calculated the effect on the base case results of including all patients requiring PICC including those not suitable for Sherlock 3CG TCS in the Sherlock 3CG TCS branch. This means taking the total number of patients in the model as 468. Of these 391 patients follow the Sherlock branch as laid out in the model. The remaining 77 patients deemed unsuitable for Sherlock 3CG TCS follow the Blind PICC placement with x-ray branch of the model. We add up the total costs for all of these patients and divide the result by 468. This changes the base case result for Sherlock (with no x-ray) from £304.90 to £309.12. Although this is a small change in the result for Sherlock 3CG TCS and does not on its own alter the outcome of the base case, the outcome of the model is marginal as to whether Sherlock 3CG TCS is cost saving.

The effect of the EAC changes to the model inputs are shown for each combination of model branches in tables 23 to 26.

Table 23 Blind PICC vs Sherlock (no x-ray) - impact of EAC input changes on sponsor base case

Scenario	Blind PICC with x-ray	Sherlock 3CG TCS no x-ray	Cost Difference	EAC comment
Base Case	£330.56	£304.90	-£25.67	
Nurse time = 62.49 minutes	£330.56	£337.08	+£6.52	
No malpositions for Sherlock without x-ray	£330.56	£272.30	-£58.26	(Malpositions with blind PICC are treated with fluoroscopy as per base case)
Re-placement is by the original method for all bedside PICC placement	£293.26	£283.19	-£10.07	
Including cost of blind PICC where Sherlock not suitable	£330.56	£309.13	-£21.43	
All above changes	£293.26	£302.63	+£9.37	

Table 24 Impact of EAC changed inputs for blind PICC vs Sherlock with x-ray

Scenario	Blind PICC with x-ray	Sherlock 3CG TCS with x-ray	Cost Difference	EAC comment
Base Case	£330.56	£342.75	+£12.19	Nurse time already 62.49 for both scenarios
Re-placement is by the original method for all bedside PICC placement	£293.26	£322.56	+£29.30	
Including cost of blind PICC where Sherlock not suitable	£330.56	£340.74	+£10.18	
All above changes	£293.26	£317.73	£24.47	

Table 25 Impact of EAC changes to inputs on comparison of Fluoroscopy vs Sherlock (no x-ray)

Scenario	Fluoroscopy	Sherlock 3CG TCS no x-ray	Cost Difference	EAC comment
Base Case	£814.93	£304.90	-£510.03	
Nurse time = 62.49 minutes	£814.93	£337.08	-£477.85	
No malpositions for Sherlock without x-ray	£814.93	£272.30	-£542.63	
Re-placement is by the original method for all bedside PICC placement	£814.93	£283.19	-£531.74	
Including cost of blind PICC where Sherlock not suitable	£814.93	£309.12	-£505.81	
Theatre cost for fluoroscopy £101	£408.75	£288.65	-£120.10	
All above changes	£408.75	£302.63	-£106.12	

Table 26 Impact of EAC changes to inputs on comparison of fluoroscopy vs Sherlock with x-ray

Scenario	Fluoroscopy	Sherlock 3CG TCS with x-ray	Cost Difference	EAC comment
Base Case	£814.93	£342.75	-£472.18	Nurse time already 62.49
Re-placement is by the original method for all bedside PICC placement	£814.93	£322.56	-£492.38	
Including cost of blind PICC where Sherlock not suitable	£814.93	£340.74	-£474.19	
Theatre cost for fluoroscopy £101	£408.75	£326.50	-£82.25	
All above changes	£408.75	£317.73	-£91.02	

4.5.1 Scenario using data from Johnston et al. (2013) and Johnston et al. (2014).

The EAC ran a scenario for patients in critical care using data from two papers from the same unit and author. Johnston et al. (2013) describe the outcomes for blind PICC insertion with x-ray confirmation for ICU patients prior to the introduction of Sherlock 3CG TCS. The Johnston et al. (2014) paper describes the outcome for a similar patient cohort following the introduction of Sherlock 3CG TCS. The use of historical controls is not ideal and could introduce bias, but as no other comparative data is available this is potentially a useful comparison drawn from data from the same centre. Since there remains a large proportion of patients with mal-positioned catheters using Sherlock in these complex patients the EAC has assumed that the technology is Sherlock 3CG TCS with x-ray confirmation and the comparator is blind PICC placement with x-ray confirmation. Re-

placement of PICC was by the original method in all cases. The inputs for the scenario taken from the papers are shown in tables 27 and 28.

Table 27 Inputs for the EAC scenario for ICU patients

Input	Value	Source
Proportion of patients able to use Sherlock 3CG TCS	95.6%	Johnston et al. (2014) 11/250 patients were excluded from analysis.
Effectiveness Sherlock 3CG TCS with x-ray	79.5%	Johnston et al. (2014)
Effectiveness blind PICC placement	49.2%	Johnston et al. (2013)
Nurse time taken	62.49 for all interventions	
Proportion of successful re-placements at the bedside	100%	assumption

Results of the ICU scenario are shown in table 28 below.

Table 28 Results of the EAC scenario for ICU patients

	Blind PICC insertion with x-ray confirmation	**PICC insertion with Sherlock 3CG TCS with x-ray**	**Cost difference**	**EAC comment**
Total cost	£413.69	£372.35	-£41.35	Based on sponsor base case model with ICU accuracy rates.

In the ICU scenario Sherlock 3CG TCS with x-ray confirmation is significantly cost saving compared with blind PICC placement with x-ray because of the significant reduction in the proportion of mal-positioned catheters that needed to be re-positioned. The limitations of this scenario are:

- the data is taken from a single centre and may not be generalisable
- the comparison data was historical data from the same centre
- the study only includes intermediate outcomes, the actual number of replacements is not reported

4.6 Conclusions on the economic evidence

In conclusion the economic model shows that:

- switching from fluoroscopy to bedside PICC placement using either Sherlock 3CG TCS or blind placement with x-ray is cost saving
- the best quality available evidence provides a case for Sherlock 3CG cost saving for ICU patients based on a lower malposition rate of 20% compared with blind PICC placement with x-ray (50%), giving a saving of £41.35 per patient, but this is based on a single centre
- the economic case for Sherlock 3CG is less clear in other scenarios.

The lack of robust comparative evidence for Sherlock 3CG TCS is a limitation of the submission that impacts on our confidence in the interpretation of the de novo economic model. This is in particular because of the use of intermediate outcomes (malposition rate determined from retrospective analysis of x-ray images). No evidence was available in which patients were followed beyond the insertion or re-insertion of the PICC.

There appears to be variation in service design for PICC placement between hospitals and within hospitals (Walker et. al.(2013), and expert advisors). Some services use nurse-led vascular access teams who insert all PICCs. Other centres have a fluoroscopy based service and some centres appear to use a mix of both. Different staff groups are involved in PICC insertion including trained nurses, medical staff with or without formal training and senior medical staff such as consultant anaesthetists and radiologists. This may partly reflect the particular patient groups requiring PICC insertion in a given locality, but there may be other factors.

The model has compared the costs of Sherlock 3CG TCS for PICC insertion with no x-ray confirmation with blind PICC placement with x-ray confirmation assuming an existing nurse-led PICC team is in place. In this comparison the model compares the additional equipment costs for Sherlock 3CG TCS with the potential cost reduction from avoiding re-positioning of the PICC because of greater accuracy of Sherlock 3CG TCS. Overall the result is close to cost-neutral, and given the uncertainty of the model inputs and some structural assumptions it is difficult to be confident of a cost saving. However the model does not include complications or adverse events, since no data is available and this could have a significant effect on the outcome. The direction of the effect is unknown.

Comparison of Sherlock 3CG at the bedside with fluoroscopy guided PICC insertion involves a change of location as well as a change in technology. Blind PICC placement can also be done at the bedside, so the cost savings from change of location cannot be claimed solely for Sherlock 3CG TCS. For centres that do not already have a bedside PICC service there would be some set-up costs incurred and these are not included in the model. The theatre costs for fluoroscopy used in the model seem excessively high compared with costs for comparable interventions from NHS reference costs 2012-13.

Published data on critical care patients was excluded by the sponsor in the economic analysis. The EAC ran the model using this data and found that for critical care patients Sherlock 3CG TCS with x-ray was cost saving when compared with blind PICC placement with x-ray. Accurate PICC placement appears to be more difficult in critical care patients, but accuracy was considerably better using Sherlock 3CG TCS requiring fewer episodes of re-insertion using blind PICC placement with x-ray. Data on critical care patients came from a single centre and therefore may not be generalisable.

5 Impact on the cost difference between the technology and comparator of additional clinical and economic analyses undertaken by the External Assessment Centre

The sponsor did not include data from Johnston et al. (2014) in the clinical submission or the submitted model. While the malposition rate reported by Johnston et al. (2014) is much higher than other evidence considered, there is a previous paper reporting malposition rates for similar patients in the same setting that demonstrates an improvement in positioning using Sherlock 3CG TCS. The EAC used this malposition data in the model to show an increased cost saving for Sherlock 3CG TCS due to the larger difference in successful placements between blind placement and ECG tip positioning. This is despite the malposition rate being high enough that the chest x-ray is still included for Sherlock 3CG TCS. Because this is a very specific setting and may not be indicative of many other uses of Sherlock 3CG TCS, this data is not included in the broader changes to the model by the EAC, reported below. The effect of including all EAC changes to the model inputs are shown in Tables 29 below. The EAC changes are:

- Nurse time is equal for Blind PICC insertion with x-ray, Sherlock 3CG TCS with x-ray, and Sherlock 3CG TCS no x-ray. The EAC used a time of 62.59 minutes (Walker 2013). X-rays are costed separately.
- Where Sherlock 3CG TCS is used without x-ray, there is an assumption of zero malpositions (within the time frame of the model) since no other tip confirmation system is used.
- Replacements for PICCs placed at bedside should be at bedside using the original method.
- Sherlock 3CG TCS is not suitable for use with all patients, the cost of treating these patients should be included.
- The cost of theatre use for fluoroscopy should be £101 (NHS reference costs 2012-13) rather than £507.18.

Table 29 Effect of all EAC input changes on comparison of Sherlock with blind PICC

	Sponsor base case	increment	EAC	increment
Blind PICC insertion with x-ray confirmation	£330.56		£293.26	
Sherlock no x-ray	£304.90	-£25.67	£302.63	+£9.37
Sherlock with x-ray	£342.75	+12.19	£3317.73	£24.47

Table 30 Effect of all EAC input changes on comparison of Sherlock with fluoroscopy

	Sponsor base case	increment	EAC	increment
Fluoroscopy	£814.93		£408.75	
Sherlock no x-ray	£304.90	-£510.03	£302.63	-£106.12
Sherlock with x-ray	£342.75	-£472.18	£317.73	-£91.02

6 Conclusions

The available evidence is sparse, for non comparative case-studies and mainly lacking in detail. From the available evidence there does seem to be agreement that Sherlock 3CG TCS results in accurate PICC placement judged by chest x-ray. There is no information available on how this translates to reinsertion or repositioning procedures, or any longer term follow up of consequences and adverse events. There is no information on patient experience or preference.

Given the lack of evidence, it is difficult to be confident of the cost model results. The sponsor carried out extensive sensitivity analysis, however the EAC disagreed with some of the key inputs. Overall the result is close to cost-neutral, and given the uncertainty of the model inputs and some structural assumptions it is difficult to be confident of a cost saving. The model does not include complications or adverse events, since no data is available and the direction of effect that this would have is unknown.

The claimed benefits for the patient are:

Better accuracy of PICC placement: The abstracts, posters and NHS questionnaires, and expert advisors who use the technology all appear to be in agreement that with the appropriate training and patient group, Sherlock 3CG TCS is an accurate method for placing PICCs. The one fully described study (Johnston et al. 2014) is rather more cautious, but indicates that accuracy is improved when compared to blind PICC placement confirmed by chest x-ray. Johnston et al (2014) state that, for ICU, Sherlock 3CG TCS would be adequate to replace routine chest x-rays for PICC placements where a broad definition of correct location was acceptable. They do not consider it adequate to replace routine chest x-ray if the acceptable location is confined to lower SVC and CAJ.

Better outcomes by reducing the incidence of catheter malposition and post procedural repositioning: There is a low level evidence to support a reduction of malpositions, no comparative studies were available. Johnston et al. (2014) can be cautiously compared to a previous study in the same setting (Johnston et al. 2013) showing a reduction of malpositions. NHS site questionnaires also support this view. None of the evidence addresses the number of repositioning procedures that occur due to these malpositions.

Removes the need for a chest x-ray or fluoroscopy to confirm tip location after PICC insertion: The sponsor states that 9 of the 14 NHS sites using Sherlock 3CG TCS have stopped using routine chest x-rays. Johnston et al. (2014) state that, for ICU, Sherlock 3CG TCS would be adequate to replace routine chest x-rays for PICC placements where a broad definition of correct location was acceptable. They do not consider it adequate to replace routine chest x-ray if the acceptable location is confined to lower SVC and CAJ.

Reduced treatment delays due to intra-procedural verification of tip position: There is no robust evidence to support this claim. The only evidence for this claim is a statement of reduced time in two posters, however there is no information on how this was measured, or what was included. Expert advisors had varied opinions as to which placement procedure would take longer. An assumption is generally made that removing the need for a chest x-ray would reduce procedure time, but this depends on the local procedures. .

Safe method for PICC tip placement with no associated adverse events or complications: The evidence does not report adverse events or complications, but the lack of detailed reporting and the short time frame for all studies, means we cannot be sure that they did not occur. The NHS sites and expert advisors contacted did not report adverse events. FDA (MAUDE) includes reports of adverse events using Sherlock 3CG TCS, but this data is not collected systematically nor is it a complete record, and there is no information comparing to other methods of PICC insertion..

PICC placement and tip confirmation in the same procedure, improving patient experience (except for patients where ECG tip confirmation not appropriate): There is no available evidence on patient experience.

Improves patient experience and increases patient's confidence in the PICC placer: There is no available evidence on patient experience.

Benefits claimed for the healthcare system are:

Process efficiency through reduced care pathway (no chest x-ray): The statement that there are NHS sites no longer using routine chest x-rays for PICC tip confirmation supports the claim that it can be eliminated, at least in some circumstances. There may be patient groups or settings where this will not be

appropriate. As already discussed, there is no real evidence of a shortened care pathway, although this may be as much due to the paucity of evidence as a lack of benefit.

Reduces staff requirements (radiologists/radiology nurses/radiographers/radiology healthcare support workers) as PICC tip confirmation by x-ray is reduced. Also reduced porters for patient transfer and doctors for x-ray assessment. There is no evidence of a reduction of staff requirements for PICC tip confirmation, routine chest x-rays are a very brief procedure and their reduction is not likely to have any noticeable impact on the staff providing the service. A change of setting for PICC placement or a significant reduction in the number of reinsertions may change staff requirements, however there is no evidence base for this.

Potential reduction of bed occupancy due to reduced delays in treatment initiation: There is no evidence to support reduced bed occupancy. There is low quality evidence to support a reduction in delays until the PICC is confirmed available to use. There is no evidence to indicate if this translates into actual reduced delays to treatment initiation.

Reduced costs of consequences of malpostioning: There is a low level evidence to support a reduction of malpositions, no comparative studies were available. Johnston et al. (2014) can be cautiously compared to a previous study in the same setting (Johnston et al. 2013) showing a reduction of malpositions. NHS site questionnaires also support this view. None of the evidence addresses the number of repositioning procedures that occur, or any other consequences of malposition.

Reduces costs of resource intensive departments such as radiology: The cost of chest x-rays is low, however placement using fluoroscopy would be more costly. All variations in the model had some level of cost saving for Sherlock 3CG TCS compared to PICC placement using fluoroscopy, but this does not include costs for setting up a new bedside PICC placement team. No evidence was provided for the proportion of PICCs currently placed using fluoroscopy.

7 Implications for research

There are currently no published studies comparing insertion of PICC using Sherlock 3CG TCS with blind insertion and x-ray confirmation. The published single arm studies report PICC placement accuracy based on retrospective evaluation of chest x-rays. Different patient groups are not well defined in the sponsor submission.

Future research should help to define important sub-groups for whom bedside PICC insertion with Sherlock 3CG would be the best option based on clinical and economic outcomes.

Future research should directly compare PICC insertion using Sherlock 3CG TCS and blind insertion with x-ray, preferably in a randomised trial. Outcome measures should include numbers of PICCs adjusted, removed and

re-inserted, and all complications and adverse events (including malposition, migration, line fracture, phlebitis, venous thrombosis, catheter-related infection, arrhythmia) should be recorded. Resource use would also be of interest. The research may include some or all of the patient groups requiring PICC insertion.

There is currently no published research comparing PICC insertion using Sherlock 3CG with fluoroscopy. Similar studies as described above would be helpful.

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Appendix 1: EAC literature search strategies

The EAC designed the search strategies for different databases as follows:

Ovid MEDLINE(R)

Ovid MEDLINE(R) <1946 to June Week 3 2014>

Search Strategy:

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1 ((sherlock or sapiens or "bard access systems") and (catheter* or PICC)).tw. (15)

2 (PICC adj5 tip adj3 (locat* or place* or detect* or position*)).tw. (15)

3 ((Peripheral* adj3 central adj3 catheter*) and (tip adj3 (locat* or place* or detect* or position*))).tw. (57)

4 (tip* and (accura* or correct* or precis*)).tw. (6527)

5 Catheterization, Central Venous/is, mt [Instrumentation, Methods] (4958)

6 4 and 5 (122)

7 1 or 2 or 3 or 6 (183)

8 exp animals/ not humans.sh. (3954108)

9 7 not 8 (178)

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <June 30, 2014>

Search Strategy:

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1 ((sherlock or sapiens or "bard access systems") and (catheter* or PICC)).tw. (1)

2 (PICC adj5 tip adj3 (locat* or place* or detect* or position*)).tw. (3)

3 ((Peripheral* adj3 central adj3 catheter*) and (tip adj3 (locat* or place* or detect* or position*))).tw. (7)

4 1 or 2 or 3 (7)

EMBASE

<1947-Present>

Search Strategy:

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1 ((sherlock or sapiens or "bard access systems") and (catheter* or PICC)).tw. (34)

2 (tip* and (accura* or correct* or precis*)).tw. (9846)

3 *peripherally inserted central venous catheter/ (468)

4 2 and 3 (29)

5 (PICC adj5 tip adj3 (locat* or place* or detect* or position*)).tw. (42)

6 ((Peripheral* adj3 central adj3 catheter*) and (tip adj3 (locat* or place* or detect* or position*))).tw. (113)

7 1 or 4 or 5 or 6 (158)

CINAHL Wednesday, July 02, 2014

#	Query	Results
S7	S1 OR S2 OR S3 OR S6	64
S6	S4 AND S5	14
S5	tip* and (accura* or correct* or precis*)	655
S4	(MM "Peripherally Inserted Central Catheters")	446
S3	(Peripheral* N3 central N3 catheter*) AND (tip N3 (locat* or place* or detect* or position*))	55
S2	PICC N5 tip N3 (locat* or place* or detect* or position*)	9
S1	(sherlock or sapiens or "bard access systems") and (catheter* or PICC)	5

Cochrane Library

Search Name: CEDAR_Sherlock

Date Run: 01/07/14

ID Search Hits

#1 ((sherlock or sapiens or "bard access systems") and (catheter or PICC)):ti,ab,kw (Word variations have been searched) 6

#2 (PICC) near tip near (locat* or place* or detect* or position*):ti,ab,kw (Word variations have been searched) 1

#3 ((Peripheral* near central near catheter*) and (tip near (locat* or place* or detect* or position*))):ti,ab,kw (Word variations have been searched) 0

#4 MeSH descriptor: [Catheterization, Central Venous] explode all trees and with qualifier(s): [Instrumentation - IS, Methods - MT] 395

#5 (tip* and (accura* or correct* or precis*)):ti,ab,kw (Word variations have been searched) 270

#6 #4 and #5 14

#7 #1 or #2 or #3 or #6 21

HEED

(peripheral* and catheter* and tip) or PICC or Sherlock

Results = 0

ECONLit

Wednesday, July 02, 2014

#	Query	Results
S7	S1 OR S2 OR S3 OR S6	0
S6	S4 AND S5	0
S5	tip* and (accura* or correct* or precis*)	60
S4	(MM "Peripherally Inserted Central Catheters")	0
S3	(Peripheral* N3 central N3 catheter*) AND (tip N3 (locat* or place* or detect* or position*))	0
S2	PICC N5 tip N3 (locat* or place* or detect* or position*)	0

S1	(sherlock or sapiens or "bard access systems") and (catheter* or PICC)	0

Web of Science

4 58 #3 OR #2 OR #1

Indexes=SCI-EXPANDED, SSCI, CPCI-S Timespan=1990-2011

3 46 TS=((Peripheral* NEAR/3 central NEAR/3 catheter*) and (tip NEAR/3 (locat* or place* or detect* or position*)))

Indexes=SCI-EXPANDED, SSCI, CPCI-S Timespan=1990-2011

2 9 TS=(PICC NEAR/5 tip NEAR/3 (locat* or place* or detect* or position*))

Indexes=SCI-EXPANDED, SSCI, CPCI-S Timespan=1990-2011

1 11 TS=((sherlock or sapiens or "bard access systems") and (catheter* or PICC))

Indexes=SCI-EXPANDED, SSCI, CPCI-S Timespan=1990-2011

National Technical Information Service (NTIS) database

(sherlock and catheter) OR (PICC and catheter) OR (peripheral and catheter and tip)

Results = 0

NHS Evidence

PICC AND catheter AND tip AND (location or placement or detection or position)

Results = 41

Pubmed (‘pubstatusaheadofprint’**)**

pubstatusaheadofprint AND catheter* AND tip AND (detect* or locat* or place* or position*)

Results= 37

CEA registry [Cost Effectiveness Analysis] https://research.tufts-nemc.org/cear4/Home.aspx

Sapiens or Bard Access systems or Sherlock

Results= 0

EconPapers http://econpapers.repec.org/

(Sapiens or Bard Access systems or Sherlock) AND (catheter or PICC)

Results= 0

ICTRP – not able to export to Reference Manager

Searched for: ‘Sherlock’ , Results = 5, 2 relevant both listed on Clinical Trials.gov

Clinicaltrials.gov – not able to export to Reference Manager

Searched for: ‘Sherlock AND catheter’ , Results = 3, 2 relevant

MAUD FDA – not able to export to Reference Manager

97 records meeting your search criteria returned - **Manufacturer:** *bard* **Brand Name:** *sherlock* **Report Date From:** *01/01/2000* **Report Date To:** *05/31/2014*

3 records meeting your search criteria returned - **Manufacturer:** *bard* **Brand Name:** *sapiens* **Report Date From:** *01/01/2000* **Report Date To:** *05/31/2014*

MHRA

Searched site for : Sherlock, bard & catheter, PICC & Bard = 0

EMA,

Searched site for : Sherlock & catheter, bard & catheter, PICC & Bard = 0

Appendix 2: EAC information on prevalence of PICCs

Paper	Setting	Period	PICC prevalence	Comments	*Mean annual PICC rate*
Nicholson, 2011	Royal Surrey County Hospital, DGH, **non-oncology patients**	3 yrs	119 total PICCs	(see also Nicholson 2010)	*40*
Kelly F, 2011	Galway University Hospitals	19 mths	194 lines in 170 patients, 5354 line days	PICCs performed by Clinical Nurse Specialist	*122*
Appleton, 2013	Wirral University Teaching Hospitals	2 yrs (Jan 2010 – Jan 2012)	294 single lumen lines in 225 patients, median line days 16 (0-368 days), 49% for parenteral nutrition.	Dedicated PICC service. (May exclude oncology patients.)	*148*
Philips, 2010	Good Hope Hospital, Sutton Coldfield	11 mths (2010)	57 PICCs, of which 3 were malpositioned on x-ray & 3 did not reach the desired depth	PICC Outreach Service, for **ward-based insertion**	*62*
Sykes, 2012	Good Hope Hospital, Sutton Coldfield	1 yr (2011)	123 PICCs (115% increase on 2010 numbers); 43% for long-term Abs, duration 1-107 days; 6 (5%) were malpositioned.	**Ward-based service** (as Philips 2010 above)	*123*
Oliver & Jones, 2013	East Kent Hospitals	?	2000 PICCs placed using ECG		*?*
Simcock, 2008	PICC Service in **Oncology**, UCL	1 yr (2005)	227 PICCs (upper arm), increasing demand since audit due to preference for PICCs for central access	Before & after change to upper arm placement. In and out patient treatments.	*227*
Finch, 2010	**ITU** (850 patients per year), Royal Devon and Exeter Hospital, Exeter	2 yrs (Jan 2008 – Dec 2009)	188 PICCs, mean duration 18 days, 0.5% misplacement	Dedicated vascular access team	*94*
Baker, 2012	**ITU** (880 patients per year), Royal Devon and Exeter Hospital, Exeter	4 yrs (2008 - 2012)	287 PICCs, mean dwell time 8 days (ICU) + 10 days (post-discharge)	Includes Finch 2010 data. Nurse-led Vascular Access Team.	*72*
Desikan, 2012	DGH, East Surrey Hospital, Redhill	2 yrs (2009 - 2010)	118 PICCs, 42 in 2009, 76 in 2010.	No report of malposition in	*42* *76*

				complications.	
Gururaj, 2013	**Heamatology patients**, Imperial College, Healthcare NHS Trust	2010-2012	36 (2010), 62 (2011), 58 (7mths in 2012)		*36* *62* *(99)*
Hughes, 2014	Velindre Hospital, Whitchurch		~460 Groshong PICCs placed annually. PICCs managed over @50 mile radius in a variety of settings.	Introduction of catheter securing device. Cost data included. All Wales **oncology** patients.	*460*
Walker & Todd, 2013	Raigmore Hospital, Inverness (577 beds)	4 mths (2012-13)	141 PICCs	Contains useful costing data?	*423*

Appendix 3: EAC quality check of sponsor model

Study name Sponsor economic model – Sherlock 3CG TCS		
Study design: Decision tree		
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	NHS & PSS
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	From the scope
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	Decision tree
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	4 published abstracts
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	n/a	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	n/a	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	n/a	Cost-consequences
13. Were the details of the subjects from whom valuations were obtained given?	n/a	
14. Were productivity changes (if included) reported separately?	n/a	
15. Was the relevance of productivity changes to the study question	n/a	

discussed?		
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	
22. Was the time horizon of cost and benefits stated?	Yes	Period to successful PICC insertion.
23. Was the discount rate stated?	n/a	No discounting was applied
24. Was the choice of rate justified?	n/a	
25. Was an explanation given if cost or benefits were not discounted?	n/a	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	n/a	
27. Was the approach to sensitivity analysis described?	Yes	One-way sensitivity analysis and multi-way scenarios were included.
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	

35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		