THE EFFECTIVENESS AND COST-EFFECTIVENESS OF ULTRASOUND LOCATING DEVICES FOR CENTRAL VENOUS ACCESS

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Authors: **Dr N Calvert, Research Fellow, ScHARR**

Dr D Hind, Research Associate, ScHARR

Dr RG McWilliams, Consultant Radiologist, Royal Liverpool University Hospital

Dr SM Thomas, Consultant Radiologist, Sheffield Teaching Hospitals

Ms C Beverley, ScHARR

Correspondence to: **Dr NW Calvert, ScHARR, University of Sheffield, Regent Court, 30 Regent St, Sheffield S1 4DA**

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ABOUT THE TRENT INSTITUTE

Trent Institute for Health Services Research is a collaborative venture between the Universities of Leicester, Nottingham and Sheffield, with support from NHS Executive Trent. Members of staff in the Sheffield Unit, based in the School of Health and Related Research (ScHARR), have been engaged in reviewing the effectiveness and cost-effectiveness of health care interventions in support of the National Institute for Clinical Excellence.

In order to share expertise on this work, we have set up a wider collaboration, InterTASC, with units in other regions. These are The Wessex Institute for Health Research and Development, Southampton University, The University of Birmingham Department of Public Health and Epidemiology, The Centre for Reviews and Dissemination, University of York.

CONTRIBUTIONS OF AUTHORS

Richard McWilliams carried out the review of the background information. Catherine Beverley undertook the electronic literature searches. Daniel Hind carried out the review of the effectiveness of the technology. Neill Calvert carried out the economic analysis and is responsible for the full report as lead author. Steve Thomas provided specialist advice and clinical guidance in the modelling work.

CONFLICTS OF INTEREST

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All responsibility for the contents of the report remains with the authors.

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Background

It has been estimated that about 200,000 central venous access procedures are performed annually in the NHS. Central venous catheters are inserted for a number of reasons including haemodynamic monitoring, delivery of blood products and drugs (e.g. chemotherapy and antibiotics), haemodialysis, total parenteral nutrition, and management of perioperative fluids. These procedures are performed in a wide range of locations within the hospital, using various insertion sites on the body, and by a variety of medical and nurse operators.

Central venous access (CVA) has traditionally been achieved using puncture of a central vein (venepuncture), passing the needle along the anticipated line of the relevant vein using surface anatomical landmarks and by knowing the expected anatomical relationship of the vein to its palpable, companion artery. This is known as the landmark method (landmark). Whilst experienced operators can achieve relatively high success rates with the landmark method with few complications (primarily arterial puncture and pneumothorax), failure rates in the literature have been reported to be as high as 35%. In high-risk patients, including ventilated and cardiac patients undergoing pacing procedures, a pneumothorax can be fatal. A recent National Confidential Enquiry into Perioperative Deaths report including a survey of some 3,000 central venous access procedures undertaken by the NHS also reported a death attributed to a pneumothorax.

The experience of radiologists suggests that venepuncture for central venous access can be achieved quickly with low failure and complication rates, through the use of ultrasonic locating devices (ultrasound). Medical ultrasound devices may be used to localise a vein in two ways. Ultrasound probes (US) generate a two-dimensional (2-D) grey-scale image of the vein and surrounding tissues. Doppler ultrasound (DUS) generates an audible sound from flowing venous blood. In practice the 2-D imaging technology is used in preference to the Doppler audio machines for this procedure.

This report has investigated the evidence for clinical effectiveness for both 2-D and Doppler ultrasound for specified outcome measures. The cost-effectiveness of real-time 2-D ultrasound has been modelled because no economic evaluations were found through the literature search.

A crude indicative estimate of the likely capital and training cost implications for the NHS is calculated to be £29 million in the year following any recommendation to promote the widespread use of 2-D real-time ultrasound. These costs would reduce significantly in subsequent years as the excess demand for new machines falls, and training of operators cascades down through the trusts.

Review of clinical effectiveness

A literature search identified references related to ultrasound locating devices and central venous lines. Where possible, the protocol was addressed by reference to RCTs; where none were available the next best evidence was sought. Only studies of the clinical effectiveness of using ultrasound or Doppler ultrasound locating devices for the placement of central venous lines were included. In terms of patient populations, only studies on groups requiring the

placement of central venous lines were included. In terms of comparators, only studies assessing 2-D ultrasound/Doppler ultrasound against the landmark method, or the surgical cutdown procedure were included. Only studies with one or more of the following outcomes were included: number of failed catheter placements, number of catheter placement complications, risk of failure on the first catheter placement attempt, number of attempts to successful catheterisation, number of seconds to successful catheterisation, rate of success after failure by the alternate method (where a crossover design was incorporated).

Twenty randomised controlled trials (RCTs) of variable methodological quality were retrieved in the literature search. The studies investigate the clinical effectiveness of ultrasound with landmark as the comparator. Outcome measures include failure rates for first and subsequent attempts, complication rates, and number of needle passes and time to successful insertion. Data extraction was performed and the results pooled for meta-analysis where appropriate.

Of the 20 RCTs, 13 address 2-D ultrasound versus landmark, 6 address Doppler ultrasound versus landmark, and 1 contains all three methods. Sample sizes vary but are generally small, and in some cases so small that statistical power is difficult to achieve if such studies are analysed in isolation. Of the 13 2-D studies, seven addressed internal jugular vein cannulation in adults, one addressed subclavian vein insertions, and one RCT addressed femoral vein insertions, both in adult patients. Three of the RCTs analysed internal jugular vein insertions in infants. One does not report the insertion site. Of the Doppler studies, four address adult internal jugular vein insertions and three address subclavian vein insertions. Only one very small study researches central venous access in children using the internal jugular vein.

The trial evidence suggests that real-time 2-D ultrasound guidance is significantly better than landmark for all five outcome variables measured for insertions into the internal jugular vein in adults. The results also favour ultrasound for insertions into the subclavian and femoral veins in adults although these results are based on only one RCT each. For the three infant studies addressing insertion into the internal jugular vein, the results again suggest that ultrasound has statistically significant beneficial outcome effects over the landmark method.

Only the results for Doppler guided insertions into the internal jugular vein in adults reported in four RCTs indicated improved failure and complication rates for Doppler over landmark. The other 3 Doppler based RCTs show little if any statistical support for Doppler over landmark for adult subclavian vein insertions and internal jugular vein insertions in children. For clinically experienced operators, proficient only with the landmark method, Doppler increased the number of failed catheter placements in attempts to catheterise the subclavian vein. The extent to which it is possible to generalise from these results for Doppler is unclear. In most of the Doppler trials, the participants were inexperienced in the ultrasound intervention, or both the intervention and the control procedure.

The use of Doppler ultrasound is less common than its 2-D imaging counterpart. This fact, together with the results of the effectiveness evidence which show Doppler to be less effective compared to 2-D ultrasound, means that only 2-D ultrasound has been considered for economic analysis in this report.

Economic Analysis

No relevant economic analyses were found in the literature. Economic modelling using a spreadsheet decision analytic model has been carried out to assess the cost-effectiveness of 2-D ultrasound versus landmark methods. Costing analysis indicates that the marginal economic cost of using ultrasound for central venous access is less than £10 per procedure. This cost analysis is sensitive to the assumptions made about machine usage and the central scenario assumes that a machine is used for 15 procedures each week for example. Other central scenario assumptions are conservative in that they have been deliberately cautious about the potential economic costs and benefits of ultrasound. For example, the model has used failure and complications rates only from RCTs where the operator was experienced in the use of the landmark method so that these outcome measures are weighted in favour of the landmark method.

Economic modelling results using the clinical effectiveness evidence to populate the model indicate that using ultrasound for venepuncture in central venous access is likely to save NHS resources as well as improve failure and complication rates. The central scenario implies that £2000 worth of resource savings result for every 1000 procedures undertaken. Most of these resource saving will be freed up time for clinicians, nurses, operating theatres, intensive therapy unit (ITU) and ward beds, though some financial saving will accrue from a reduced need to treat complications.

Sensitivity analysis indicates that the results of modelling appear robust to the central assumptions used and that the resource saving assumptions result is likely to hold for the three main insertion sites, and for both adults and children. The modelling results are most sensitive to ultrasound machine usage assumptions implying that it will be important that purchased machines are used sufficiently often to make them economically efficient. Staff training programmes must also be set up in a cost-effective way.

Implications for the NHS

Ultrasound guided central venous access is a skill that needs to be learned if procedure induced complications are to be avoided. Radiology has lagged behind surgery in the development of skills laboratories where techniques are learned and initial errors made at the bench rather than at the bedside. Perhaps not everyone can learn ultrasound guided venous access, but it is highly likely that most individuals who need to, can learn these skills. There are significant training implications if the ultrasound-guided procedure is to be advocated. Economic modelling indicates that training schemes must be set up in a cost-effective way in order to ensure that the ultrasound procedure is itself cost-effective. Training of medical and nursing staff will need to be co-ordinated and agreed amongst the professional bodies.

In emergency situations where a line needs to be inserted without delay, landmark insertions may still be appropriate. It is important that training in ultrasound-guided access must allow operators to remain skilled in the landmark methods. Again the professional bodies will have a role to play in ensuring that this happens.

The clinical and cost-effectiveness evidence presented in this report is favourable towards the use of ultrasound for central venous access of the internal jugular vein. The evidence for insertion at other sites such as the subclavian and femoral veins is also positive and statistically significant although only one trial is reported for each. If machines are purchased to guide internal jugular vein insertions, then policy makers will need to consider how ultrasound should be used for central venous access for non-internal jugular vein insertions,

primarily the subclavian vein. If subclavian insertions were to be performed without ultrasound, when machines are available, this could lead to avoidable complications, which in the worst scenarios could lead to medico-legal implications if patients were to pursue litigation. Likewise, the implications of a policy of more widespread use of ultrasound for operators already experienced in the use of landmark methods, and with good failure and complication rates, will also need to be addressed.

If ultrasound is not to be recommended for real-time subclavian insertions or experienced operators, but ultrasound machines are available, policy makers and the professional bodies may want to consider a compromise policy of advocating ultrasound for patency checking and vessel localisation as a minimum for experienced operators and other insertion site scenarios.

Increased use of ultrasound will have short-term resource implications for trusts both in terms of purchase of machines and training of operators. This will mean both short term and ongoing capital and training investment.

Further Research

No RCT evidence was found for the effectiveness of using ultrasound for peripherally inserted central catheters (PICCs) or for ultrasound versus surgical cutdown. These areas could be targeted for further research. Nursing staff are increasingly being trained to insert central venous lines. A recent study based in Manchester demonstrated that nurses can safely insert Hickman catheters in cancer patients using landmark method and image guidance using fluoroscopy. This service development, which can free up the relatively expensive time of junior and senior doctors alike, has not been addressed in the current review. The possible economic and clinical implications of nurse operators in the NHS may be a useful area for further research.

Conclusions

In conclusion, this report has presented evidence for the effectiveness and cost-effectiveness of ultrasound-guided venepuncture versus more traditional landmark methods. The effectiveness and economic modelling evidence indicates that 2-D ultrasound is both more effective and likely to be resource saving for internal jugular veins in both adults and children. A small volume of RCT evidence also supports the use of ultrasound for subclavian and femoral vein insertion. Wider use of ultrasound for internal jugular vein insertions will have implications for staff training, potential issues of deskilling, and issues of policy implementation for non-internal jugular vein insertions. The implications of any recommendations for more widespread use of ultrasound for operators already experienced and skilled in landmark procedures for all insertions sites will also need to be addressed.

LIST OF ABBREVIATIONS

CICU	Coronary intensive care unit
CPR	Cardiopulmonary resuscitation
CVA	Central venous access
CVC	Central venous catheter
CVL	Central venous line
DUS	Doppler ultrasound
FV	Femoral vein
HDU	High dependency unit
HTA	Health technology assessment
ICU	Intensive care unit
IJV	Internal jugular vein
LIJV	Left internal jugular vein
LM	Landmark method
MTO	Medical technical officer
NCEPOD	National confidential enquiry into perioperative deaths
NHS EED	NHS economic evaluations database
PICC	Peripherally inserted central catheter
RCT	Randomised controlled trial
RIJV	Right internal jugular vein
SHO	Senior house officer
SV	Subclavian vein
ULD	Ultrasonic locating device
US	Ultrasound

1 AIM OF THE REVIEW

Central venous access (CVA) including catheter insertion is routinely practised in a variety of emergency and elective situations and for a variety of clinical reasons. Traditionally the venepuncture procedure for central venous access has been done using blind 'landmark' methods (LM) to locate and guide needle insertion into the target vessel. Occasionally, though more rarely, a surgical cut-down procedure has been used to achieve central venous access.

This rapid review investigates the effectiveness and cost-effectiveness of using ultrasound locating devices (ULDs) for the venepuncture procedure. The report focuses on the use of 2-dimentional real-time grey scale ultrasound imaging as an alternative to the traditional landmark method.

2 BACKGROUND

2.1 THE UNDERLYING NEED FOR CENTRAL VENOUS ACCESS

Central venous access including catheter insertion is routinely practised in emergency and elective situations for haemodynamic monitoring, delivery of blood products and drugs (e.g. chemotherapy and antibiotics), haemodialysis, total parenteral nutrition, and management of perioperative fluids. Patients needing central venous access include cancer patients, dialysis patients, patients admitted to Intensive Therapy Units (ITU) and High Dependency Units (HDU), and patients undergoing coronary and other major surgery. Given that no routine data are collected, it is difficult to estimate how many catheters are placed each year in the NHS, although in a paper published in 1994 it was estimated that there are around 200,000 central venous access procedures performed in the NHS each year.[1]

Central venous catheters are inserted in a wide range of settings within a hospital by a diverse group of doctors including radiologists, anaesthetists, nephrologists, oncologists, surgeons, and general medical doctors. Nurse specialists in the USA and increasingly in the UK are also undertaking catheter insertions.[2] The range of settings includes operating theatres, emergency rooms, nephrology, oncology and other wards, radiology departments and intensive care, and high dependency units.

Central venous access can be achieved using various puncture sites on the human body but most commonly using the internal jugular vein (IJV), the subclavian vein (SV), femoral vein (FV), or upper limb veins (using peripherally inserted central catheters-PICCs). The choice of access route depends on multiple factors including the reason for central venous access, the anticipated duration of access, the sites available and the available skills.

If high flow rates are needed through a central venous catheter then a large diameter catheter is needed which precludes access from the small peripheral veins of the arm. High flow rates are needed for patients requiring large volumes of blood products and those undergoing haemodialysis. The large veins that may be accessed are the femoral, subclavian and jugular veins. Although good data are not available nationally to breakdown the number of procedures by site of access, it is likely that the majority of central venous access procedures are attempted initially by the internal jugular vein. Some clinicians use the subclavian route by preference although the internal jugular vein is generally considered to be technically easier and to have a lower complication rate. Femoral venous access is used infrequently as there is a higher risk of catheter infection as the catheter tracks through the groin area and also a greater risk of catheter-related venous thrombosis.

When the anticipated duration of central venous access is short then non-tunnelled lines are used where there is no subcutaneous tunnel and the catheter exits the skin through the same site that the vein is punctured. Infection and accidental line withdrawal are important risks of long-term venous access. To minimise these risks a tunnelled line may be used. Central venous access is achieved in the same way as for non-tunnelled lines. However, the catheter passes through a subcutaneous tunnel from

the point of venous access to exit the skin several centimetres away. The subcutaneous portion of the catheter contains a cuff of synthetic material that causes local scarring, which both holds the catheter in place and reduces the risk of bacteria passing from the skin surface to the bloodstream.

The first step in establishing percutaneous venous access is safe puncture of a central vein (venepuncture). This may be achieved by passing the needle along the anticipated line of the relevant vein using surface anatomical landmarks and by knowing the expected anatomical relationship of the vein to its palpable, companion artery, in the case of the internal jugular vein. This "landmark technique" has been the traditional approach to venepuncture. Surgical 'cut-down' is a more invasive and alternative method for gaining central venous access, although this technique is rarely used. This report is primarily concerned with examining the most effective and cost-effective way of achieving successful and safe venepuncture during the placement of central venous lines.

2.2 VENEPUCTURE COMPLICATIONS

It is not always possible to achieve a successful catheter placement using the chosen puncture site. Anatomical relationships are variable and variant anatomy will result in failure when the operator passes the puncture needle in a direction that the vein does not follow. A long-term complication of central venous access is vein thrombosis. Many patients undergoing central venous access procedures will have had multiple previous episodes of central catheterisation. If the relevant vein has thrombosed then the landmark method will fail irrespective of the anatomical course of this thrombosed vein.

Each pass of a needle during the venepuncture procedure carries with it the risk of complications. Successful access at the first attempt is clearly the ideal for minimising the risk of complications. In the case of a thrombosed vein, for example, an operator may make numerous needle passes before realising that access is not possible at the chosen puncture site. Each pass of the needle increases the risk of complication as well as delaying subsequent catheter placement. Failure or delayed central venous access may delay important treatments in ill patients

The complication rate from these procedures varies. The complications of central venous access procedures range from minor issues to uncommon but possibly fatal haemorrhage. The most common complications are arterial puncture, arteriovenous fistula, pneumothorax, nerve injury and multiple unsuccessful attempts with delayed treatment. The risks and the consequences of complications vary substantially across patients and patient groups. For example, infants, obese patients, and patients with short necks are more difficult to puncture. Also, patients with clotting problems, ventilated patients, and cardiac patients undergoing emergency pacing procedures may suffer more serious consequences (including death) from a venepuncture complication. A recent report of the National Confidential Enquiry into Perioperative Deaths (NCEPOD) indicates that in a survey of over 3,000 central venous access procedures undertaken in the NHS, one death occurred as a result of a procedure induced pneumothorax.[3] It is particularly important that the risks of failed insertion and complications are minimised. Having said this, any procedure undertaken in resource intensive surroundings like theatres and ITU/HDU make it important, from

both a clinical and a resource point of view, that venepuncture for central venous access is achieved as quickly and as safely as possible.

2.3 CURRENT SERVICE PROVISION

The preceding discussion highlights the difficulties of deriving estimates of the number of central venous catheter (CVC) placed annually within the NHS. Based on sales figures from appropriate catheter suppliers, one of our expert advisers has estimated the number of central venous catheterisations for a teaching trust in Liverpool to be in the region of 1,500 per annum. This figure includes all tunnelled Hickman and dialysis lines, temporary central venous access lines, and peripherally inserted central catheters. A similarly derived estimate for the Sheffield Teaching Hospitals NHS Trust is over 3,700 catheters per annum.

Data are not readily available to break down these figures for different speciality groups, sites of access, and insertion technique employed. The Sheffield Teaching Hospitals NHS Trust has estimated that their own figures imply that 46% of the total is accounted for by cardiac surgery and coronary intensive care unit (CICU), 32% by general ITU/HDU units, and 8% for renal patients. In major renal centres such as Leeds, the proportion of catheter placements might be expected to be higher for renal patients. Better data are available from the United States where it is recorded that of 835,003 central venous catheter insertions in 1999, 80% were temporary non-tunnelled lines and 20% were tunnelled permanent lines.[4] Radiologists inserted 15% of temporary and 20% of tunnelled lines in 1999. Surgeons placed the majority (72%) of tunnelled lines. Anaesthesiology (36%) and surgery (24%) were the major speciality groups inserting non-tunnelled central venous catheters.

Although there are likely to be some differences in these percentages in England and Wales, it is highly probable that anaesthetists and surgeons, as in the United States, insert the majority of non-tunnelled lines. It is also probable that surgeons and anaesthetists insert the majority of tunnelled lines.

It is difficult to estimate the cost of venepuncture in CVL placement because of the paucity of costing data in this area. The disposable equipment, such as the needle used in the procedure will cost pence rather than pounds. The major cost of the procedure will be the time resource for the operator to achieve successful venepuncture. This will normally be only a few minutes, although failed insertions can take up to three-quarters of an hour.[5,6] In an expensive ITU unit and using a highly qualified operator for example, the opportunity cost of a difficult insertion will be considerably more than a successful venepuncture achieved with the first pass of the venepuncture needle. Complications induced by the venepuncture may have only minor resource implications. Alternatively, a serious complication such as pneumothorax in a high-risk patient who then needs to be hospitalised for a number of days for treatment and monitoring can use hundreds or even thousands of pounds worth of resources.

2.4 DESCRIPTION OF THE NEW INTERVENTION

Ultrasound has traditionally been the domain of radiologists and ultrasonographers. Radiologists use ultrasound to guide percutaneous procedures at multiple sites such as

the kidneys, liver, arterial and venous circulation, pleural cavity, gallbladder, joints and bowel. This expertise is applied to central venous access procedures where there are large series that record 100% success for right internal jugular access with no clinically important complications.[7] One of the largest series from the interventional radiology literature records a 99.4% initial success rate in deployment of tunnelled central lines with no major complications in a group of 880 consecutive patients.[8] Central venous access in all these patients was achieved with real-time ultrasound guidance.

The previous discussion has shown the diverse clinical indications requiring venepuncture for central venous catheter placement and the numerous sites where the procedure is undertaken both within the hospital and on the human body. Portable ultrasound machines now exist with the functionality for high quality imaging and can be used in theatres, ITU/HDU suites, and at the bedside on the hospital ward, as well as in the radiology suite. It is now standard practice for radiologists to use ultrasound imaging to guide the venepuncture procedure in central venous catheter placement. However, radiologists do not perform the majority of central access procedures. Anaesthetists, renal physicians, surgeons and cardiologists all regularly establish central venous access. Some of these doctors already use some form of ultrasound localisation. In principle, and with adequate training for the operator, it is theoretically possible that ultrasound-guided venepuncture be used for all of the clinical scenarios discussed above.

The ultrasound image can be used to confirm the anatomy and patency of the vein (the state of being freely open or exposed). It has been reported that the sensitivity and specificity of ULD for detecting thrombosed vessels for example is 100%.[9] Having established these, the ultrasound machine can be dispensed with at the time of venous puncture.[10] Most radiologists, however, would go on to use the ultrasound to guide the venous puncture in real-time.

Two main types of ultrasound have been used for this procedure in recent years.

Audio Guided Doppler Ultrasound
Continuous wave Doppler ultrasound may be used to generate an audible sound from flowing venous blood. The audio-guided technique relies on the Doppler principle, which is the frequency shift that occurs when an ultrasound pulse is reflected by a moving object. The reflectors in veins are moving red blood cells and the frequency shift that occurs when ultrasound is reflected from veins in a breathing patient results in a characteristic pattern of sound that can be used to localise a vein and differentiate the vein from its companion artery. If the vein is localised then its site can be marked to assist percutaneous puncture. This technique can be used with reusable hand-held continuous wave pencil-like Doppler probes and also with single-use needles that contain an ultrasound crystal at their tip. Neither of these techniques is widely used.

2-Dimensional Image Ultrasound

The most commonly used ULD is an ultrasound probe linked to an ultrasound machine to provide real-time grey-scale imaging of the anatomy. A grey-scale image is generated by an ultrasound probe and machine. Superficial structures such as the jugular veins are best seen with ultrasound frequencies in the range 5-10MHz. A real-time image allows the operator to identify the vein and distinguish the vein from its companion artery. The vein does not pulsate, if patent is compressible and is of more variable shape than its companion artery.

Some experience of ultrasound anatomy is necessary to reliably interpret ultrasound images. For example, cervical lymph nodes in patients with lymphoma, who often need venous access, can look remarkably like a vein on a single cross-sectional image of the neck. Many ultrasound machines incorporate a Doppler facility with the ability to generate grey-scale images. This dual-mode or duplex scanning allows the operator to image the vein and confirm with certainty that this is not an artery by the additional use of Doppler ultrasound. In practice, this additional functionality is rarely needed.

The ultrasound image is generated by a series of crystals in the ultrasound probe, which transmit and receive ultrasound waves. When this is understood, the operator can image the vein and know which part of the probe is generating the image of the vein. Thus, if the vein is directly in the middle of the image a needle passed through the skin where the middle of the probe contacts the skin will travel in the direction of the vein. Some ultrasound probes incorporate a needle-guide either as an integral part of the probe or as a removable attachment. The needle-guide controls the movement of the needle in a predetermined and defined path in the image plane. The ultrasound machine plots the line of the needle on the monitor and as the needle is now fixed in one plane, an initial three-dimensional problem is reduced to a two-dimensional one.

Some ultrasound imaging equipment is dedicated solely to superficial imaging of the neck. These machines are cheaper than newer portable machines but the image quality of the dedicated machines is inferior. As well as providing better image quality the newer portable machines open up other possibilities for the wider use of medical ultrasound. A machine with additional functionality on an intensive care unit may, with training, allow for ultrasound-guided drainage of pleural effusions, rapid diagnosis of cardiac tamponade, aspiration of ascites and other procedures. This will have implications for the cost-effectiveness of ultrasound-guided CVL placement.

Real-time scanning during needle passage is a skill that is not universal and has the potential to cause complications in the hands of untrained operators. Ideally the operator should hold the probe in a sterile cover in one hand and pass the puncture needle using the other hand guided by the ultrasound image. Some series record this as involving two people – one to hold the probe and the other to pass the needle.[11] This two-operator technique is cumbersome, unnecessary when experienced, adds to the expense of the procedure and compromises the potential of ultrasound-guided access in emergency situations.

Resource Implications

The purchase cost of these portable machines currently varies between £7,000 and £15,000.[12] The additional disposables necessary for the ultrasound-guided procedure cost less than £1 per procedure. Estimates made in this report indicate that the additional cost of using ultrasound equipment for the central venous access procedure is likely to be less than £10 per procedure. This is discussed further in section 4.

What is less clear is how many machines need to be purchased if ultrasound were to be adopted as standard practice for central venous access across the NHS in England and Wales. This will depend on both the extent of the policy recommendations, and the current supply of suitable portable ultrasound machines in NHS trusts.

In order to provide a ballpark estimate of the possible costs of a policy to adopt widespread use of ultrasound for central venous access, a crude estimate of the possible capital and training costs implications has been calculated. Such an analysis carries many caveats. A DoH website quoting hospital activity statistics[13] indicates that there are approximately 2000 operating theatres (excluding dedicated daycase theatres) in England. The data are disaggregated to trust level analysis. Assuming one ultrasound machine for every three theatres, the estimated number of machines required by each trust has been estimated (rounding up or down to the nearest whole number) and aggregated to 660 machines for England as a whole.

The health service financial database[14] indicates that there are 193 English trusts (teaching, acute, and small to large multi-service units) and 16 Welsh trusts. Pro rata, this implies a total of 715 machines required for England and Wales operating theatres. Assuming three additional machines per trust to service ITH/HDU, A&E, and ward use implies a total of 1,342 machines. Costing at £11,000 per machine gives a total machine cost of circa £15m. Existing available machines will mean that this figure is an over estimate. Additional ward and specialist (e.g. renal) unit requirements may mean this figure is underestimated.

Training costs are the other major resource requirement. Again only a ballpark figure carrying many caveats is presented for indicative purposes. It is assumed (for illustrative purposes only) that a consultant radiologist/anaesthetist/surgeon has half of their time allocated to training relevant trust staff in the year following possible policy implementation. Assuming a Consultant staff cost of £134,000,[15] the estimated training cost is £14.0m for England and Wales in year one of implementation. In subsequent years this cost might be expected to fall as skills are cascaded downwards and the trained become trainers. This cost estimate does not include the trainee's time, or any capital cost requirement for training laboratories and dummies.

Thus, for the year following an assumed policy implementation, a crude estimate of capital and training costs is £29m. This figure is clearly indicative only and carries many caveats.

Anecdotal evidence gathered during the preparation of this report indicates that the current availability of suitable machines varies from trust to trust. The Sheffield Teaching Hospitals trust, for example, has only one machine that is used occasionally by an anaesthetist. In Leeds, on the other hand, some 12 or so machines are available

for use in their theatre and ITU/HDU suites. The resource implications of wider adoption of ultrasound for central venous catheter placement will clearly vary significantly by trust.

Other Uses

It is often stated that ultrasound assists only with the venous puncture and does not help with guide wire introduction. This is not so in experienced hands, where the guide wire can be imaged in the jugular vein and ultrasound at the root of the neck can be used to confirm that the wire has passed into the brachiocephalic vein and not the subclavian vein. Ultrasound also confirms that the wire has not passed through the posterior wall of the jugular vein into the carotid artery, which is potentially the beginning of the rare complication of an arteriovenous fistula. This additional use of ultrasound is not difficult to learn. Ultrasound is not used during the introduction of the dilators and sheaths prior to line introduction and the hazards that are relevant to these stages are not avoided with ultrasound but may be avoided by the use of fluoroscopy. Traditional ultrasound techniques have not been used to assess the position of the line tip and this is achieved either with fluoroscopy at the time of insertion or with a post-procedural chest radiograph.

This report only concerns itself with the evidence for the effectiveness and cost-effectiveness of using ultrasound in the venepuncture part of central venous catheter placement.

3 EFFECTIVENESS

3.1 METHODS FOR REVIEWING EFFECTIVENESS

3.1.1 Search strategy

The search aimed to identify references related to ultrasound locating devices and central venous lines. The searches were conducted in September and October 2001.

3.1.2 Sources searched

Fifteen electronic bibliographic databases were searched, covering biomedical, science, social science, health economic and grey literature (including current research). A list of databases is provided in Appendix 1.

In addition, the reference lists of relevant articles were checked and various health services research related resources were consulted via the Internet. These included health economics and HTA organisations, guideline producing agencies, generic research and trials registers, and specialist sites. A list of these additional sources is given in Appendix 2.

The sponsor submissions were hand searched for any new potential randomised controlled trial citations.

3.1.3 Search terms

A combination of free-text and thesaurus terms were used. Central venous line search terms (e.g. catheterisation, central venous/, central venous line, PICC, venous cannulation, central venous catheter, pulmonary artery flotation, central line insertion, Hickman line, etc.) were combined with 'ultrasound' terms (e.g. ultrasonics, ultrasonography, imaged guidance, ultrasound, Doppler, etc.) Copies of the search strategies used in the major databases are included in Appendix 3.

3.1.4 Search restrictions

Where possible (e.g. in the smaller databases), searches were not restricted by publication type or study design. However, methodological filters aimed at identifying guidelines, systematic reviews, clinical trials, economic evaluations, and quality of life studies, were used in Medline (refer to Appendix 4 for details of the filters used). Date and language restrictions were not used.

3.1.5 Inclusion and exclusion criteria

Only studies of the clinical effectiveness of using ultrasound or Doppler ultrasound for locating devices for the placement of central venous lines were included. In terms of patient populations, only studies on groups requiring the placement of central venous lines were included. In terms of comparators, only studies assessing 2-D ultrasound/Doppler ultrasound against the landmark method, or the surgical cutdown

procedure were included. Only studies with one or more of the following outcomes were included: number of failed catheter placements, number of catheter placement complications, risk of failure on the first catheter placement attempt, number of attempts to successful catheterisation, number of seconds to successful catheterisation, rate of success after failure by the alternate method (where a crossover design was incorporated).

The abstracts of potentially relevant citations were reviewed. After examining the full manuscripts of all potentially relevant abstracts, those deemed to be potential randomised controlled trials relating directly to the scope question were obtained, i.e. the effectiveness of ULD against the landmark method or surgical cutdown procedure with respect to central venous access.

All non-English language papers were excluded, as were trials with a quasi-random design. Trials that dealt with the use of ultrasound for vessel localisation, but not for insertion, were dealt with separately from those that dealt with both.

3.1.6 Data extraction strategy

Data extraction was undertaken by one researcher and checked by another. Disagreement was resolved by consensus. Data on the number of catheters and/or the number of patients were abstracted the way they were reported, as were data about mechanical complications. The numbers of patients with complications were pooled for purposes of meta-analysis; where known, the individual complications were reported in Table 13, Appendix 5. Catheters were the unit of analysis when data were pooled, which is to say that the number of catheter placements, rather than the number of patients were recorded.

3.1.7 Quality assessment strategy

Randomised controlled trials were *not* rated according to the validated quality scale devised by Alejandro Jadad and others.[16] This is because the Jadad system relies heavily on blinding without allowing for the fact that blinding is not possible in trials of certain interventions (ULD's being a case in point). Instead, a component approach[17] was adopted to assess trial quality. This took into account six individual quality domains and their associated biases.

First, the number of patient characteristics reported out of five key variables was recorded: the greater number, the greater the external validity of the study. Following the approach taken by Randolph *et al.*,[18] the selected variables were: age, sex, diagnoses, coagulopathy and body surface area or height weight ratio. The last two are commonly associated with risk assessment in the insertion of central venous catheters. Second, the standardisation of the insertion method was recorded, a factor affecting the internal statistical validity of the trial. Third, the method of randomisation was recorded, where reported, to assess the potential for bias. Fourth and fifth, the number of post-randomisation exclusions was recorded, as well as whether or not intention-to-treat analysis was performed. These last two factors were included to reflect the potential presence of attrition bias.

3.1.8 Data Analysis

Data analysis was performed using the Cochrane Collaboration's Review Manager 4.1 software package. Data to estimate the relative risk and associated 95% confidence limits across studies using the random effects model were combined. Statistical heterogeneity (major differences between studies in the estimates of apparent effects of the interventions) was tested for to assess whether the observed variance in effect size between studies is greater than that expected to occur by chance. Using the null hypothesis that the relative risks were the same across studies, the *p*-value for the heterogeneity test indicates the statistical significance of the differences in study results. The significance of this p-statistic in the test for heterogeneity, is that the pooling of studies that are shown to be heterogeneous can lead to the reporting of insignificant p-values for the outcome variable of interest, when this p-value may actually be significant for homogeneous subsets of the pooled studies. A significant outcome variable p-value, combined with a significant heterogeneity test p-value result, implies that the outcome variable is statistically significant despite the presence of heterogeneity.

3.2 RESULTS

3.2.1 QUANTITY AND QUALITY OF RESEARCH AVAILABLE

3.2.1.1 Number of studies identified and excluded

Twenty-seven RCTs were identified, which evaluated the clinical effectiveness of using ultrasound/Doppler ultrasound versus the landmark method in the context of central venous access. Three were excluded on the grounds that the method of allocation was unclear and the trials were not described as randomised.[19,20,21] Two quasi-randomised trials, which used alternate or sequential designs, were excluded.[22,23] No additional studies were identified from the sponsor submissions.

3.2.1.2 Number and type of studies included

There were 20 prospective, randomised trials (including two abstracts[24,25]), as well as one meta-analysis,[18] assessing 2-D ultrasound-guided vessel localisation followed by 2-D ultrasound-guided venepuncture versus a control, three of which[26,27,28] incorporated a cross-over element (Appendix 5, Table 8). The abstracts have been included in the data extraction, but excluded from the meta-analyses. The authors felt it unnecessary to look for further evidence on this central issue. There were also two prospective, randomised trials concerned with Doppler ultrasound-guided vessel localisation followed by blind venepuncture.[29,30] These are discussed in Section 3.3.1.

In each included trial, the comparator was the landmark method, except for one[31] where the comparator was blind venepuncture preceded by ULD-guided vessel-localisation; there were no trials which compared the use of ULD against surgical cut down for the clinically effective placement of central venous catheters. In each case, the unit of analysis was the catheter placement (as opposed to the individual patient; an individual receiving two placements *would* be recorded twice), but the sample size

varied enormously. Eight studies recorded the placement of under fifty catheters and only two studies recorded the placement of over two hundred catheters.[32,26]

There were 20 RCTs evaluating ultrasound guidance or Doppler ultrasound guidance for placement of central venous catheters. Seven evaluated Doppler ultrasound guidance against landmark method, twelve evaluated ultrasound guidance against landmark method and one evaluated both Doppler ultrasound and ultrasound guidance against a control as well as each other (Appendix 5, Table 9).

The Doppler ultrasound guidance methods included: the SMART® Needle Doppler[26,27,33,5,34] with the 14 MHz continuous-wave probe in the needle (Peripheral Systems Group, Mountain View, CA, USA); pulsed (4 MHz)[6,32]and continuous-wave[32] transducers (Vermon SA, Tours, France).

The non-Doppler ultrasound guidance methods included: the Site Rite® 7.5 MHz[35,36,5] or 9 MHz[37] transducers (Dymax Corporation, Pittsburgh, PA, USA) (another trial[10] also used a Dymax portable, 2-D ultrasound 7.5 MHz transducer, but the model name was not reported); the Sonos 100 7.5 MHz[38] and Sonos 500 5 MHz[36] 2-D ultrasound transducers, the 7702A 5 MHz real-time 2-D ultrasound[28] and an unspecified 2-D, 5-MHz surface ultrasound transducer[39] (all Hewlett-Packard, Andover, MA, USA); 650 CL. 7.5 MHz real-time ultrasound probe (Aloka, Tokyo, Japan); the SDR[40] (Phillips, Eindhoven, Netherlands), with 7.5 MHz probe; the CS9100 (Picker International (now Marconi) Medical Systems, Highland Heights, OH, USA); and the SSA 270A[11] 5MHz transducer (Toshiba, Tokyo, Japan). Two further trials that used a 5 MHz 2-D real time ultrasound transducer[24] and a 7.5 MHz probe did not specify the manufacture or model of the devices.

It should be noted that one trial[36] used both the Site Rite® 7.5 MHz and Sonos 500 5.0 MHz in the same ultrasound arm of the trial without distinguishing on which patients each was used. Another[5] used the SMART® Needle Doppler in one arm, the Site Rite® 7.5 MHz in the second and the landmark method in the third.

Catheter size was specified in only seven studies but, even from those, it is clear that a variety of gauge-measurements were in use between and even within[39] trials. The use of fluroscopy was not recorded for any trial. Only two studies[35,5] reported the use of a needle-guide.

Lines were placed by anaesthetists in seven studies[33,34,39,32,37,5,10] and by medical staff in four.[25,26,28,41] Only one study involved 2-D ultrasound-guided line-placement by junior radiologists,[40] and none by nurses. The remaining nine studies did not make the specialty or profession of the operator clear. The range of experience, both with respect to the medical career and use of the intervention, differed greatly from study to study. Six studies described the operators as having up to five years postgraduate experience,[41,27,35,38,37,25] eight as having more than five years,[26,10,33,28,34,39,32,5] and two as varying in experience.[31,6]
Four trials did not record the career experience of the operator.[24,40,36,11]

In terms of experience in the use of the ULD, only one study[39] made a claim of expertise for the operator, although this was not quantified. One study[32]

acknowledged that its lone operator had no experience prior to the trial, as one purpose of the trial was to gauge the learning curve. In three studies,[27,41,37] the operators were inexperienced both with ULD-guidance *and* with the landmark method. In a further six,[6,26,35,34,38,25] the operators were inexperienced with ULD-guidance and did not refer to their relative experience with the landmark method. Where this inexperience was defined, it was only in one study[35] where the operator had cannulated more than ten (but less than thirty) patients with the ULD. Four more[41,37,34,38,6] all recorded less than ten 2-D ultrasound-guided cannulations prior to the trial, and in one of these,[6] the operators only had to demonstrate one successful cannulation, using the ULD, prior to the trial. Nine studies did not record the operators' ULD experience.[5,31,24,10,11,40,36,28,33]

Few of the studies were clear about the where cannulation took place within the hospital. Six, took place on the intensive care/trauma units.[28,35,32,24,38,27] Two took place in emergency rooms,[25,41] In the seven studies involving patients scheduled for cardiac surgery, cannulation is most likely to have taken place on the way into theatre.[10,37,5,39,36,34,33] Only three, seem likely to have taken place on wards or in clinics.[26,40,11]

In all trials, insertion sites were the internal jugular, subclavian or femoral veins; none addressed the placement of PICCs or ports, both of which can be considered types of central venous catheter. Fifteen trials reported outcomes for the internal jugular vein (five right internal jugular vein,[34,10,36,40,38] two both sides,[39,31] eight side not reported[28,27,33,5,6,24,11,37]), four for the subclavian vein (two both sides,[35,32] two side not reported[26,6]) and one for the femoral vein (both sides).[41] One trial[25] did not specify the insertion point. One trial[6] investigated the intervention's efficacy in the cannulation of both the internal jugular vein and the subclavian vein.

Patient characteristics differed from trial to trial (Appendix 5, Table 8, Table 11). Most of the studies were concerned with catheter insertion in adults, only three trials[10,37,5] recording patient populations of infants or neonates. All the latter cases involved patients about to undergo cardiac surgery. In the adult trials, four studies[39,36,34,33] involved patients scheduled for cardiovascular/cardiothoracic surgery; five [28,35,32,24,38] concerned patients in ICU; two,[31,6] patients undergoing dialysis; one,[27] patients in ICU or on dialysis; two,[25,41] patients in the emergency room; one,[26] patients receiving chemotherapy; one,[40] patients undergoing transjugular liver biopsy; and one[11] merely described cannulation as 'routine'.

Three trials[26,27,40] deliberately targeted high-risk patients with coagulopathies or obesity, factors associated with increased risk for failure or complication with respect to catheter insertion; low-risk patients were excluded in these trials. Two trials[32,6] deliberately excluded patients for whom CVA was high-risk, because of coagulopathies or obesity, and included only low-risk patients. Only one trial[26] recorded including patients with a history of surgery or radiotherapy in the area, also associated with increased risk for failure or complication. Three trials[10,32,39] reported deliberately excluding patients with these factors.

The studies were of varying quality (see Section 3.1.7). In terms of the number of patient variables (age, sex, diagnoses, coagulopathy and body surface area or height

weight ratio), only one study[32] recorded all five key variables. Five studies[26,36,40,27,33] recorded four variables, three[41,39,24] recorded three, one[38] recorded two, five recorded one,[5,34,31,10,37] and five[6,11,35,25,28] recorded none of the variables. All of the studies except the two abstracts[24,25] had clearly standardised the catheter insertion method. Eleven studies did not report the randomisation method.[28,36,34,27,33,24,10,25,40,38,11] All the others reported truly random allocation methods (computer-generated numbers, random tables, lot). Only two studies[33,35] reported post-randomisation exclusions. Neither undertook intention-to-treat analysis, and the systematic differences between comparison groups, in terms of withdrawals or exclusions of participants from the study sample, suggests the results were affected by 'attrition bias'.[42] Attrition bias arises because of inadequacies in accounting for losses of participants due to dropouts or exclusions, leading to missing data in the results. The statistical validity of a report displaying attrition bias is questionable. Only in one of the abstracts[24] was it unclear whether intention-to-treat analysis had taken place or not. There was no apparent attrition bias in any of the other reports.

3.2.1.3 Discussion of results

The choice of outcome measures varied between trials. We selected the following for record (where available), in line with the scoped question of the review and the existing meta-analysis:[18] failure rate, time to successful placement; number of attempts before successful placement; complication rate; and rate of success after failure by the alternate method.

Definitions of placement failure differed greatly from study to study. Failure was variably defined as inability to place the catheter after fifteen,[41] six,[40,28] four,[33] three,[35,27] or two[26] passes of the needle, that is to say, skin punctures. In one trial inability to insert the line after seven attempts or forty-five minutes both constituted failure.[37] In another study, failure was defined as placement not being achieved after five attempts, or after encountering arterial puncture or haematoma.[5] One further trial set a 30-minute time limit for placement.[6] In ten trials, there was no definition of placement failure.[32,11,38,10,24,31,25,39,34,36] In one of these studies it was reported that one patient had 15 insertion attempts and two more had six and ten attempts, respectively, before stopping due to arterial puncture.[36]

While a number of trials investigated the effects of 2-D ultrasound/Doppler ultrasound rescue after catheterisation failure in the control group,[6,35,31,40] only three trials incorporated a true crossover element.[26,27,28] In two of the latter,[26,27] Doppler ultrasound was more effective than landmark method as a rescue measure, but in neither was this result statistically significant. In the other trial,[28] there were no failures in the ultrasound group to and, therefore, no cross over to landmark method; all the landmark method failures were successfully catheterised using 2-D ultrasound.

In the seventeen studies where time factors for a successful catheterisation were recorded they were measured in a variety of ways. Two studies[36,31] measured the time from anaesthesia to venepuncture. Four studies[5,37,38,10] measured the time from the initial skin puncture to syringe aspiration of venous blood. Two studies[39,27] measured the time from initial skin puncture to the placement of the guide wire. One study[33] measured the time from the injection of local anaesthetic to the insertion of the cannula into the internal jugular vein. One study[41] recorded the time from the point at

which the ultrasound machine was turned on and in position at the bedside, two femoral line catheterisation kits were open, the groins had been swabbed with povidone-iodine, and sterile gloves were on the investigator to the point at which a flash of blood was obtained (and also to when a functional catheter placement was achieved). Six studies did not make explicit what the recorded time interval represented.[11]

3.2.2 ASSESSMENT OF EFFECTIVENESS

Trial data for five of the six outcome measurements were combined in the Cochrane Collaborations Review Manager 4.1: the results are displayed in Appendix 6. No meta-analysis of crossover success was attempted because there were only four studies to pool, which were diverse in terms of interventions, populations and outcomes.

Unlike in the meta-analysis by Randolph *et al*.,[18] the results of studies assessing 2-D ultrasound were not pooled with those considering Doppler ultrasound: the use of these different machines involves qualitatively different forms of attentive engagement and, therefore, a different kind of practical mastery on the part of the operator. Results are pooled using entry site as a distinguishing variable.

In the following sections, statistical heterogeneity is not statistically significant unless stated otherwise.

3.2.3 THE EFFECTS OF 2-D ULTRASOUND

3.2.3.1 Internal jugular vein (adults)

In terms of the effect of 2-D ultrasound guidance on the number of failed catheter placements (appendix 6-figure 3), the pooled effect size of 0.14 represents an 86% reduction in the risk of failed catheter placements. This result is highly significant (p=0.00001). [28,31,38,40,39,11,36] In terms of the effect on the number of catheter placement complications (appendix 6-figure 4), the pooled effect size of 0.43 represents a 57% reduction in the risk of catheter placement complications. This result is statistically significant at the 2% level (p=0.02). [31,38,40,39,11,36]

In terms of the effect of 2-D ultrasound guidance on the risk of failure on the first catheter placement attempt (appendix 6-figure 5), the pooled effect size of 0.59 represents a 41% reduction, statistically significant at the 1% level (p=0.009) despite significant heterogeneity at the 8% level. The Forrest plot indicates that all four studies favour 2-D ultrasound.[28,31,38,36]

In terms of the effect on the number of attempts to successful catheterisation (appendix 6-figure 6), it took, on average, 1.5 fewer attempts to successfully catheterise a patient using 2-D ultrasound-guidance, statistically significant at the 1% level (p=0.004) despite significant heterogeneity at the 1% level. The Forrest plot indicates that all three studies strongly favour 2-D ultrasound.[40,39,36]

In terms of the effect on the number of seconds to successful catheterisation (appendix 6-figure 7), the effect size is small (2-D ultrasound-guided catheterisation is 20.47 seconds faster) and not statistically significant (p=0.7). However, there is significant heterogeneity at the 1% level indicating that it may not be appropriate to pool these results. While four trials were significantly faster with 2-D ultrasound-guidance, it took (on average, 240 seconds) longer in the fifth.[40] Unlike other trials in which time to success was an outcome, this study by Soyer and others included the time taken to set up the ULD in the outcome measurement (Section 3.2.1.3). Set up time will always be a part of the procedure, but it need not be the operator's time which is used in finding and readying the machine. When this study is removed from the meta-analysis (appendix 6-figure 8), heterogeneity is no longer significant (p=0.52). The pooled result shows that catheterisation is, on average, 69 seconds faster with the ULD than with the landmark method, and is highly statistically significant (p<0.00001).[31,38,39,36]

3.2.3.2 Subclavian vein (adults)

There was only one study which analysed the effect of 2-D ultrasound on subclavian catheterisation.[35] In terms of the effect of 2-D ultrasound guidance on the number of failed catheter placements (appendix 6-figure 3), the effect size of 0.14 represents an 86% reduction in the risk of failed catheter placements, statistically significant above the 1% level (p=0.006). In terms of the effect of 2-D ultrasound guidance on the number of catheter placement complications (appendix 6-figure 4), the effect size of 0.10 represents a 90% reduction in the risk of catheter placement complications, statistically significant at the 2% level (p=0.02). These results are statistically significant, despite the trial's small sample size.

The findings are less clear for the catheterisation of the subclavian vein than for the internal jugular. The relative experience of operators may be a factor here. In the single trial investigating subclavian access, the operators were relatively inexperienced in the landmark method and 2-D ultrasound-guidance.[35] This trial produced a failure rate of 15/27 (55%) lines using the landmark method and a 2/25 (8%) failure rate for the 2-D ultrasound technique. Extracted data from more experienced operators using Doppler ultrasound/landmark method for subclavian venous access [26,6,32] yielded a 9-19% failure rate for the landmark method. Experienced operators would certainly have a lower failure rate using the landmark method, than those in the study by Gualtieri *et al.*[35] Therefore it remains to be established that ultrasound is a safe and effective way of achieving subclavian access.

3.2.3.3 Femoral vein (adults)

There was only one study which analysed the effect of ultrasound on femoral catheterisation. [41] In terms of the effect of ultrasound guidance on the number of failed catheter placements (appendix 6-figure 3), the effect size of 0.29 represents a 71% reduction in the risk of failed catheter placements. This result is significant at the 9% level (p=0.09). The operators also took, on average, 2.7 fewer attempts to catheterise patients using 2-D ultrasound-guidance (appendix 6-figure 6), statistically significant at the 4% level (p=0.04). However, there was little effect on the number of seconds to successful catheterisation, which was, on average, just 3.2 seconds faster (p=0.9: Figure 7).

It is difficult to generalise from the results of the single available RCT on femoral access.[41] The patients in this trial were undergoing cardiopulmonary resuscitation and therefore would be unlikely to have a femoral arterial pulse, the most commonly used anatomical marker during femoral venous access with the landmark method. Therefore, it is hardly surprising that, in this situation, ultrasound has a significant effect. While this, in itself represents a strong argument for the presence of ULD's in the emergency room,[43] the majority of femoral venous lines will not be inserted under these conditions; therefore it seems inappropriate to place a great significance on this study.

However, supporting evidence comes from another trial, which was not included in this review due to its sequential protocol (which is to say it was not an RCT).[20] The study involved operators who were experienced in the landmark method (but not in the use of 2-D ultrasound), working in non-emergency conditions, catheterising sixty-six patients (28 2-D ultrasound versus 38 landmark method) scheduled for acute dialysis. Cannulation of the femoral vein was achieved in all patients (100%) using ultrasound and in 34 patients (89.5%) using the landmark-guided technique. The vein was entered on the first attempt in 92.9% of patients using ultrasound and in 55.3% using the landmark method technique ($P < 0.05$). Average access time (skin to vein) was similar but total procedure time was 45.1 ± 18.8 s by the ultrasound approach and 79.4 ± 61.7 s by the landmark method approach ($P < 0.05$). Using ultrasound, puncture of the femoral artery occurred in 7.1% of patients, and haematoma in 0%. Using external landmark technique, puncture of the femoral artery occurred in 15.8% of patients, and haematoma in 2.6%.

3.2.3.4 Internal jugular vein (infants)

Only three trials studied the effect of 2-D ultrasound-guidance on the catheterisations of infants, all of which concerned the cannulation of the internal jugular vein.[10,37,5] In Figure 9, the pooled outcome effect of 0.15 represents an 85% reduction in the risk of failed catheter placements, statistically significant at the 1% level (p=0.01). In Figure 10, the pooled outcome effect of 0.27 represents a 73% reduction in the risk of catheter placement complications, statistically significant at the 3% level (p=0.03).[10,37,5] In Figure 11, the number of attempts to successful catheterisation was reduced by an average of 2, a highly significant result, statistically (p<0.00001).[37] In Figure 12 the pooled effect of 2-D ultrasound-guidance is that successful cannulation is achieved, on average 349 seconds quicker than with the landmark method though this result is only statistically significant at the 13% level.[10,37,5]

3.2.4 THE EFFECTS OF DOPPLER ULTRASOUND

3.2.4.1 Internal jugular vein (adults)

In terms of the effect of Doppler ultrasound guidance on the number of failed catheter placements (appendix 6-figure 13), the pooled effect size of 0.39 represents a 61% reduction in the risk of failed catheter placements, statistically significant at the 3% level (p=0.03).[6,27,33,34] In terms of the effect on the number of catheter placement complications (appendix 6-figure 14), the pooled effect size of 0.43 represents a 57%

reduction in the risk of catheter placement complications, statistically significant at the 6% level (p=0.06).[27,33,34] In terms of the effect on the risk of failure on the first catheter placement attempt (appendix 6-figure 15), the pooled effect size of 0.57 represents a 43% reduction in the risk of failed catheter placements, statistically significant at the 1% level (p=0.01).

In terms of the effect of Doppler ultrasound guidance on the number of attempts to successful catheterisation (appendix 6-figure 16), the effect size of the pooled studies was an average of 0.59 fewer attempts to catheterise patients, a statistically non-significant result (p=0.4). There is, however, significant heterogeneity at the 7% level (p=0.07), indicating that it may not be appropriate to combine the individual studies. Considered individually, Gratz[33] shows a statistically significant effect size (1.4 fewer attempts on average, p=0.037) but Branger[6] demonstrated only a small effect. Both of these studies have small sample sizes with weak statistical power.

It took, on average, 35 seconds longer to successfully catheterise patients using Doppler ultrasound guidance than it did with the landmark method (appendix 6-figure 17), a non-significant effect (p=0.4).[6,27,33,34] Individually, most of the studies favour the landmark method, aside from one study[34] where one arm was composed of patients who were 'difficult' to catheterise (e.g. because of obesity).

3.2.4.2 Subclavian vein (adults)

In terms of the effect of Doppler ultrasound guidance on the number of failed catheter placements (appendix 6-figure 13), the pooled effect size of 1.48 represents a significant *increase* in the risk of failed catheter placements at the 3% level (p=0.03), which is to say that the landmark method was preferable to the Doppler ultrasound guidance technique.[26] In Figure 14, the pooled effect size of 0.57 represents a 43% fall in the risk of catheter placement complication. This result is not statistically significant (p=0.5).

Only one study[32] recorded the effect of Doppler ultrasound guidance on the risk of failure on the first catheter placement (appendix 6-figure 15). The effect size of 1.04 represents slight increase in the risk of catheter placement complications through the use of Doppler ultrasound, although this result is not statistically significant (p=0.8).

Only one study recorded the effect of Doppler ultrasound guidance on the number of attempts to successful catheterisation (appendix 6-figure 16). On average, it took 0.4 fewer attempts to successfully catheterise patients using Doppler ultrasound, a highly statistically significant result (p=0.0002).[6] The same study was the only one to record the effect of Doppler ultrasound guidance on the number of seconds to successful catheterisation (appendix 6-figure 17). Doppler ultrasound-guidance was significantly (on average 209 seconds) slower than the landmark method (p<0.00001).[6]

The operators in two of these trials[26,32] were considerably more experienced in landmark method-guided cannulation than they were with Doppler, but both studies had relatively large populations and neither noted a significant training effect. Doppler ultrasound guidance appears not to be an effective alternative to the landmark method for subclavian insertion in adults.

3.2.4.3 Internal jugular vein (infants)

Only one trial studied the effect of Doppler ultrasound on infants.[5] The sample size of this study is small making it difficult to demonstrate statistical power. The study found that Doppler ultrasound increased the risk of failed catheter placements (appendix 6-figure 18) but not significantly so (p=0.8). The intervention slightly decreased the risk of a catheter placement complication (appendix 6-figure 19) but, again, not significantly so (p=0.8). It took an average of 138 seconds longer for operators to catheterise the patient using Doppler ultrasound (appendix 6-figure 20) but, once more, this outcome was not held to be statistically significant (p=0.3).

3.3 RELATED ISSUES

Several issues were not addressed by the included RCTs. First, the effectiveness of ULD's for vessel location followed by blind venipuncture; second, the suitability of ultrasound for detecting the vessel patency and variant anatomy; third, the effectiveness of 2-D ultrasound against the landmark method for the placement of PICCs; and, fourth, the effectiveness of ULD's versus surgical cutdown procedure for CVA. The literature was systematically searched for RCTs on these subjects: where none were available, the best available evidence has been systematically retrieved and reviewed.

3.3.1 ULD's for vessel location followed by blind venepuncture

All of the trials discussed hitherto were concerned with the use of ULD's for not only the location of blood vessels, but also the guidance of venepuncture. Two RCTs investigated the use of Doppler ultrasound to locate the vessel before blind catheter insertion.

The first,[29] was a large RCT, in which 821 patients (411 Doppler ultrasound versus 410 landmark method) underwent subclavian catheterisation in non-emergency conditions. The operators (physicians) had a wide range of experience in landmark method-guided catheterisation, but all had relatively little with the use of Doppler ultrasound. There was no benefit to the use of Doppler ultrasound, either in terms of the failure rate or complications.

The other study,[30] was a smaller RCT in which operators (of unknown specialty and experience) catheterised 43 patients (22 Doppler ultrasound versus 21 landmark method) via the right internal jugular vein, prior to cardiovascular surgery. The only outcome recorded was the rate of success on the first attempt: 77.3% with Doppler and 28.6% without.

In summary, there is no evidence that it is more clinically effective to use Doppler ultrasound for vessel location, prior to blind venepuncture of the subclavian vein, than it is to use the landmark method for the whole procedure. There is evidence that such a procedure would be effective prior to the cannulation of the internal jugular vein.

3.3.2 ULD's for the assessment of vessel patency and vessel location

Successful use of the anatomic landmark approach to catheterisation requires that the vein be 'patent' and normal, both in size and in its expected position.[44] Patency refers to the state of the vessel being present with no evidence of thrombosis. The literature recognises central venous catheterisation as a significant risk factor in the formation of a thrombus of the internal jugular, subclavian or femoral veins,[45] so that it becomes increasingly likely with repeated procedures (for instance, in the case of chemotherapy patients).

A case series by Caridi *et al.*,[44] which used 2-D ultrasound guidance to assess the patency and physiology of patients scheduled for central venous access via the right internal jugular vein, also provided a table reviewing the result of this and other studies.[46,19,10] Across the studies, ultrasound diagnosed between 9% and 20% of patients as having either a variant anatomy or thrombosed veins, which would have compromised access using landmark techniques.

No comparable studies were found for the detection of thrombosis/variant anatomy in the subclavian or femoral veins.

3.3.3 Peripherally inserted central catheters

Only one comparative study detailed the efficacy of ultrasonography in peripheral venous cannulation.[47] In this retrospective sequential study, the same nurse catheterised a diverse population of 431 patients using the landmark method and 326 patients using ultrasonography. The ultrasound approach required 42% fewer attempts to successful catheterisation and demonstrated a 26% greater chance of successful cannulation on the first attempt.

3.3.4 Ultrasound versus surgical cutdown procedure

No papers were found comparing 2-D ultrasound alone with the surgical cutdown procedure. Only one paper was found comparing image-guidance with both surgical cutdown procedure and the landmark method.[48] However, this study was performed in a radiology suite and, unlike the studies discussed hitherto also employed fluoroscopy. The success and infection rates of radiological placement were similar to those of surgical placement. Radiological placement required fewer attempts.

3.4 CONCLUSION

Table 1 summarises the results of the meta-analyses for 2-D ultrasound for both adults and children. In the case of adult internal jugular vein insertion there is very strong statistical evidence that ultrasound-guided central venous access is more effective for all five outcome variables analysed. In terms of the number of trials for subclavian vein and femoral vein insertions the evidence base is not as strong as for internal jugular vein, however, the results are still statistically significant in favour of ultrasound for failed insertions and for complication rates where measured.

For the three infant studies (relatively small sample sizes) investigating insertions into the internal jugular vein, the results again suggest that ultrasound has statistically significant effects over the landmark method. The exception is the seconds to success outcome variable, which is only significant at the 13% level, although the significant heterogeneity test may mean that it is inappropriate to pool these results and that pooling may be masking a significant effect for this variable.

TABLE 1. SUMMARY OF SIGNIFICANCE OF OUTCOME MEASURES FOR 2-D ULTRASOUND (US)

US (Adults)	**IJV**	**SV**	**FV**
Number of failed catheter placements	**0.00001**	**0.006**	**0.09**
Number of catheter placement complications	**0.02**	**0.02**	n/a
Risk of failure on the first catheter placement attempt	**0.009**	n/a	n/a
Number of attempts to successful catheterisation	**0.004**	n/a	**0.04**
Number of seconds to successful catheterisation	**0.7†/ <0.00001**	n/a	**0.9**
US (Infants)	**IJV**	**SV**	**FV**
Number of failed catheter placements	**0.010**	n/a	n/a
Number of catheter placement complications	**0.03**	n/a	n/a
Risk of failure on the first catheter placement attempt	n/a	n/a	n/a
Number of attempts to successful catheterisation	**0.00001**	n/a	n/a
Number of seconds to successful catheterisation	**0.13**	n/a	n/a

Bold text indicates that the outcome favours 2-D ultrasound; *Italic* text indicates that the outcome favours the landmark method; '†' indicates the outcome prior to the removal of the study by Soyer *et al*. (see above); 'n/a' indicates data not available.

Table 2 summarises the results of the meta-analyses for Doppler ultrasound. In general, the results are far less favourable for Doppler ultrasound. For internal jugular vein insertions ultrasound has statistically significant improved effects in terms of failure to insert and immediate complications. Number of attempts and time to success favours the landmark method though the result is not statistically significant however, significant heterogeneity tests cast doubt on the pooling of these results. The study results imply that Doppler is less effective than landmark for subclavian insertions. Only one small study for Doppler internal jugular vein insertions was found and was too small to achieve statistical significance. No studies on the femoral vein were reported for adults or children for Doppler versus landmark.

TABLE 2. SUMMARY OF SIGNIFICANCE OF OUTCOME MEASURES FOR DOPPLER ULTRASOUND (DUS)

DUS (Adults)	**IJV**	**SV**	**FV**
Number of failed catheter placements	**0.03**	*0.03*	n/a
Number of catheter placement complications	**0.06**	**0.5**	n/a
Risk of failure on the first catheter placement attempt	**0.01**	*0.8*	n/a
Number of attempts to successful catheterisation	**0.4**	**0.0002**	n/a
Number of seconds to successful catheterisation	*0.4*	*<0.00001*	n/a
DUS (Infants)	**IJV**	**SV**	**FV**
Number of failed catheter placements	*0.8*	n/a	n/a
Number of catheter placement complications	**0.8**	n/a	n/a
Risk of failure on the first catheter placement attempt	**-**	n/a	n/a
Number of attempts to successful catheterisation	-	n/a	n/a
Number of seconds to successful catheterisation	*0.3*	n/a	n/a

Bold text indicates that the outcome favours Doppler ultrasound; *Italic* text indicates that the outcome favours the landmark method; 'n/a' indicates data not available.

4 ECONOMIC ANALYSIS

4.1 EXISTING ECONOMICS EVIDENCE

A systematic search of electronic databases including the economic evaluation databases NHS Economic Evaluation Database (NEED) and OHE Health Economic Evaluation Database (HEED) have been conducted as discussed in section 3. These searches have been supplemented by strategies designed to find economic evaluations. The literature search failed to reveal any economic or ultrasound costing papers for CVL insertion. Furthermore, none of the industry submissions found any published economic evaluations, nor attempted to present any themselves. Two of the industry submissions have identified a paper by Neuman *et al.,*[49] but this paper is not relevant in the context of this report, as it assesses the cost-effectiveness of PICCs compared with venepuncture at other insertion sites. There is no economic evaluation of ultrasound in the Neuman paper. In view of the lack of published evidence, the costs and benefits of ultrasound versus landmark venepuncture in central venous access is assessed in this report using an economic model. A simple decision analysis approach has been taken using Microsoft Excel.

4.2 METHODS FOR ECONOMIC ANALYSIS

4.2.1 Estimation of net benefits

The benefits of ultrasound for needle insertion in central venous access include fewer failed insertions, fewer complications, and faster venepuncture, thereby improving subsequent catheter insertion rates. This implies clinical and comfort benefits for patients. It has been reported that the sensitivity and specificity of ultrasound for detecting thrombosed vessels for example is 100%.[9] A thrombosed vein cannot be used for venous access and this can be determined using ultrasound.

The clinical effectiveness review indicates that use of ultrasound for central venous access requires fewer needle passes compared with the landmark method (appendix 6-figure 7). The benefits of this are twofold. Firstly, access will be quicker with comfort benefits for the patient and need for fewer staff time resources. Additionally, complication rates (primarily failed insertion, arterial puncture, haematoma, and pneumothorax) have been shown to be correlated with the number of needle pass attempts required before successful insertion.[36] Therefore, if ultrasound results in fewer needle passes before successful puncture then complication rates will be reduced with both clinical and resource benefits for patients and trusts. Furthermore, the literature provides evidence that where failure to gain access to vessels using landmark method has been observed, the subsequent use of ultrasound has resulted in first time successful puncture.[36,28] The resource advantages may be substantial, especially as the majority of insertions are performed in high costs theatre and ITU environments, where delays may have significant cost and clinical implications. Quicker and safer access are clearly beneficial in terms of patient anxiety and comfort, as well as preventing delays in subsequent treatment and reduced risks of further complications. In extreme cases, the complications of venepuncture can be fatal,[36] and so it is possible that reduced complication rates will prevent deaths.

4.2.2 Estimation of net costs

The costs of using ultrasound for venepuncture in central venous access include purchase costs, maintenance contract costs, the costs of training operators, and the costs of disposable equipment. The first three of these resource categories require assumptions about machine usage.

4.2.2.1 Purchase cost

Costs for purchase of a portable ultrasound machine range from about £7,000 to £15,000 depending on specification. For capital equipment such as ultrasound machines, it is necessary to estimate life expectancy and to annualise costs using discounting rates. Because technology improves over time and machines become obsolete relatively quickly, it has been assumed that a machine purchased today will be replaced with a scrap value of zero in 3 years time. Using a 6% discounting assumption, the annualised cost for an £11,000 machine is, for example, £3,882.

The cost of the procedure can be estimated by making assumptions about the number of times that a machine is used. Table 3, below, presents some procedure purchase cost estimates, varying both the purchase cost itself, and the number of times that the ultrasound machine is used each week.

TABLE 3. PURCHASE COSTS PER PROCEDURE

	Purchase Cost		
Times used per week	**£7,000**	**£11,000**	**£15,000**
1	£47.51	£74.66	£101.81
10	£4.75	£7.47	£10.18
20	£2.38	£3.73	£5.09

The table illustrates the sensitivity of the procedure purchase cost to changes in the 2 input assumptions. The estimated cost is particularly sensitive to the usage assumption, illustrating that the cost-effectiveness of ultrasound for central venous access will be dependent on purchased machine being used sufficiently often in cost-effective procedures. The above analysis does not necessarily assume that the ultrasound machine is purchased solely for use in CVL placement. Ultrasound machines can be legitimately used for purposes other than those being investigated in this report (e.g. pleural drainage). Using it for other purposes would mean a legitimate reduction in costs incurred for the CVL venepuncture. Doubling the use of the machine for any purpose would halve the ultrasound estimated costs.

4.2.2.2 Maintenance Costs

An expert advisor has indicated an annual maintenance charge of £1,350 per annum for one of their machines in Liverpool; however, a Site Rite machine costing £7,500 at the Royal Hallamshire in Sheffield carries no maintenance contract with it. The procedure cost for the maintenance charge is calculated in the same way as was the purchase costs in Table 3, so that the unit cost is dependent on usage. Assuming, for example, a maintenance charge of £1,350 pa, and 10 procedures per week per machine, implies an estimated maintenance cost of £2.60 per insertion.

4.2.2.3 Training Costs

The costs of a training scheme will be highly dependent on how a scheme is set up, including which, and how many operators are to be trained, by whom, and how many times the trainee will put their ultrasound skills into practice. The calculation of costs at procedure level also requires an assumption about the remaining working life of the trainee. For example, training costs per insertion will be higher for intensive training courses provided by highly qualified radiologists or anaesthetists, where the trainee is highly qualified, with few working years left and, unlikely to use their new skills much on a weekly basis.

Making the assumption that a consultant radiologist incurs an annual cost of £134,300 (including salary cost, on costs, overheads, and educational/general training costs) and it is assumed that they are employed for half of their time to run such a programme. Then assuming 20 trainees per annum (approximately 1 every 2 working weeks) implies a cost per trainee of £3,357. Alternatively, assuming that a consultant radiologist trains a consultant anaesthetist for 10 half hour supervised insertions. Including the salary costs of both the trainer and trainee, the training cost estimate is £1090 per trainee.

Table 4, below, presents estimates of the discounted (6%) training costs per ultrasound procedure for a range of assumptions about the cost per trainee, working years remaining, and number of procedures undertaken by the trained operator per week.

TABLE 4. ESTIMATES OF DISCOUNTED TRAINING COSTS PER ULTRASOUND PROCEDURE

Cost per Trainee	£1090		£3357		Venepunctures per wk
Remaining working life	5yrs	40yrs	5yrs	40yrs	
	£5.42	£1.52	£16.71	£4.68	**1**
	£1.08	£0.30	£3.34	£0.94	**5**
	£0.54	£0.15	£1.67	£0.47	**10**

Using this broad range of assumptions, cost estimates vary from as little as 15 pence to £17 per insertion. Once again the cost estimate is sensitive to the number of procedures undertaken per week by the trained operator.

4.2.2.4 Disposables

Use of the ultrasound machine requires gel and a disposable cover. These costs have been estimated at £0.67 per CVL insertion by one of the expert advisors to this report.

4.2.3 COST-EFFECTIVENESS

In view of the absence of published economic evaluations in the literature, a simple decision analytic model has been constructed in order to derive initial estimates of the cost-effectiveness of ultrasound for venepuncture in central venous access. Where possible we have used evidence from the randomised controlled trials reported in the review of clinical effectiveness in section 3. Modelling assumptions are made explicit in the text and are tested using sensitivity analysis.

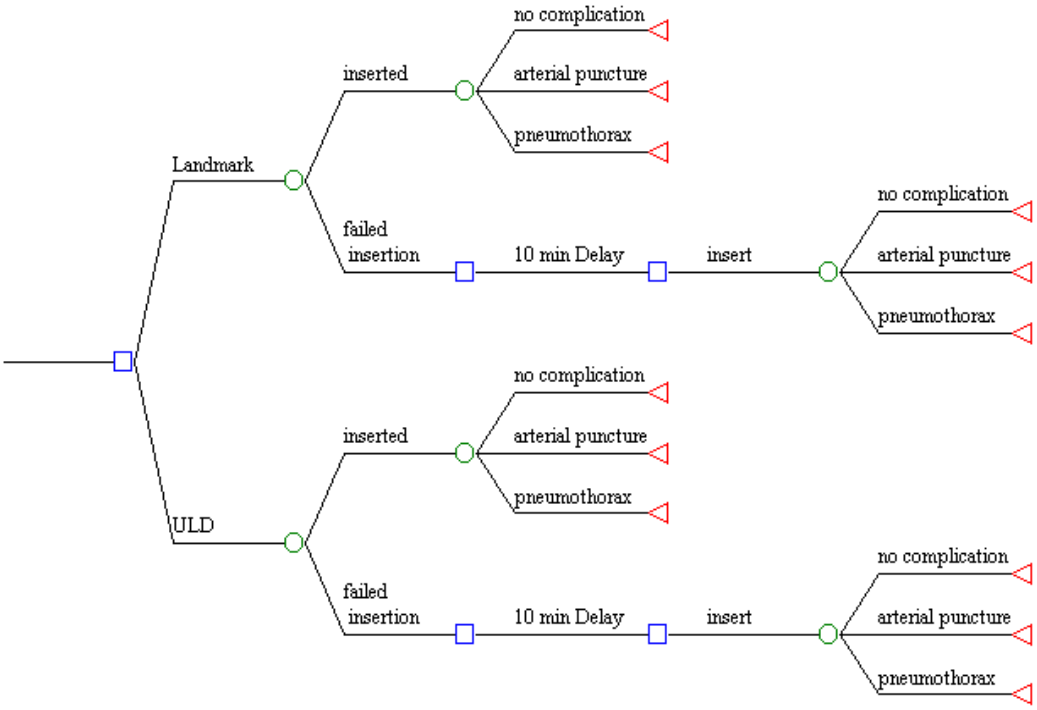
4.2.3.1 The Model

Given the numerous different types of operator, insertion sites, hospital locations, etc. where this procedure can be undertaken, a number of alternative models were considered. In view of the fact that most CVLs are inserted using the internal jugular vein in theatre and ITU environments, the decision was made to present a theatre-based internal jugular vein model. The implications for other insertion sites and bedside ward-based insertions are discussed. Also, given that real-time greyscale 2-D is the technology being considered for wider use in this report, the model analyses this technology in contrast to the Doppler audio technology.

The model thus contains a theoretical cohort of 1000 adult patients undergoing surgery and in which the risk of complications is considered to be low to moderate. Thus, infants and adult patients considered more difficult to puncture, such as obese or short-necked patients are not explicitly modelled. In developing the model we have chosen to present a conservative model in terms of possible ultrasound benefits. So, for example, we assume that the operator is experienced in the use of the landmark method venepuncture method, thereby presenting relatively conservative failure and complication rates for the landmark method arm of the model. The implications of the model results for other scenarios and higher risk patients are discussed.

The structure of the decision tree model is presented in Figure 1 and illustrates identical structure (shape) of the ultrasound and landmark sub-trees. It is the probabilities attached to the chance node events and the subsequent costs and chances of complications that distinguish the 2 policy arms of the model.

FIGURE 1. DECISION TREE



The first sub-tree of the model depicts how a proportion of patients will fail to have a successful needle insertion whilst the remainder have a successful insertion either without or with immediate complications. The only complications considered in the model are arterial puncture and pneumothorax. The model assumes that successful punctures take the same time to achieve for both approaches. There is strong evidence from the review of clinical effectiveness that that ultrasound requires fewer needle passes to achieve successful venepuncture than does landmark method (appendix 6-figure 6). It might therefore be expected that time to successful puncture from the time of attempting the first needle pass will be faster using ultrasound. This is supported by the review of clinical evidence. Excluding the paper by Soyer *et al.*[40] in which the preparation time for the ultrasound machine has been included in timings, the ultrasound-guided venepuncture is achieved 70 seconds faster ($p<0.00001$) than using landmark method (appendix 6-figure 8) Including the non-significant results for the femoral vein analysis, the average time for successful insertion is still 59 seconds faster using ultrasound ($p<0.001$). These timings do not include the additional time necessary for failed catheter insertions, which are more common using landmark method. Although minimal, the additional time necessary to set up the ultrasound machine needs to be offset against the time to achieve successful needle puncture as indicated by Soyer *et al.*[40]

In the case of a failed venepuncture at the initial insertion site, the operator (at consultant level) is assumed to have spent 10 minutes trying to insert prior to failure and changing insertion site before achieving successful insertion. Given reported evidence that failure takes between 5 and 10 minutes,[36] and given that some time will be needed to drape and prepare the new insertion site before insertion can be

attempted at a new site, our assumption seems reasonable. Some operators spend around 30 to 45 minutes trying to achieve successful insertion.[6,37]

The model assumes 100% success at the second insertion site. We also assume no new line equipment for the second insertion attempt. New lines may be necessary in reality[35] and will carry resource implications.

The model assumes that the operating theatre is staffed by a consultant surgeon, assisted by a senior house officer (SHO) and an E-grade theatre nurse. A consultant anaesthetist, assisted by a medical technical officer (MTO) (grade 2/3) is also assumed present for the operation. Hourly staff cost estimates are given in Table 5. The 10-minute delay for the failed procedures is assumed to incur a cost equivalent to 10 minutes for each of these theatre staff, and 10 minutes of theatre time estimated at £125 per hour.

TABLE 5. STAFF COSTS PER HOUR

Theatre Staff and Time	Costs per hour	Source
Consultant Surgeon	£106	[15]
Consultant Anaesthetist	£106	[15]
SHO	£35	[15]
MTO	£31	[50]
E-grade Theatre Nurse	£31	[15]
Theatre Suite	£125	Based on [51]

Staff costs include, overheads, on costs, and education costs.

4.2.3.2 Event Probabilities

The papers presenting the results of RCTs and reviewed in this report are used to populate the model for risk of failure and complications. Given the scenario to be modelled, papers for internal jugular vein insertion in adults excluding emergency (CPR) and high-risk patients were selected. Also, papers reporting results for inexperienced operators and those using Doppler ultrasound were set aside. This exclusion process reduced the number of papers to be used to populate the model with risk probabilities to three.[39,36,28]

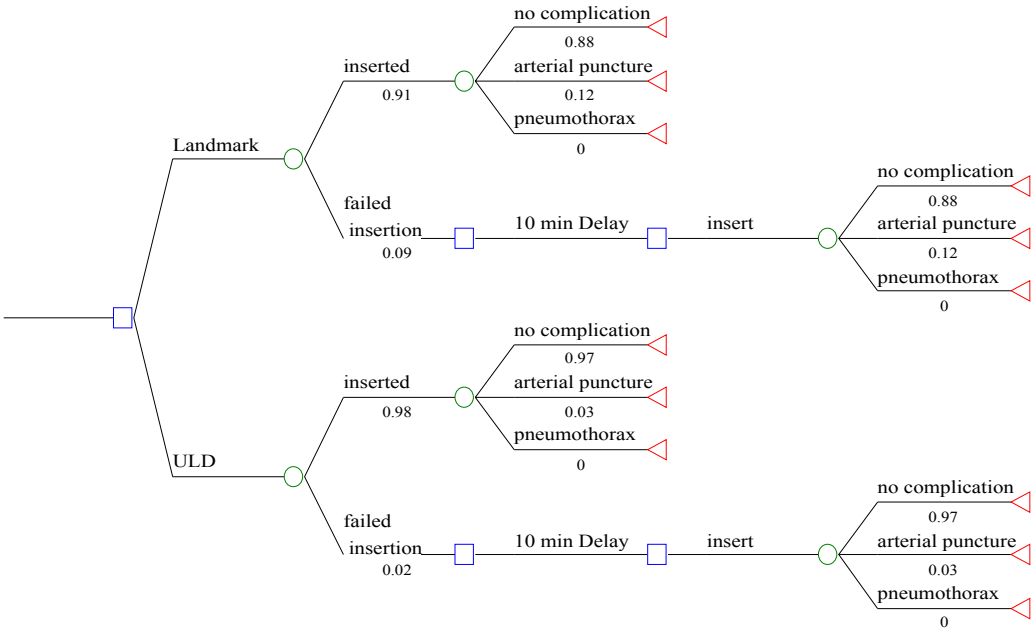
Fourteen (9%) failures out of 160 landmark attempts were recorded in the 3 RCTs compared with 3/149 (2%) failures using real time imaging ultrasound. Nine percent and two percent failure rates are therefore assumed in the model.

The paper by Mallory [28] does not report non-failure complication rates and so could not be used to derive complication parameter estimates for the model. The remaining two RCTs reported complication rates for arterial puncture. Seventeen arterial punctures were reported for 143 landmark attempts (12%), compared with 4 in 137 (3%), using ultrasound. None of the selected papers reported pneumothorax complications.

The results of the subclavian Doppler RCT reported by Lefrant[32] illustrates the increased risk of complications following failed catheterisation. For example, the complication rate rose from 3.2% in the successful group to 21.1 %(4/19) in the

Doppler group and from 15.4% to 30.8% (4/13) in the landmark group. Our model ignores this phenomenon and simply assumes a constant complication rate irrespective of initial insertion success or failure. This assumption has no implications for our analysis, as we are only concerned with estimating the total number of complications for ultrasound versus landmark methods. Adding the modelled probabilities to the decision tree gives the results depicted in figure 2.

FIGURE 2. DECISION TREE POPULATED WITH RISK PROBABILITIES



4.2.3.3 Costs

Based on data from a local teaching trust, it is estimated that approximately 1600 central lines are placed in cardiac surgery patients each year in Sheffield. This equates to about 30 lines per week. The model assumes that the theatre machine is used to insert 15 lines per week. Assuming a machine cost of £11,000, (the equivalent of a machine costing £9,500 with a maintenance contract cost of £1,500) the discounted purchase and maintenance cost is estimated at £4.98 per procedure.

Assuming that the anaesthetist operator was trained by a consultant radiologist during 10 supervised half-hour sessions, and assuming that the operator has 20 years working life remaining, and undertakes only 2 procedures per week, the discounted training cost per ultrasound procedure is estimated at £1.00 per procedure. Adding the purchase and training costs to the disposable equipment costs produces a central scenario estimate of £6.64 per insertion using ultrasound. These procedure costs measure only the additional (marginal) cost of using ultrasound in the venepuncture procedure. They do not measure the total costs of needle insertion such as the costs of disposable needles and other procedure costs common to both the landmark method and the ultrasound procedure.

Cost estimates for arterial puncture and pneumothorax have been taken from the Boland study,[2] which estimated average costs of £316 for pneumothorax and £40 for arterial puncture. The complications were costed using patient specific figures for the whole range of minor and major types of complications that occurred in their study.

4.2.3.4 Model outputs

The central scenario assumptions result in modelled outputs represented in table 6.

TABLE 6. OUTPUTS FOR CENTRAL SCENARIO

	Landmark	ULD
Cost	£11,397	£9,305
Arterial puncture	120	30
Pneumothorax	0	0

The results of modelling show that ultrasound not only avoids 90 arterial punctures for every 1000 patients treated, but saves almost £2,000, an average of £2 per patient. In other words, the policy to use ultrasound for central venous access dominates the landmark method by being both more effective and less costly in our modelled scenario.

4.2.3.5 Sensitivity analysis

A threshold sensitivity analysis has been undertaken in which we examine by how much key variables need to change before the cost saving result from the use of ultrasound becomes a cost neutral result. Table 7 presents the results of the univariate threshold analysis.

TABLE 7. UNIVARIATE THRESHOLD SENSITIVITY ANALYSIS

Variable	Baseline Value	Threshold Value
Failure rate (LM)	9%	6%
Failure rate (US)	2%	5%
Arterial Puncture rate (LM)	12%	7%
Arterial Puncture rate (US)	3%	8%
Cost per US procedure	£6.64	£8.72
Ultrasound machine cost	£11,000	£15,584
Training cost per operator	£1,090	£3,360
Operator procedures per week	2	0.65
US Procedures per week	15	10.6
Cost of failure delays	£73	No solution
Cost of arterial puncture	£40	No solution

The cost saving result for ultrasound is robust for a range of parameter estimates. For example the cost of the ultrasound machine would have to rise from the assumed £11,000 to over £15,500 to eradicate the cost-saving modelling result. Alternatively the assumed ultrasound failure rate of 2% would have to increase to 5% to achieve a cost neutral result. In only one RCT of puncture of internal jugular vein in adults using real time 2-D ultrasounds did the ultrasound failure rate reach 5% (appendix 6-figure 2), and this is one of the 3 studies included in our modelled estimate. The

arterial puncture complication rate for ultrasound would need to increase from the modelled 3% to 8% to negate the cost saving result.

A cost neutral result would occur if landmark insertion achieves a failure rate of 6% or an arterial puncture complication rate of 7%. Only one of the adult internal jugular vein real-time RCTs reported a failure rate below 6% [36] (appendix 6-figure 3) and again this is one of the 3 studies used to populate the model.

The modelled result is most sensitive to the cost of the ultrasound procedure. The estimated marginal costs of the ultrasound procedure only needs to rise from the assumed £6.64 to £8.72 before the ultrasound cost saving result is eradicated. Having said this, it is the usage variables that are most important for cost-effectiveness in this context. Table 7 shows that the cost saving result is relatively insensitive to both the purchase cost of the machine and the training cost per operator. However, the cost saving result is eradicated if the assumed 15 procedures per machine per week is reduced below 10.6, and if the assumed ultrasound procedures per week per trained operator falls below 0.65. These results highlight in particular the need for purchased ultrasound machines to be used sufficiently for them to be cost-effective.

It should be borne in mind that even if the thresholds presented and discussed above are exceeded, then this means only that the cost-saving dominant result for ultrasound would be replaced by a positive cost-effectiveness ratio. The threshold values presented in Table 7 would have to be exceeded further before a cost-effective conclusion for ultrasound would be brought into question.

It should also be borne in mind that the failure and complication risks modelled are favourable to the landmark method in that RCTs using operators already experienced in the landmark method were selected to populate the model. Using the combined failure and complication rate risks for all the adult internal jugular vein trials presented in this report (appendix 6-figure 3) the model indicates a net cost saving in favour of ultrasound of £11,009 and 80 fewer complications per 1000 patients treated. This result gives some indication of the conservative nature of the assumptions used in the modelled scenario presented above.

4.2.3.6 Discussion

Modelling by definition implies the simplification of reality, and so a number of simplifying assumptions were made in the model presented. In addition to points made above, the following modelling assumptions may be biased against ultrasound and in favour of the landmark method:

- The pneumothorax complication rates have been assumed to be zero in the internal jugular vein model presented. Despite the evidence from the RCTs, pneumothorax is a risk even in internal jugular vein cannulation. Based on the evidence for complications presented in this report, inclusion of pneumothorax rates are likely to further increase the cost-effectiveness of ultrasound compared to landmark. On average, the costs of pneumothorax are significantly higher than for arterial puncture (£300 versus £40) as well as being clinically more risky for patients and may contribute to increased mortality.

- The model structure allows for only 2 complications, namely pneumothorax and arterial puncture. On the basis of both the clinical effectiveness evidence and the modelling results, inclusion of other complications would be likely to favour ultrasound further. Death, for example, is an uncommon but possible outcome of insertion complication in high-risk patients e.g. ventilated patients or patients undergoing a cardiac pacing procedure.
- Delays caused by failure have been limited to 10 minutes. Two papers defined failure as failure to insert after 30 and 45 minutes.[6,37] Longer delays would further increase the net resource savings for ultrasound.
- The model forces success at the 2nd attempt following initial failure to insert catheter. Though uncommon, it may be necessary to attempt insertion at 3rd and subsequent sites with further time resource implications, and the increased likelihood of needing alternative catheters for alternative catheter positions. At least one publication indicates that resources will be consumed for new lines.[35]
- The model assumes that ultrasound machines are used only for venepuncture in central venous line access. It has been explained in this report that some portable greyscale 2-D machines can be used to guide other procedures such as pleural drainage (unlikely in a theatre environment). Using purchased ultrasound machines for other cost-effective procedures will further reduce the ultrasound procedure costs estimated in this report.
- The model assumes a purchase cost for ultrasound machines of £11,000. At least one portable machine used in NHS hospitals, and in some of the reported papers can be purchased for £7,500 with no maintenance contract costs.
- The ultrasound costing assumption includes a 3 year machine life. This is likely to be a conservative estimate.
- The model has not considered possible financial implications of litigation. If patients experience complications following landmark method insertion when ultrasound could have been used, and successfully pursue litigation, then further resources implications for the landmark method arm of the model would result.
- The model assumes that successful insertion takes the same time to achieve in both arms of the model. Although only a matter of a minute or two, the evidence suggests that successful insertion is achieved more quickly using ultrasound. This will have both resource and clinical benefits.

The following modelling assumptions may be biased against landmark and in favour of the ultrasound method:

- Modelling has emphasised the need for machines to be used often to make them cost-effective. This implies that trusts should be careful not to over-purchase. Contrary to this, any treatment delays caused by machines being unavailable because they are being used elsewhere will have time resource, as well as possible clinical implications. This scenario would also increase the risk of litigation costs.
- It is possible that the use of ultrasound may increase the risk of infection at the site of insertion if the ultrasound machine is not effectively controlled for infection. If so, this will have resource and clinical implications. None of the literature reported infection complication rates.

- The model makes no allowance for additional preparation time when using ultrasound. In practice this is minimal but will carry some time resource implications.
- Given the correlation between failure and complication rates, it may be unrealistic to vary either of these variables independently of the other. As such, the univariate threshold values for these variables may not be so wide as indicated in the sensitivity analysis.
- Better quality and more versatile ultrasound machines will be used more frequently and may need higher maintenance, or have higher replacement cycles than modelled, thus increasing costs.

The model presented is for internal jugular vein insertion in adult patients, however it is likely that the modelled results are generalisable to other scenarios. Although there is only one RCT reported for each of the subclavian and the femoral insertion sites, both indicate failure rate and complication rate advantages using ultrasound (appendix 6-figures 3 and 4). Although the trial sizes are very small, the results still achieve acceptable levels of statistical significance. Furthermore, the risk of the more serious and costly complication of pneumothorax is more common at the subclavian insertion site. Assuming that ultrasound will improve the pneumothorax complication rate in subclavian vein insertions, then the model will again indicate a cost-saving result. For example, the literature search found no cases of pneumothorax caused by 2-D ultrasound. A paper by Lefrant[32]reports a 2% pneumothorax complication rate for the landmark method in the subclavian vein. Adding this complication rate to the central case scenario model (assuming no cases of pneumothorax from ultrasound) increases the cost saving ultrasound result from £2,000 to over £8,000 assuming an average cost per pneumothorax of £316 per case.

In terms of where the insertion procedures is performed, it is not difficult to show that a bedside ward based treatment scenario will produce similar cost dominant results for the ultrasound procedure. Although a ward-based model may involve fewer and less highly qualified staff than the theatre model presented, less qualified staff are likely to have higher failure and complication rates. Also, the less critical treatment setting of the ward compared to theatre is likely to mean that operators are more likely to spend longer trying to insert before failure. Time spent locating and obtaining more qualified assistance is likely to be longer for a ward setting.

Infants were excluded from the model. Because of their smaller vessels, central venous access in infants is expected to be more difficult than in adults a priori. The evidence from the RCT literature presented in this report (appendix 6-figures 9 and 10) imply that the failure and complication rate differences between landmark method and ultrasound methods are even greater than those modelled for adults above. Thus, the costs and benefits of ultrasound for central venous access in infants are likely to be greater than those indicated by the modelling for adults presented above.

4.2.3.7 Conclusions of Economic Analysis

Based on a model for internal jugular vein insertion in adults, modelling has given a strong indication that the use of ultrasound for venepuncture in central venous access

is likely to save resources as well as improve failure and complication rates. Based on the results of the clinical effectiveness review presented in this report, it is likely that this dominant resource saving result is generalisable to other insertion sites, infants, and bedside ward based insertions. The evidence base is clearly strongest for the internal jugular vein insertion site. No evidence has been reported for peripherally inserted central catheters PICCs and so no economic analysis has been performed for PICCs.

The economic analysis has deliberately concentrated on the favoured real-time ultrasound method, which uses grey scale 2-D imaging as opposed to the Doppler audiological technology. The effectiveness evidence is clearly less favourable for Doppler ultrasound and in the case of adult subclavian vein insertion, for example, the effectiveness evidence (and by implication the economic evidence) is that landmark method is more effective than Doppler ultrasound.

It should be noted that the resources savings indicated by the economic modelling might not manifest themselves as financial savings to the NHS. These resource savings are legitimate opportunity cost savings for staff time, and it is right to include them in an economic analysis. In circumstances where insertion failure causes lengthy delays, theatre lists may have to be curtailed with further resource and clinical implications, The increased use of ultrasound for central venous access will free up medical and nursing staff time as well as freeing up theatre time and valuable ITU and hospital ward beds. Any financial saving would accrue from reduced need to treat complications.

The model indicates that two of the key factors for achieving the ultrasound resource saving result are that purchased machines are used sufficiently often to justify the costs, and that the required training programme for staff is itself set up in a cost-effective way. Should a policy of wider use of ultrasound for central venous access be recommended, it will be important to ensure that machines are utilised sufficiently, but not compromising the need for machines to be available when needed. Lack of availability at the appropriate time will itself cause treatment delays and have resource implications.

5. IMPLICATIONS FOR OTHER PARTIES

Implications for other parties are few. Reduced risk of complications may reduce the financial risks from possible litigation.

If the increased use of ultrasound for central venous access leads to fewer complications, then more procedures may be amenable to day ward and outpatient treatment. This could mean shorter patient length of stay so that relatives and carers need to make fewer hospital visits.

The evidence presented in this report strongly favours the use of ultrasound for central venous access of the internal jugular vein. The evidence for insertion other sites such as the subclavian and femoral veins is also positive, but has a poorer evidence base. If machines are purchased to guide internal jugular vein insertions, then operators will have to judge whether or not ultrasound should be used to guide central venous access at the other insertion sites. There may be ethical issues about the use or non-use of ultrasound in these situations.

6. FACTORS RELEVANT TO NHS

Training

The recommendation to use ultrasound-guided central venous access will have significant training implications for the NHS. It is not feasible for all access procedures to be performed in radiology departments, nor is it feasible for radiologists to provide a peripatetic service for all procedures. Many procedures are performed on an emergency basis at the bedside in a diverse number of locations and most of these procedures are undertaken by non-radiologists. Whilst some of these operators already use ultrasound to guide venous access it is likely that the majority are either sited using percutaneous landmark techniques or by surgical exposure of the vein. A change to ultrasound-guided central venous catheter insertion will thus involve a change in practice for the majority of central venous access procedures.

Radiology has lagged behind surgery in the development of skills laboratories where techniques are learned and initial errors made at the bench rather than at the bedside. Perhaps not everyone can learn ultrasound-guided venous access, but it is highly likely that most individuals who need to, can learn these skills. Modelling these anatomical challenges should not be difficult for a training unit. The anatomy of jugular venous access is not complex and can easily be modelled in a skills-laboratory. It not thought difficult to teach the skill of ultrasound-guided vein puncture to most individuals. A 90% success rate has been recorded for ultrasound-guided femoral vein access in a small series where the investigators received no formal training in ultrasound.[41] However, in the absence of suitable training there is the potential for ultrasound to make a negative contribution.

The economic analysis presented in this report highlights the need for training to be set up in a cost-effective way so as not to compromise the cost-effectiveness of the ultrasound procedure itself.

Deskilling

Another important training issue is that a potential consequence of the wider availability of ultrasound machines for venous access is the development of dependence on ultrasound imaging. That is a potential for the deskilling of operators in landmark insertion. In emergency situations where a line needs to be inserted without delay, landmark insertions may still be appropriate. It is important that training in ultrasound-guided access must not allow trainers to dispense with teaching the landmark methods. This issue will need to be addressed by policy makers and the professional bodies.

Ethics and Litigation

The clinical effectiveness evidence presented in this report strongly suggests that the use of ultrasound increases the safety of central venous access using internal jugular vein insertion in adult patients. The quality of the evidence for subclavian and femoral insertions is less good than for internal jugular vein, although what RCT evidence there is, is positive towards the ultrasound-guided procedure. If machines are made available to trusts for the internal jugular vein procedure, decisions may need to be made about whether it is then ethical to withhold the ultrasound option for patients requiring central venous access venepuncture using other insertion sites.

If, for example, trusts decide not to use ultrasound for subclavian insertions pending stronger research evidence, as well as decreasing the cost-effectiveness of ultrasound for internal jugular vein insertions, there is a potential risk that patients experiencing complications following a landmark guided insertion could decide to pursue litigation.

Guidance implementation

If ultrasound-guided central venous access were to be recommended as standard practice, a view will need to be taken on whether operators already experienced in the landmark method and with a track record of good success rates should be made to switch to the ultrasound-guided method. There is evidence that ultrasound is effective for patency checking and vessel localisation reported within (section 3.3.2 and 3.3.1) and also referred to in this review.[9] Any experienced operators reluctant to use ultrasound to guide real-time needle insertion, could be directed to use ultrasound for patency checking and vessel localisation prior to a landmark venepuncture for example. Policy makers and the professional bodies will need to give clear guidance on this issue.

Resources

Increased use of ultrasound will have short-term resource implications for trusts both in terms of purchase of machines and training of operators. This will mean both short term and ongoing capital and training investment. The economic analysis presented in this report strongly suggests net resource savings to the NHS using ultrasound guidance for central venous access. The majority of these savings are likely to be staff time, theatre and ITU/HDU time, and bed resources rather than financial savings.

7. DISCUSSION

Background

The pertinent question appears to be whether real-time 2-D imaging ultrasound is effective and cost-effective compared to landmark insertions for central venous access. A wide range of patients, operators, and locations within the hospital experience this procedure. Doppler ultrasound is an alternative ultrasound technology, which is used less commonly than real-time 2-D ultrasound. This trend in practice is supported by effectiveness evidence presented in this report.

The financial implications to the NHS are uncertain given that demand for new machines is unknown. This will depend on the policy recommendations of NICE and current availability of appropriate machines in the NHS. A ballpark indicative cost of £29m across the NHS in England and Wales has been estimated if adoption of ultrasound for central venous access is to be recommended. This cost will diminish over time once machines are in place and as training is cascaded downwards through trusts. Anecdotal evidence suggests that availability and therefore resource implications will vary significantly by NHS trust.

The use of a ULD has been shown to reduce the complications of venous access. However, it is important to recognise that the use of a ULD does not eliminate other potentially fatal complications of venous access, such as: air embolus at line introduction; mediastinal venous laceration when large dilators or sheaths are passed; and cardiac tamponade from atrial wall erosion. It should be noted that non-venepuncture complications may be avoided by other radiological technologies such as fluoroscopy during the stages of the procedure after venous access is achieved. This issue is beyond the scope of this report.

Review of evidence for clinical effectiveness

The clinical effectiveness evidence is fairly consistent in pointing to the conclusion that 2-D real-time ultrasound imaging leads to fewer catheterisation failures, fewer complications, and requires fewer attempts and less time to achieved successful access. The quantity and quality of evidence is strongest for insertions into the jugular vein. Few papers address the subclavian and femoral vein insertion sites though they too show statistically significant results in favour of real-time ultrasound compared with landmark insertions. The evidence for Doppler ultrasound is much weaker and possibly negative for insertion sites other than the jugular vein. No RCT evidence considering the effectiveness of ultrasound for PICCs or for ultrasound versus surgical cutdown was found. Surgical cutdown is rarely used in practice.

Economic Analysis

No published evidence addressing the costs or cost-effectiveness of ultrasound in central venous access venepuncture was found in the literature. A simple spreadsheet decision analytical economic model was used to analyse the cost-effectiveness of real-time 2-D ultrasound imaging. This model was populated using RCT effectiveness evidence from the literature, local data, and expert opinion where necessary. The analysis provides a strong argument that the use of ultrasound for this procedure, as well as being safer, will achieve net resource savings compared to landmark

venepuncture. Sensitivity analysis and other discussion presented in section 4 of this report implies that the cost saving and dominant result of the economic model is likely to hold for common insertion sites and for theatre, ITU/HDU and ward scenarios. It is argued that the model was weighted in favour of landmark method, further strengthening the robustness of the model results.

Modelling has indicated that the marginal cost per procedure when using the ultrasound machine is about £6. This cost is most sensitive to usage variables. That is, the number of times that a machine is put to use and the number of procedures undertaken by the trained operator. Some of the better machines, although more expensive, have more versatile uses such as guiding pleural drainage procedures. The more a machine is used for cost-effective procedures, the better the cost-effectiveness result for ultrasound in the central venous access context.

These results highlight the need for machines to be used sufficiently often and for training programmes to be set up in a cost-effective way.

Although not modelled, the surgical cutdown approach to central venous access uses high cost operating theatre and staff resources. The surgical procedure is certain to consume more resources than either the landmark or ultrasound approaches, and may carry a higher risk of infection, which can have considerable resource implications.

Implications for NHS

The financial implications to the NHS are uncertain given that demand for new machines is unknown. This will depend on the policy recommendations of NICE and current availability of appropriate machines in the NHS. Anecdotal evidence suggests that availability and therefore resource implications will vary significantly by NHS trust.

The NHS resource and training implications of a policy to increase the use of ultrasound for central venous access have been highlighted and will need careful implementation planning and involvement of the professional bodies affected. How this should be done has not been addressed by this report.

Because of the need to undertake landmark venepuncture in emergency situations, when an ultrasound machine may not be available, it is important that operators do not become deskilled in the art of the landmark procedure.

Further Research

Clearly the existing RCT evidence in this area is weakest (though positive) for insertions into the subclavian and femoral sites. We found no RCT effectiveness for using ultrasound for PICCs or compared with surgical cutdown. These areas could be considered for further research, however, this report has indicated the ethical and the economic arguments which put significant question marks over the appropriateness of not using available ultrasound machines for insertions at these other sites. It is hard to argue against using the machines for all insertion sites even if only for checking vessel patency and localisation prior to needle insertion, if not to guide the needle insertion in real-time. The cost-effectiveness of using ultrasound in the context of

checking patency and vessel localisation prior to a non-ultrasound-guided venepuncture has not been addressed in this report.

One paper found in the literature search investigated the cost-effectiveness of PICCs compared to insertions at other puncture sites. This paper was not reviewed in this report as it did not address ultrasound and was therefore beyond the scope of the report. Its implications may need to be researched further.

There is evidence that nursing staff are increasingly being trained to insert CVLs.[2] The Manchester study undertaken by Boland *et al.*[2] has demonstrated that nurses can safely insert Hickman catheters in cancer patients using landmark method and image guidance using fluoroscopy. This service development, which can free up the relatively expensive time of junior and senior doctors alike, has not been addressed in this report. The possible economic and clinical implications of nurse operators in the NHS may be a useful area for further research.

Any future trials must be of sufficient size to ensure statistical power and should collate information on resource uses as well as clinical effectiveness data.

8. CONCLUSIONS

This report has presented evidence on the effectiveness and cost-effectiveness for using ultrasound guidance in the venepuncture element of the central venous access procedure.

The effectiveness evidence gives strong statistical evidence that 2-D real-time ultrasound is more effective than the landmark method in the venepuncture procedure for central venous access in both adults and children. This is true for internal jugular vein insertions in particular, but also for subclavian and femoral insertions, although the number of trials for the latter 2 sites is small. The evidence for Doppler ultrasound is weak, if not negative except for internal jugular vein insertions in adults.

No publications were found by the literature search reporting the cost-effectiveness of the procedure under review. Modelling has provided strong evidence that the use of ultrasound during central venous access will not only reduce complications but is likely to save resources. Resource savings will manifest themselves primarily as savings in operator and theatre time and freeing up of ward beds rather than in cash savings. Sensitivity analysis implies that the resource saving assumption is likely to hold for the internal jugular, subclavian, and femoral vein insertion sites, for high cost environments in theatres, but also on the wards, and for children as well as adults. The modelling results indicate that the cost-effectiveness of ultrasound is responsive to usage assumptions, so that it is important that ultrasound machines are used sufficiently often for cost-effective procedures once purchased.

The main implications for the NHS surround training and deskilling of those who undertake central venous access, and what guidance is to be issued for insertions at sites other than the internal jugular vein.

The evidence for the effectiveness of ultrasound insertion sites other than the internal jugular vein is positive, though less strong in terms of the quantity and quality of the trial evidence. It may be considered unethical or lacking in common sense to withhold the use of available machines which will certainly help operators to determine the location and patency of target vessels.

The training implications of a policy to increase the use of ultrasound for central venous access have been highlighted and will need careful implementation planning and involvement of the professional bodies affected. Any training programme must itself be cost-effective. The need to ensure that operators do not become deskilled in landmark venepuncture has been highlighted.

9. APPENDICES

APPENDIX 1. ELECTRONIC BIBLIOGRAPHIC DATABASES SEARCHED

1. Biological Abstracts
2. CCTR (Cochrane Controlled Trials Register)
3. CDSR (Cochrane Database of Systematic Reviews)
4. Cinahl
5. EBM Reviews
6. Embase
7. HEED (Health Economic Evaluations Database)
8. HMIC (Health Information Management Consortium - comprising DH-Data, the King's Fund Database, and Helmis)
9. Medline
10. NHS DARE (Database of Assessments of Reviews of Effectiveness)
11. NHS EED (Economic Evaluations Database)
12. NHS HTA (Health Technology Assessment)
13. PreMedline
14. Science Citation Index
15. Social Sciences Citation Index

APPENDIX 2. OTHER SOURCES SEARCHED

1. AHRQ (Agency for Healthcare Research and Quality)
2. Alberta Clinical Guidelines Programme
3. AltaVista
4. American College of Cardiology
5. ARIF (Aggressive Research Intelligence Facility)
6. Bandolier
7. CCOHTA (Canadian Co-ordinating Centre for Health Technology Assessment)
8. CCT (Current Controlled Trials)
9. CenterWatch Trials Register
10. Centre for Clinical Effectiveness, Monash University
11. Centre for Health Economics, University of York
12. ClinicalTrials.gov, NIH Clinical Trials Database
13. COIN/POINT, Department of Health publications databases
14. Copernic
15. CRiB (Current Research in Britain)
16. eGuidelines
17. HSTAT (Health Services/Technology Assessment Text, US National Library of Medicine)
18. INAHTA (International Network of Agencies for Health Technology Assessment) Clearinghouse
19. Index to Theses
20. OMNI (Organising Medical Networked Information)
21. MRC (Medical Research Council) Funded Projects Database
22. National Guideline Clearinghouse
23. National Research Register
24. NCCHTA (National Co-ordinating Centre for Health Technology Assessment)
25. NHS CRD (Centre for Reviews and Dissemination), University of York
26. NHS R&D Programmes
27. NIH (National Institutes of Health) Consensus Development Programme
28. North of England Guidelines, University of Newcastle
29. OMNI (Organising Medical Networked Information)
30. ReFeR (Research Findings Register)
31. SBU (Swedish Council for Health Technology Assessment)
32. ScHARR Library Catalogue
33. SIGN (Scottish Intercollegiate Guidelines Network)
34. SumSearch
35. Trent Working Group on Acute Purchasing
36. TRIP (Turning Research into Practice) Database
37. Health Evidence Bulletins, Wales
38. Wessex DEC (Development and Evaluation Committee) Reports
39. West Midlands DES (Development and Evaluation Services) Reports

APPENDIX 3. SEARCH STRATEGIES USED

Biological Abstracts
1985-2001
SilverPlatter WebSPIRS
Search undertaken October 2001

#1 central venous line* or central line* or hickman line* or central venous catheter* or central vein* catheter*
#2 ultrasound or ultrasonic* or ultrasonograph* or imag* guid* or radiolog*
#3 #1 and #2

CDSR and CCTR
2001 Issue 3
The Cochrane Library, Update Software (CD ROM version)
Search undertaken September 2001

#1 catheterization-central-venous*:me
#2 central-venous-pressure*:me
#3 (central next venous next line*)
#4 (central next venous next pressure)
#5 (venous or vein*) near (cannulation or access or catheter*)
#6 (pulmonary bext art* next flotation*)
#7 (central next line* next insertion*)
#8 (hickman next line*)
#9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
#10 ultrasonics*:me
#11 ultrasonography*:me
#12 (imag* near guid*)
#13 (ultrasound* or ultrasonic* or doppler)
#14 #10 or #11 or #12 or #13
#15 #9 and #14

Cinahl
1982-2001
Ovid Biomed
Search undertaken October 2001

1 exp catheterization, central venous/
2 exp central venous catheters/
3 central venous pressure/
4 central venous line$.tw
5 central venous pressure.tw
6 ((venous or vein$) adj2 (cannulation or access or catheter$)).tw
7 pulmonary arter$ flotation$.tw
8 central line$ insertion$.tw
9 hickman line$.tw
10 or/1-9

11 exp ultrasonics/
12 exp ultrasonography/
13 (imag$ adj5 guid$).tw
14 (ultrasound or ultrasonic$ or doppler).tw
15 or/11-14
16 10 and 15

Citation Indexes (Science and Social Sciences)
1981-2001
Web of Science
Search undertaken September 2001

Title=(ultrasound* or ultrasonic* or imag* guid* or doppler or ultrasonograph*) and (central venous or venous cannulation or venous catheter* or vein* cannulation or vein* catheter* or pulmonary arter* flotation* or central line* or hickman line*); DocType=All document types; Languages=All languages; Databases=SCI-EXPANDED, SSCI; Timespan=All Years

CRD Databases (NHS DARE, EED, HTA)
CRD Web site - complete databases
Search undertaken September 2001

ultrasound of ultrasonic or ultrasono or doppler/All fields AND vein or venous or pulmonary artery/All fields AND central or line or hickman/All fields

Embase
1980-2001
SilverPlatter WebSPIRS
Search undertaken October 2001

#1 'central-venous-catheterization' / all subheadings
#2 'central-venous-pressure' / all subheadings
#3 central venous line*
#4 central venous pressure
#5 (venous or vein*) near2 (cannulation or access or catheter*)
#6 pulmonary arter* flotation*
#7 central line* insertion*
#8 hickman line*
#9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
#10 'ultrasound-' / all subheadings
#11 explode 'echography-' / all subheadings
#12 imag* near5 guid*
#13 ultrasound* or ultrasonic* or doppler
#14 #10 or #11 or #12 or #13
#15 #9 and #14

HEED (Office of Health Economics Health Economic Evaluation Database)
CD ROM version
Search undertaken September 2001

Search terms:

- (ultrasound or ultrasonic or ultrasonics or image guidance or image guided or doppler or ultrasonography or ultrasonographic)
  AND
- (catheter or catheters or catherization or catheterisation or vein or veins or venous or line or lines or pulmonary artery)

Fields searched:

- Abstract
- All data
- Article title
- Book title
- Keywords
- Technology Assessed

Medline
1966-2001
Ovid Biomed
Search undertaken September 2001

1 catheterization, central venous/
2 central venous line$.tw
3 central venous pressure.tw
4 central venous pressure/
5 ((venous or vein$) adj2 (cannulation or access or catheter$)).tw
6 pulmonary arter$ flotation$.tw
7 central line insertion$.tw
8 hickman line$.tw
9 picc.tw
10 peripheral$ insert$ central catheter$.tw
11 or/1-10
12 exp ultrasonics
13 exp ultrasonography/
14 (imag$ adj5 guid$).tw
15 (ultrasound or ultrasonic$ or doppler).tw
16 or/12-15
17 11 and 16

APPENDIX 4. METHODOLOGICAL SEARCH FILTERS USED IN OVID MEDLINE

Guidelines

1 guideline.pt
2 practice guideline.pt
3 exp guidelines/
4 health planning guidelines/
5 or/1-4

Systematic reviews

1 meta-analysis/
2 exp review literature/
3 (meta-analy$ or meta analy$ or metaanaly$).tw
4 meta-analysis.pt
5 review academic.pt
6 review literature.pt
7 letter.pt
8 review of reported cases.pt
9 historical article.pt
10 review multicase.pt
11 or/1-6
12 or/7-10
13 11 not 12

Randomized controlled trials

1 randomized controlled trial.pt
2 controlled clinical trial.pt
3 randomized controlled trials/
4 random allocation/
5 double blind method/
6 or/1-5
7 clinical trial.pt
8 exp clinical trials/
9 ((clin$ adj25 trial$)).ti, ab
10 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti, ab
11 placebos/
12 placebos.ti, ab
13 random.ti, ab
14 research design/
15 or/7-14
16 comparative study/
17 exp evaluation studies/
18 follow up studies/
19 (control$ or prospectiv$ or volunteer$)).ti, ab
20 prospective studies/
21 or/16-20
22 6 or 15 or 21

Economic evaluations

1 economics/
2 exp “costs and cost analysis”/
3 economic value of life/
4 exp economics, hospital/
5 exp economics, medical/
6 economics, nursing/
7 economics, pharmaceutical/
8 exp models, economic/
9 exp “fees and charges”/
10 exp budgets/
11 ec.fs
12 (cost or costs or costed or costly or costing$).tw
13 (economic$ or pharmacoeconomic$ or price$ or pricing).tw
14 or/1-13

Quality of life

1 exp quality of life/
2 quality of life.tw
3 life quality.tw
4 qaly$.tw
5 quality adjusted life year$.tw
6 (sf36 or sf 36 or short form 36).tw
7 (eq5d or eq 5d or euroqol).tw
8 or/1-7

APPENDIX 5. DATA EXTRACTION

Table 8. Study characteristics

Study	Study type	Patient population	Comparator	Sample Size	Patients/placements
Alderson *et al.* 1993[10]	Prospective, randomized, study.	Children (< 2 yrs); pathology not stated; cardiac surgery; risk not stated.	LM	US 20; LM 20.	40/40
Bold *et al.* 1998[26]	Prospective, randomized, crossover trial.	Adult chemotherapy patients [cancer types not specified]; High risk (for failure/complications).	LM	DUS 119; LM 121.	240/240
Branger *et al*. 1994[6] [Internal Jugular]	Randomised, prospective study.	Patients needing hemodialysis, aphresis or parenteral nutrition requiring central venous catheterization [pathology not stated]; Low risk of complications [high rish patients excluded].	LM	DUS 15; LM 15.	30/29.
Branger *et al.* 1994[6] [Subclavian]	Randomised, prospective study.	Patients needing hemodialysis, aphresis or parenteral nutrition requiring central venous catheterization [pathology not stated]; Low risk of complications [high rish patients excluded].	LM	DUS 50; LM 50.	100/98.
Gilbert *et al*. 1995[27]	Prospective, randomized, crossover clinical study.	Adult patients [pathology not stated] at high-risk from complications [obesity or coagulopathy].	LM	DUS 32; LM 44.	76/76
Gratz *et al.* 1994[33]	Prospective, randomized trial.	CT/ vascular surgery patients [age and pathology not stated].	LM	DUS 21; LM 20.	41/40
Gualtieri *et al*. 1995[35]	Prospective, randomised study.	Critical care patients [age, pathology and risk not stated] non-emergency procedures.	LM	US 25; LM 27.	33/53
Hilty *et al.* 1997[41]	Prospective, randomised, paired subject-controlled clinical trial	Patients [age, pathology and risk not reported] undergoing CPR.	LM	US 20; LM 20.	20/40

Table 8. Study characteristics [cont.]

Study	Study type	Patient population	Comparator	Sample Size	Patients/placements
Johnson *et al.* 1994[24] [abstract]	Randomized prospective study.	Critically ill patients.	LM	US 33; LM 37.	70/70
Lefrant *et al.* 1998[32]	Prospective, randomised study	Critically ill adults [pathology and risk not stated] non-emergency.	LM	DUS 143; LM 143.	286/286
Mallory *et al*. 1990[28]	Prospective, Randomised Trial	Critically Ill adult ICU patients, [pathology not stated], high risk and low risk.	LM	US 12; LM 17.	29/29
Nadig *et al.* 1998[31]	Prospective, randomized study.	Dialysis patients [age, pathologies and risk level not reported].	Blind venepuncture following US-guided vessel location.	US 36; LM 37.	65/73
Slama *et al.* 1997[38]	Prospective, randomized study.	Adults in intensive care [pathology not reported, no risk assesment].	LM	US 37; LM 42.	79/79
Soyer *et al.*. 1993[40]	Prospective, randomized study.	Adult patients with liver dysfunction requiring transjugular liver biopsy [no risk assessment].	LM	US 24; LM 23.	47/47
Sulek *et al.* 2000[39]	Prospective randomised study.	Adults scheduled for abdominal, vascular or cardiothoraic procedures with general anaesthesia and mechanical ventilation [pathology and risk assessment not reported].	LM	RIJV/LM 30; RIJV/US 30; LIJV/LM 30; LIJV/US 30.	120/120
Teichgräber *et al.* 1997[11]	Prospective, randomized trial.	Patients undergoing routine catheterization of the IJV [age, pathology and risk-assessment not reported].	LM	US 50; LM 50.	100/100
Troianos *et al.* 1991[36]	Prospective Randomised Study	Cardio-thoracic surgical patients [age, pathology and risk factor not recorded]	LM	US 77; LM 83.	160/160
Verghese *et al*. 1999[37]	Prospective, randomized study.	Infants scheduled for cardiovascular surgery, < 12 months, < 10 kg [pathology and risk assessment not reported]	LM	US 43; LM 52.	95/95
Verghese *et al*. 2000[5]	Prospective, randomized study.	45 infants scheduled to undergo internal jugular cannulation during cardiac surgery.	LM	DUS 13; US 16; LM 16.	45/45
Vucevic *et al.* 1994[34]	Prospective, randomised study.	Cardiac surgery and ICU patients.	LM	DUS 20; LM 20.	40/40
Woody *et al.* 2001[25] [abstract]	Prospective, randomized trial.	Emergency.	LM.	US 40; LM 43.	83/83

Table 9. Therapy details

Study	ULD type	Catheter size	Needle-guide	Insertion point	Study setting	Operator
Alderson *et al.* 1993[10]	US: Portable, two-dimensional ultrasound scanner (Dymax Corporation), mechanical liquid-path 7.5 MHz transducer that allows high resolution.	16-G	No.	RIJV	Not reported.	Anaesthetist: Experienced cardiac anaesthetist.
Bold *et al*. 1998[26]	DUS: Smart Needle. 14 MHz continuous-wave Doppler instrument with probe in the needle. [Smart Needle]	Not reported.	-	SV. Side not reported.	"Controlled nonemergency conditions".	Medic: 18 surgical oncology fellows (postgraduate year 6-10). Instruction in the use of the Smart Needle and "demonstrated competence" in the use of the Doppler probe.
Branger *et al*. 1994[6] [Internal Jugular]	DUS: Vermon 4MHz pulsed Doppler system probe with a transducer. [audio]	Not reported.	-	IJV. Side not reported.	Not reported.	Unclear: 14 junior postgraduate students with fewer than 5 years of clinical experience and 8 senior staff members with more than 5 years of experience, from nephrology, emergency and intensive care. Taught the Doppler technique over two weeks, achieved at least one venous catheterization before entering study.
Branger *et al.* 1994[6] [Subclavian]	DUS: Vermon 4MHz pulsed Doppler system probe with a transducer. [audio]	Not reported.	-	SV. Side not reported.	Not reported.	Unclear: 14 junior postgraduate students with fewer than 5 years of clinical experience and 8 senior staff members with more than 5 years of experience, from nephrology, emergency and intensive care. Taught the Doppler technique over two weeks, achieved at least one venous catheterization before entering study.
Gilbert *et al.* 1995[27]	DUS: Smart Needle. Audio-guided Doppler US.	Not reported.	-	IJV. Side not reported.	ICU and OR.	Unclear: No. not reported. Junior housestaff "relatively inexperienced in using either technique".
Gratz *et al.* 1994[33]	DUS: Smart Needle. Doppler US guidance (14.3 MHz probe in needle).	20-gauge.	-	IJV. Side not reported.	Not reported.	Anaesthetist: Number not reported. "Experienced anesthesiologists."

Table 9. Therapy details [cont.]

Study	ULD type	Catheter size	Needle-guide	Insertion point	Study setting	Operator
Gualtieri *et al.* 1995[35]	US: Site Rite. 7.5 MHz real-time, portable battery-operated US transducer. [Site Rite]	20-25 cm long	Yes	SV. Both sides.	20 bed trauma-surgical-medical-ICU.	Unclear: 18 physicians with <30 procedures.
Hilty *et al.* 1997[41]	US: Aloka 650 CL. Real-time US guidance (7.5 MHz linear array probe).	Not reported.	No.	FV. Both sides.	Emergency Department.	Medic: 2 emergency medicine residents in postgraduate years 3 and 4. 15-20 procedures LM; 6-10 procedures US.
Johnson *et al*. 1994[24] [abstract]	US: 5 MHz ultrasound transducer.	Not reported.	No.	IJV. Side not reported.	ICU.	Unclear.: Not reported.
Lefrant *et al.* 1998[32]	DUS: Vermon. Pulsed and continuous Doppler US guidance [described as real time].	Not reported.	-	SV. Both sides.	ICU.	Anaesthetist: 1 staff anaesthetist, untrained in Doppler guidance before the study.
Mallory *et al*. 1990[28]	US: US guidance (Hewlett-Packard 7702A real-time two-dimensional ultrasound unit with a 5 MHz resolution). [image]	Not reported.	No.	IJV. Side not reported.	ICU.	Medic: Senior ICU staff and critical care fellows. Number not reported. Mean 6 years exp.
Nadig *et al.* 1998[31]	US: Picker CS9100, Convex 3.5 MHz US.	Not reported.	No.	IJV. Both sides.	Not reported.	Unclear: Physicians. Clinical experience 1 to 7 years.
Slama *et al*. 1997[38]	US: Sonos 100 (Hewlett-Packard). Two-dimensional ultrasound scanner, 7.5 MHz transducer.	Not reported.	No.	RIJV.	ICU.	Unclear: Junior house staff (interns or residents) under the direct supervision of a senior physician after at least three demonstrations by an experienced operator and three attempts of RIJV using LM.
Soyer *et al*. 1993[40]	US: Portable SDR (Phillips) US unit with 7.5MHz probe. [image]	18-G needle catheter	No.	RIJV.	Not reported.	Radiologist: 2 radiologists with the same experience.

Table 9. Therapy details [cont.]

Study	ULD type	Catheter size	Needle-guide	Insertion point	Study setting	Operator
Sulek *et al*. 2000[39]	US: Hewlett Packard. A 2-D, 5-MHz surface ultrasound transducer.	Either 7-Fr triple-lumen or 9-Fr introducer sheath.	No.	IJV. Both sides.	Operating room of a university affiliated hospital.	Anaesthetist: Anaesthetist. All operators experienced in IJV cannulation (at least 60 IJV catheter placements) with known expertise in the use of ultrasound-guided IJV technique.
Teichgräber *et al.* 1997[11]	US: Toshiba SSA 270A. US 5-MHz linear transducer.	Not reported.	Unknown.	IJV. Side not reported.	Clinic.	Unclear: Physicians. Number and experience not reported.
Troianos *et al*. 1991[36]	US: Site Rite, (Dymax) 7.5 MHz and Sonos 500 (Hewlett-Packard) 5.0 MHz transducers).	18-gauge x 6.35-cm-long radiopaque catheter.	Unknown.	RIJV.	Not reported.	Unclear: Not reported.
Verghese *et al*. 1999[37]	US: Site Rite. Real-time US 9-MHz transducer.	18-gauge.	Yes.	IJV. Side not reported.	Theatre.	Anaesthetist: Number not reported. Board-eligible anesthesia fellows who completed residency training in anesthesia.
Verghese *et al*. 2000[5]	DUS & US: Smart Needle Doppler probe, 14 MHz transducer OR Site Rite 7.5 MHz transducer.	18-G	Yes (for US).	IJV. Side not reported.	Theatre.	Anaesthetist: Number not reported. Paediatric anaesthesia fellows.
Vucevic *et al.* 1994[34]	DUS: Smart Needle.	Not reported.	-	RIJV	Not reported.	Anaesthetist: 2 consultant anaesthetists; 10 procedures.
Woody *et al.* 2001[25] [abstract]	US: 7.5 MHz probe.	Not reported.	Unknown	Not reported.	High-volume urban Emergency Department.	Medic: Emergency medicine resident. One hour's training.

Table 10. Study site, and inclusion/exclusion criteria

Study	Study site	Inclusion criteria	Exclusion criteria
Alderson *et al*. 1993[10]	Canadian Urban Children's Hospital.	Children under 2 yr, scheduled for cardiac surgery.	Prior cardiac surgery.
Bold *et al.* 1998[26]	US Tertiary care, outpatient oncology centre.	Patients stratified for 3 known risk factors: prior surgery in the subclavian vein region, prior radiotherapy at the attempted catheterization site and an abnormal weight-height ratio. All patients had at least 1 factor that may be associated with increased risk for failure or complication (body mass index, prior surgery in region or subclavian vein, or prior radiology at catheterizaion site).	None listed.
Branger *et al*. 1994[6] [Internal Jugular]	French teaching hospital.	Patients needing hemodialysis, aphresis or parenteral nutrition requiring central venous catheterization.	Known risk factors such as thoracic abnormality, respiratory distress, major obesity, or restlessness.
Branger *et al*. 1994[6] [Subclavian]	French teaching hospital.	Patients needing hemodialysis, aphresis or parenteral nutrition requiring central venous catheterization.	Known risk factors such as thoracic abnormality, respiratory distress, major obesity, or restlessness.
Gilbert *et al.* 1995[27]	US Tertiary care, teaching hospital.	High-risk patients with pre-existing obesity or coagulopathy requiring internal jugular cannulation.	None described.
Gratz *et al.* 1994[33]	US Tertiary care, teaching hospital.	CT/ vascular surgery patients.	None recorded.
Gualtieri *et al*. 1995[35]	US Urban, teaching hospital	Clinical indications requiring central venous access: assessment of CVP; administration of nutrition/drugs/fluid; and as a conduit for pulmonary artery catheterization.	Patient required central venous access after cardiopulmonary arrest and other emergency situations; informed consent unavailable.
Hilty *et al.* 1997[41]	US Urban, teaching hospital ED, during CPR	Patients presenting in cardiopulmonary arrest to the ED.	None recorded.
Johnson *et al.* 1994[24] [abstract]	Not reported.	Critically ill.	None reported.
Lefrant *et al.* 1998[32]	French teaching hospital	Low-risk patients, requiring catheterization of the subclavian when both the single operator and the US probe were available.	Patients <18 years old; significant coagulopathy; previous subclavian cannulation attempts; prior surgery in the area; emergency central venous access required.

Table 10. Study site, and inclusion/exclusion criteria [cont.]

Study	Study site	Inclusion criteria	Exclusion criteria
Mallory *et al.* 1990[28]	US Tertiary care, teaching hospital.	Conscious patients requiring urgent or urgent-elective ij cannulation; informed consent.	Not recorded.
Nadig *et al.* 1998[31]	German teaching hospital.	None recorded.	None recorded.
Slama *et al*. 1997[38]	French University Hospital.	Admission to ICU, requiring insertion of CVC.	None recorded.
Soyer *et al*. 1993[40]	French hospital [type not reported].	Thrombocytopenia, severe coagulopathy, or marked ascites.	Patients indicated for standard percutaneous transhepatic liver biopsy.
Sulek *et al*. 2000[39]	US university affiliated hospital; operating room.	Adult patients without previous internal jugular venous catheter placement.	Patients were excluded from randomisation if there was a history of radical neck dissection, carotid endarterectomy, carotid artery stenosis, contraindications to the Trendelenburg position or refusal to participate.
Teichgräber *et al*. 1997[11]	German University Teaching Hospital.	Patients undergoing routine catheterization of the IJV.	Not reported.
Troianos *et al*. 1991[36]	US Tertiary care, teaching hospital.	Cardiothoracic surgery patients.	None recorded.
Verghese *et al*. 1999[37]	US University Teaching Hospital.	Infants scheduled for cardiovascular surgery, younger than 12 months, weighing less than 10 kg.	None recorded.
Verghese *et al*. 2000[5]	US University Teaching Hospital.	Infants scheduled to undergo internal jugular cannulation during cardiac surgery.	None recorded.
Vucevic *et al.* 1994[34]	British hospital	Cardiac surgery and ICU patients.	None recorded.
Woody *et al.* 2001[25] [abstract]	US urban hospital.	Not reported.	None reported.

Table 11. Patient characteristics

Study	Age	Sex	Diagnoses	Coagulopathy	Height-weight ratio	Other factors	Baseline comparability
Alderson *et al*. 1993[10]	LM 281 (218) days; US 258 (170) days. Each group contained three neonates and 17 infants.	Not reported.	Not reported.	Not reported.	Weight only.		Yes.
Bold *et al.* 1998[26]	US 50; LM 30.	DUS 44:75; LM 53:68.	Recorded not reported.	Not reported.	Reported.		Not recorded.
Branger *et al*. 1994[6] [Internal Jugular]	Not recorded.	Not recorded.	Not recorded.	Not recorded.	Not recorded.		Unknown.
Branger *et al.* 1994[6] [Subclavian]	Not recorded.	Not recorded.	Not recorded.	Not recorded.	Not recorded.		Unknown.
Gilbert *et al.* 1995[27]	Obesity LM 58.4 ± 13.3; Obesity DUSG-RT 62.7 ± 13.4; Coagulopathy LM 57.9 ± 14.2; Coagulopathy DUSG-RT 55.8 ± 15.7.	M:F Obesity LM 15:8; Obesity DUSG-RT 5:10; Coagulopathy LM 17:18; Coagulopathy DUSG-RT 9:17.	Not recorded.	Recorded. High risk coagulopathic patients were recruited.	Recorded. High risk obese patients were recruited.	Tragus-to-notch distance.	Yes.
Gratz *et al.* 1994[33]	Yes.	Yes. M:F 27:14	Not recorded.	Not recorded.	Recorded.		Yes.
Gualtieri *et al*. 1995[35]	Not recorded.	Not recorded.	Not recorded.	Not recorded.	Not recorded.		No.

Table 11. Patient characteristics [cont.]

Study	Age	Sex	Diagnoses	Coagulopathy	Height-weight ratio	Other factors	Baseline comparability
Hilty *et al.* 1997[41]	65 ± 15 years.	Recorded - M:F 13:7	Not recorded.	Not recorded.	Recorded.	No femoral scars from previous surgery/injection drugs. 8/20 patients had no palpable pulse with CPR.	Yes.
Johnson *et al*. 1994[24] [abstract]	Yes.	Not reported.	Not reported.	Recorded not reported.	Recorded.	APACHE III score; neck anatomy.	Yes.
Lefrant *et al.* 1998[32]	DUSG 67 median; LM 68 median.	M:F - DUSG 84/59 median; LM 68 median.	Recorded.	Recorded not reported.	Recorded.	Ventilated patients.	Yes.
Mallory *et al*. 1990[28]	Not recorded.	Not recorded.	Not recorded.	Not recorded.	Not recorded.		No.
Nadig *et al.* 1998[31]	US 1.7	Not recorded.	Not recorded.	Not recorded.	Not recorded.	IJV Cross Section (cm3).	Yes. [for age only]

Table 11. Patient characteristics [cont.]

Study	Age	Sex	Diagnoses	Coagulopathy	Height-weight ratio	Other factors	Baseline comparability
Slama *et al*. 1997[38]	LM 66 ± 16; US 65 ± 17.	LM 69% Male; US 66%.	Not recorded.	Not recorded.	Height and Weight recorded only.	APACHE II score; simplified acute physiologic score (SAPS); neck width at the thyroid cartilage; distance between sternum and thyroid cartilage (neck length); maximal diameter of IJV; presence of thrombus or abnormal position of the jugular vein noved.	Yes.
Soyer *et al*. 1993[40]	Mean 49 years.	M:F 27:20	Reported.	Recorded not reported.	Not reported.	None recorded.	Yes.
Sulek *et al*. 2000[39]	RIJV LM: 58 ± 7; RIJV US: 61 ± 5; LIJV LM: 60 ± 6; LIJV US: 57 ± 8.	RIJV LM: 25:5; RIJV US: 23:7; LIJV LM: 26:4; LIJV US: 25:5.	Not reported.	Not reported.	Recorded.	Demographic data analysed using Analysis of Variance (ANOVA).	No.
Teichgräber *et al*. 1997[11]	Not reported.	Not reported.	Not reported.	Not reported.	Not reported.		Unknown.
Troianos *et al.* 1991[36]	Recorded not reported.	Recorded not reported.	Recorded not reported.	Not reported.	Recorded not reported.		Yes.

Table 11. Patient characteristics [cont.]

Study	Age	Sex	Diagnoses	Coagulopathy	Height-weight ratio	Other factors	Baseline comparability
Verghese *et al.* 1999[37]	LM 5.9 ± 4.4 months (median 6.0); US 6.4 ± 3.8 months (median 6.0)	Not recorded.	Not recorded.	Not recorded.	Weight only.		Yes.
Verghese *et al.* 2000[5]	1 day to 12 months	Not recorded.	Not recorded.	Not recorded.	Weight only.		Yes.
Vucevic *et al.* 1994[34]	Not recorded.	Not recorded.	Not recorded.	Not recorded.	Recorded.	Previous cannulations; previous unsuccessful attmepts.	Yes.
Woody *et al.* 2001[25] [abstract]	Not reported.	Not reported.	Not reported.	Not reported.	Not reported.		Unknown.

Table 12. Quality assessment

Study	Pt characteristics	Insertion method standardised	Randomization method	Post-randomization exclusions	Intention-to-treat-analysis
Alderson *et al*. 1993[10]	1	Yes.	Not reported.	No.	Yes.
Bold *et al.* 1998[26]	4	Yes.	Computer-generated block randomization process.	No.	Yes.
Branger *et al*. 1994[6] [Internal Jugular]	0	Yes.	Random tables.	Yes.	No.
Branger *et al*. 1994[6] [Subclavian]	0	Yes.	Random tables.	Yes.	No.
Gilbert *et al.* 1995[27]	4	Yes	Not reported	No	Yes
Gratz *et al.* 1994[33]	4	Yes	Not reported	1/41	No
Gualtieri *et al*. 1995[35]	0	Yes	Random number	1/53	No
Hilty *et al.* 1997[41]	3	Yes.	Computer-generated randomization chart.	No.	Yes.
Johnson *et al*. 1994[24] [abstract]	3	Unclear.	Not reported.	No.	Unclear.
Lefrant *et al.* 1998[32]	5	Yes.	Random number.	No.	Yes.
Mallory *et al*. 1990[28]	0	Yes	Not reported	No	Yes
Nadig *et al.* 1998[31]	1	Yes.	By lot.	No.	Yes.
Slama *et al*. 1997[38]	2	Yes.	Not reported.	No.	Yes.
Soyer *et al.* 1993[40]	4	Yes.	Not reported.	No.	Yes.
Sulek *et al*. 2000[39]	3	Yes.	Computer-generated randomization table.	No.	Yes.
Teichgräber *et al*. 1997[11]	0	Yes.	Not reported.	No.	Yes.
Troianos *et al.* 1991[36]	4	Yes	Not reported	No	Yes
Verghese *et al*. 1999[37]	1	Yes.	Computer generated randomization table.	No.	Yes.
Verghese *et al*. 2000[5]	1	Yes.	Computer generated randomization table.	No.	Yes.
Vucevic *et al.* 1994[34]	1	Yes	Not reported	No	Yes
Woody *et al.* 2001[25] [abstract]	0	Unclear.	Not reported.	No.	Yes.

Table 13. Findings

Study	Intervention	Failures	Attempts to success	Complications	Secs to success	No. US successes post LM failure	No. successes on first attempt
Alderson *et al*. 1993[10]	LM	4/20	2.0 (1.0)	8 inability to pass Seldinger wire into superior vena cava; 2 carotid artery puncture.	56.4 (range 48.9)	-	Not recorded.
	US	0/20	1.35 (0.7)	3 inability to pass Seldinger wire into superior vena cava. 1 carotid artery puncture.	23.0 (range 27.4)		Not recorded.
	DUS	-	-	-	-		-
Bold *et al.* 1998[26]	LM	23/121	Not recorded.	1/121 (0.8%) (hemothorax [sic.])	Not recorded.	18/21 (LM 27/34)	Not recorded.
	US	-	-	-	-		-
	DUS	36/119	Not recorded.	2/119 (1.7%) (1 haematoma, 1 catheter malposition)	Not recorded.		Not recorded.
Branger *et al*. 1994[6] [Internal Jugular]	LM	5/15	2.4 ± 0.6	Unclear.	187 ± 73	3/5	Not reported.
	US	-	-	-	-		-
	DUS	1/14	2.3 ± 0.4	Unclear.	401 ± 380		Not reported.
Branger *et al*. 1994[6] [Subclavian]	LM	4/50	1.9 ± 0.7	Unclear.	153 ± 56	2/4	Not reported.
	US	-	-	-	-		-
	DUS	3/48	1.5 ± 0.3	Unclear.	362 ± 105		Not reported.
Gilbert *et al.* 1995[27]	LM	17/44	1.7	13/49 (8 carotid artery puncture; 5 hematoma formation).	188.5 ± 193	12/17 (LM 12/21)	13/44
	US	-	-	-	-		-
	DUS	5/32	1.4	3/49 (1 carotid artery puncture; 2 hematoma formation).	283.5 ± 228		18/32
Gratz *et al.* 1994[33]	LM	5/20	2.8 ± 2.9	0/20	226.0 ± 332	-	11/20
	US	-	-	-	-		-
	DUS	0/20	1.4 ± 0.9	0/20	283.5 ± 228		17/20

Table 13. Findings [cont.]

Study	Intervention	Failures	Attempts to success	Complications	Secs to success	No. US successes post LM failure	No. successes on first attempt
Gualtieri *et al*. 1995[35]	LM	15/27	2.5 (No SD or range given)	11/27: 3 arterial puncture; 5 hematoma; 3 malposition.	Not recorded.	12/15	Not recorded.
	US	2/25	1.4	1/25: 1 Arterial puncture.	Not recorded.		Not recorded.
	DUS	-	-	-	Not recorded.		Not recorded.
Hilty *et al.* 1997[41]	LM	7/20	5 ± 5	None reported.	124.2 ± 69	-	Not recorded.
	US	2/20	2.3 ± 3 (p=.0057)	None reported.	121.0 ± 60 (p=.0001)		Not recorded.
	DUS	-		-	-		-
Johnson *et al*. 1994[24] [abstract]	LM	2/37 (5%)	3.2 ± 2.1	14/37 (carotid puncture and hematoma)	210 ± 255	-	16%
	US	1/33 (3%)	1.6 ± 1.2	5/33	77 ± 108		67%
	DUS	-	-	-	-		-
Lefrant *et al.*. 1998[32]	LM	13/143	Median 1	24/143 (16.8%): arterial puncture 11; Pneumothorax 3; Wrong position of the catheter tip 11.	27 (range 15-240)	-	94/143 (65.7%)
	US	-	-	-	-		-
	DUS	19/143	Median 1	8/143 (5.6%): arterial puncture 5; Pneumothorax 2; Wrong position of the catheter tip 1. NS.	300 (range 94-900)		92/143 (64.3%)
Mallory *et al*. 1990[28]	LM	6/17	3.1	Not recorded.	Not recorded.	6/6 (LM 0/0)	7/17
	US	0/12	1.8	Not recorded.	Not recorded.		7/12
	DUS	-	-	Not recorded.	Not recorded.		-

Table 13. Findings [cont.]

Study	Intervention	Failures	Attempts to success	Complications	Secs to success	No. US successes post LM failure	No. successes on first attempt
Nadig *et al.* 1998[31]	LM	13/37	Not recorded.	0/37	288 ± 132	10/13	30 (83%)
	US	0/36	Not recorded.	0/36	204 ± 54		13 (35%)
	DUS	-	-	-	-		-
Slama *et al.* 1997[38]	LM	10/42	Not recorded.	5/42: 5 carotid artery punctures (12%)	235 ± 408	-	11/42 (26%)
	US	0/37	Not recorded.	5/37: 5 carotid artery punctures (14%)	95 ± 174 ($p<0.06$)		16/37 (43%)
	DUS	-	-	-	-		-
Soyer *et al.* 1993[40]	LM	5/23 (22%)	4 ± 1.53	1/23 (4%) (carotid artery puncture).	Mean 240 ± 120	5/5	Not recorded.
	US	0/24 (0%) ($P<.05$)	1.54 ± 0.66 ($p < .001$)	0/24 (0%)	Mean 480 ± 120		Not recorded.
	DUS	-	-	-	-		-
Sulek *et al.* 2000[39]	LM	RIJV 1/30; LIJV 4/30.	RIJV 2.1 ± 0.9; LIJV 3.5 ± 1.3.	RIJV 4/30 patients (4 arterial puncture, 4 Haematoma; 1 failed guidwire); LIJV 8/30 (6 arterial puncture, 6 Haematoma; 4 failed guidwire).	RIJV 137 ± 139; LIJV 247 ± 176.	-	Not recorded.
	US	RIJV 1/30; LIJV 2/30.	RIJV 1.5 ± 2.0; LIJV 2.3 ± 0.7.	RIJV 2/30 patients (1 arterial puncture, 2 Haematoma; 1 failed guidwire); LIJV 4/30 (2 arterial puncture, 4 Haematoma; 2 failed guidwire).	RIJV 58 ± 71; LIJV 138 ± 139.		Not recorded.
	DUS	-	-	-	-		-
Teichgräber *et al.* 1997[11]	LM	26/50 (52%)	Not recorded.	14/50 (Neck haematoma 10%; plexus irritation 6%; carotid artery puncture 12%).	Mean 51.4 (range 3-820)	-	Not recorded.
	US	2/50 (4%)	Not recorded.	3/50 (Neck haematoma 2%; plexus irritation 4%; carotid artery puncture 0%).	Mean 15.2 (range 8-76)		Not recorded.
	DUS	-	-	-	-		-

Table 13. Findings [cont.]

Study	Intervention	Failures	Attempts to success	Complications	Secs to success	No. US successes post LM failure	No. successes on first attempt
Troianos *et al.* 1991[36]	LM	3/83	2.8 ± 3.0	7/83 (7 carotid artery punctures).	117 ± 136	-	45/83
	US	0/77	1.4 ± 0.7	1/77 (1 carotid artery puncture).	61 ± 46		56/77
	DUS	-	-	-	-		-
Verghese *et al.* 1999[37]	LM	12/52 (23.1%)	3.3 ± 2.8	13/52 (25%): all carotid punctures	840 ± 906	-	Not recorded.
	US	0/43 (0%)	1.3 ± 0.6	0/43	252 ± 168		Not recorded.
	DUS	-	-	-	-		Not recorded.
Verghese *et al.* 2000[5]	LM	3/16 (18.7%)	Median: 2	3 (19%) Carotid artery pucture.	396 ± 318	-	-
	US	1/16 (6%)	Median: 1 ($p<0.05$ LM and SM vs. IM)	1 (6%) Carotid artery pucture.	270 ± 222		-
	DUS	3/13 (23%)	Median: 2	2 (15%) Carotid artery pucture.	534 ± 366		-

Table 13. Findings [cont.]

Study	Intervention	Failures	Attempts to success	Complications	Secs to success	No. US successes post LM failure	No. successes on first attempt
Vucevic *et al*. 1994[34]	LM	1/20	20.5	1/20	Easy group: 59.2 ± 38.7; Difficult group 322.6 ± 173.9	-	Not recorded.
	US	-	-	-	-		-
	DUS	2/20	17.0	1/20	Easy group: 91.8 ± 38.7; Difficult group 167.6 ± 90.4		Not recorded.
Woody *et al*. 2001[25] [abstract]	LM	Not reported.	3.111	Not reported.	457.407 (no SD ro range)	-	Not reported.
	US	Not reported.	1.394 ($p < 0.0002$)	Not reported.	60.938 (no SD ro range)		Not reported.
	DUS	-	-	-	-		-

APPENDIX 6. META-ANALYSES

Meta-analyses were performed in the Cochrane Collaboration's Review Manager 4.1 software (http://www.cochrane.de/cochrane/revman.htm).

Data was combined to estimate the relative risk and associated 95% confidence intervals across studies using the random effects model for the following outcomes:

- the number of failed catheter placements;
- the number of catheter placement complications; and
- the risk of failure on first catheter placement attempt.

Data was combined to estimate the weighted mean difference and associated 95% confidence intervals across studies using the random effects model for the following outcomes:

- the number of attempts to successful catheterisation; and
- the number of seconds to successful catheterisation.

Outcomes reported in abstracts have been excluded from the meta-analyses. Outcomes for doppler ultrasound have been reported separately from those for ultrasound. Outcomes for infants have been reported separately from those for adults.

Figure 3. Effect of ultrasound (US) guidance on number of failed catheter placements (adults)

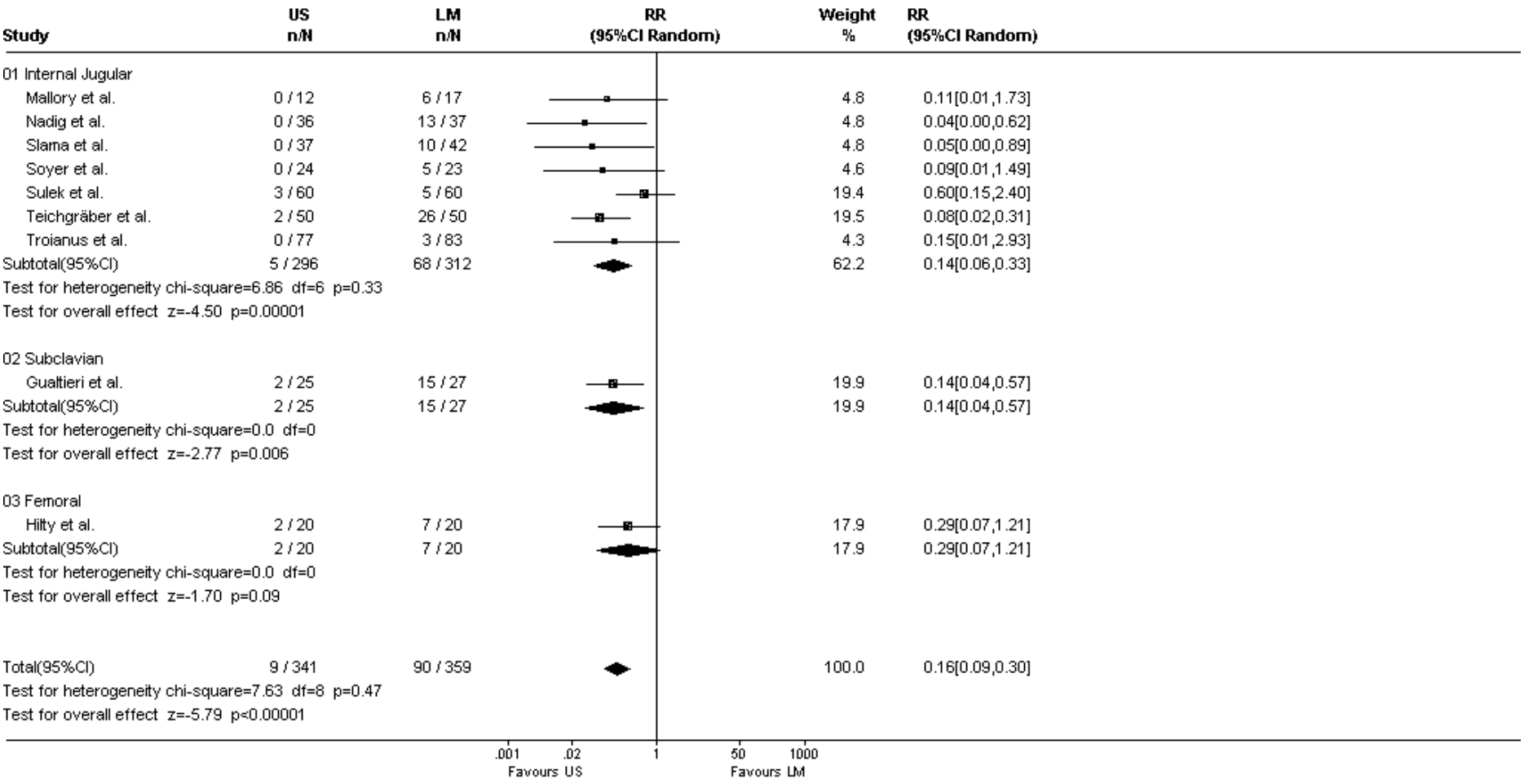


Figure 4. Effect of ultrasound (US) guidance on the number of catheter placement complications (adults)

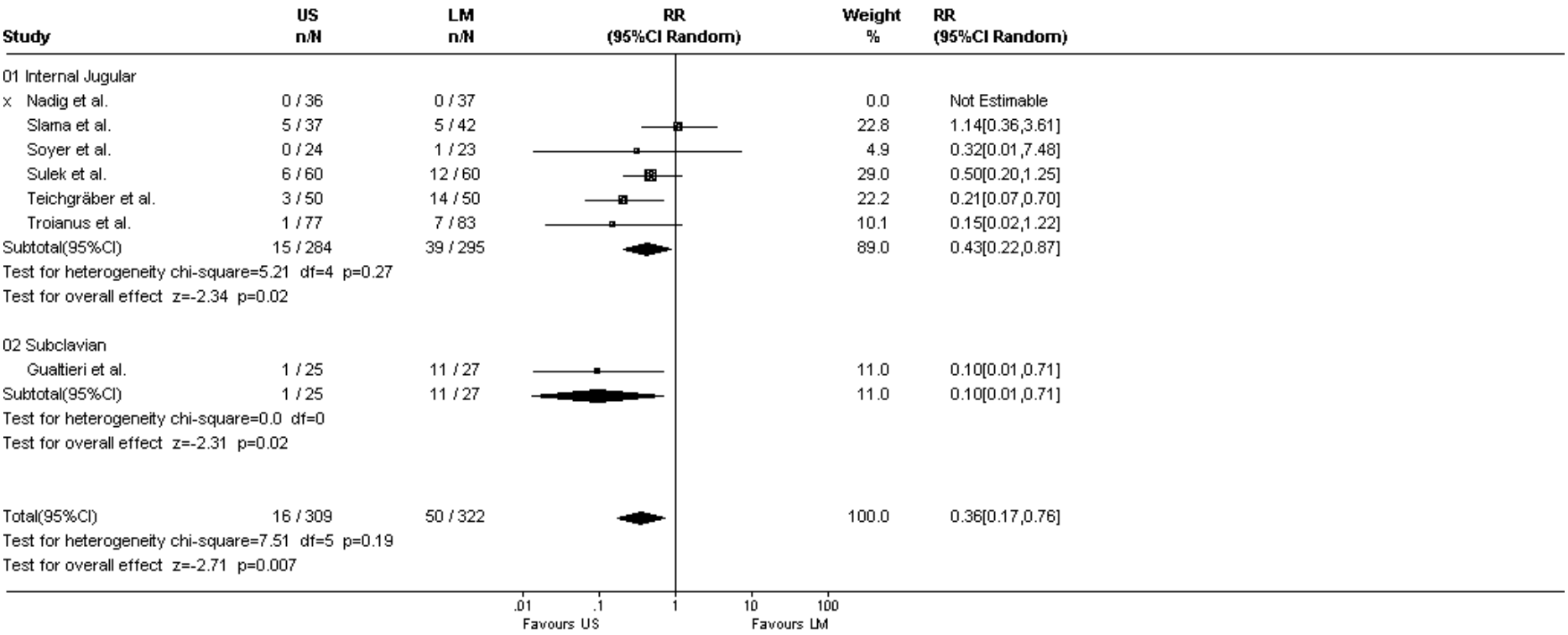


Figure 5. Effect of ultrasound (US) guidance on the risk of failure on first catheter placement attempt (adults)

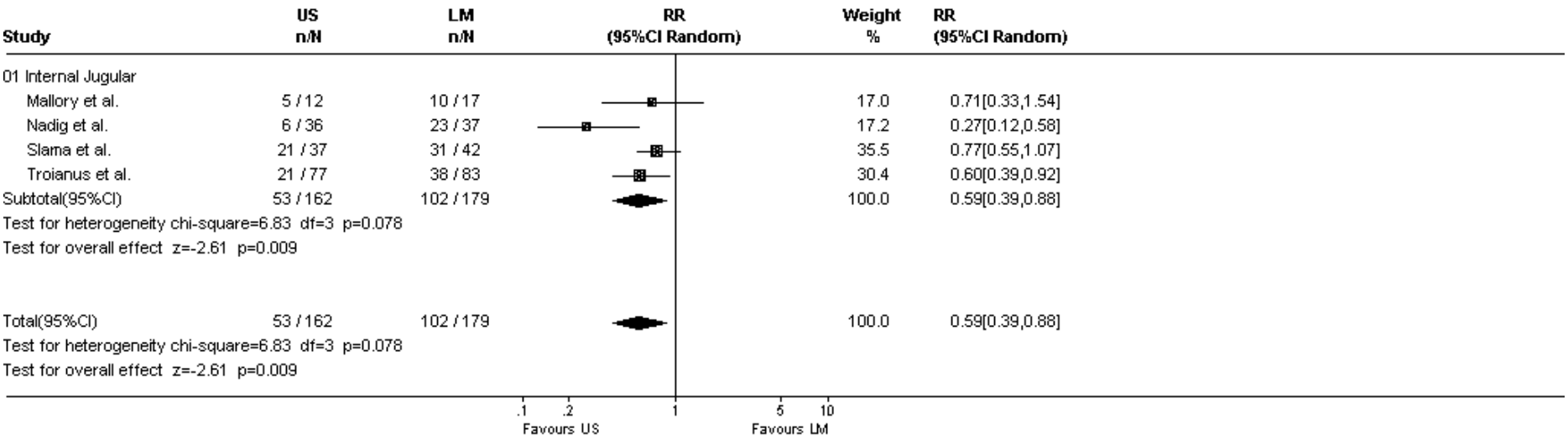


Figure 6. Effect of ultrasound (US) guidance on the number of attempts to successful catheterisation (adults)

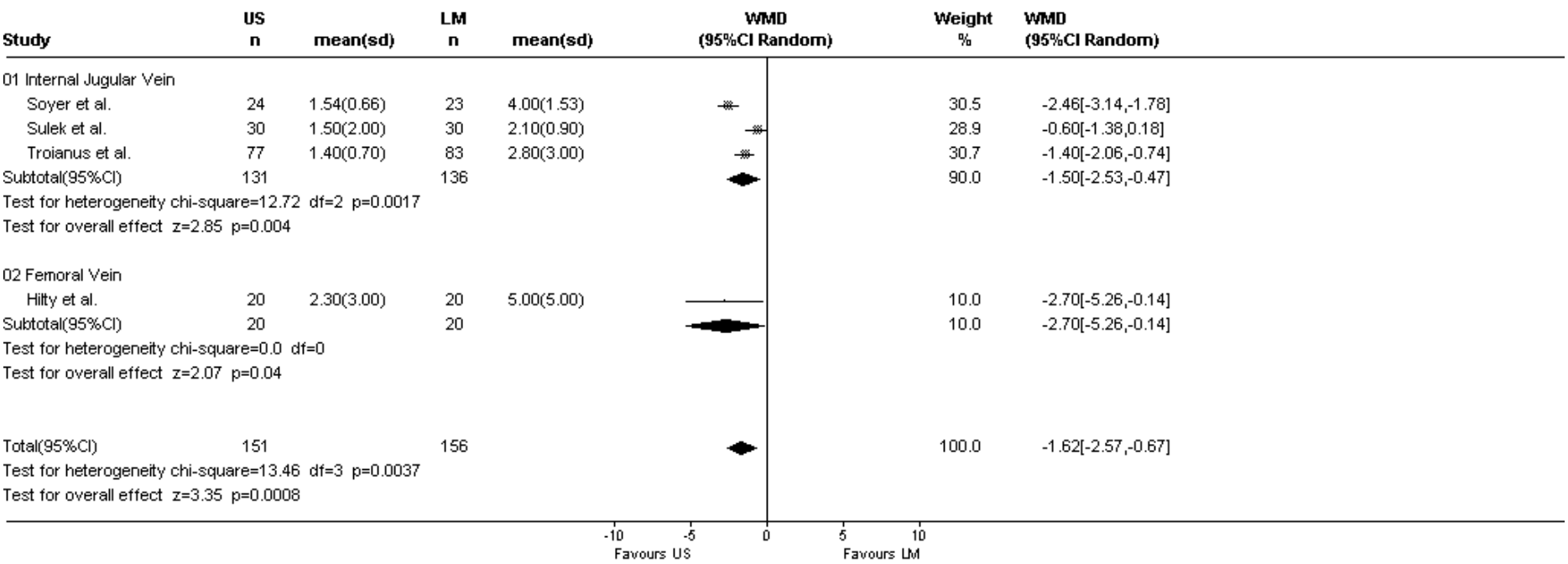


Figure 7. Effect of ultrasound (US) guidance on the number of seconds to successful catheterisation (adults)

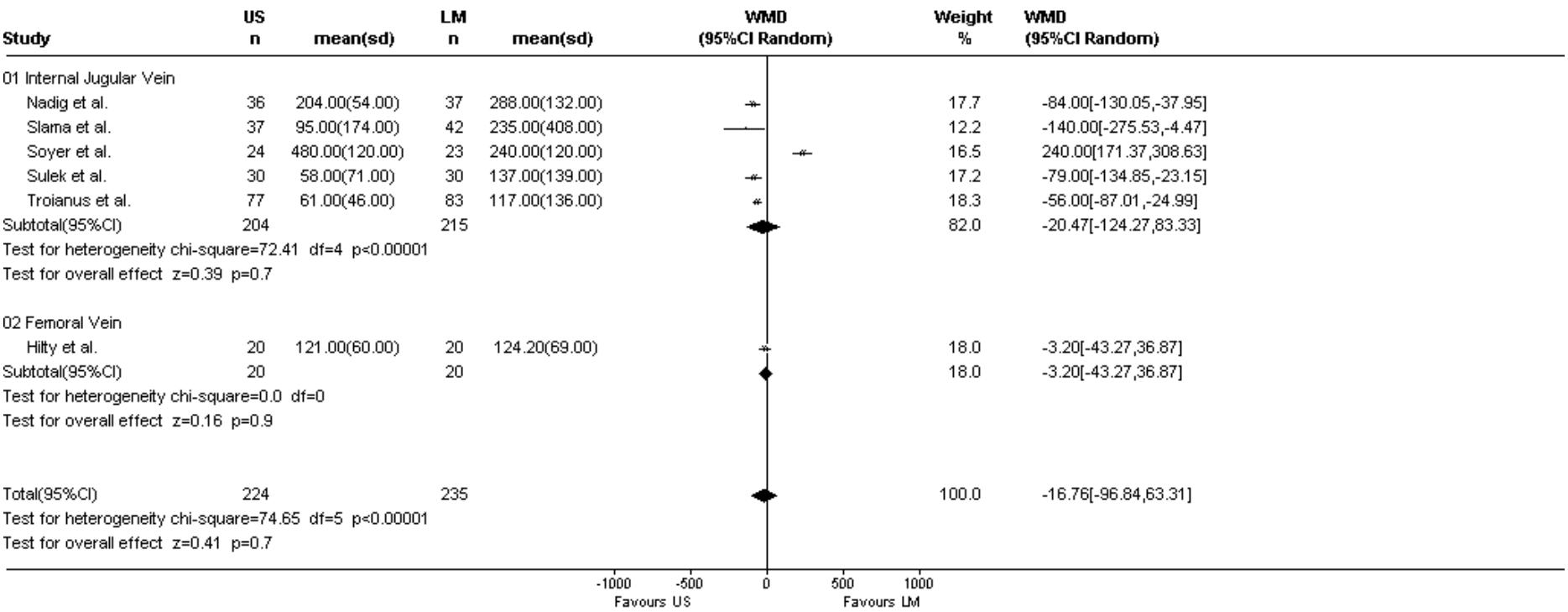


Figure 8. Effect of ultrasound (US) guidance on the number of seconds to successful catheterisation (adults, excluding outcomes from Soyer *et al.*)

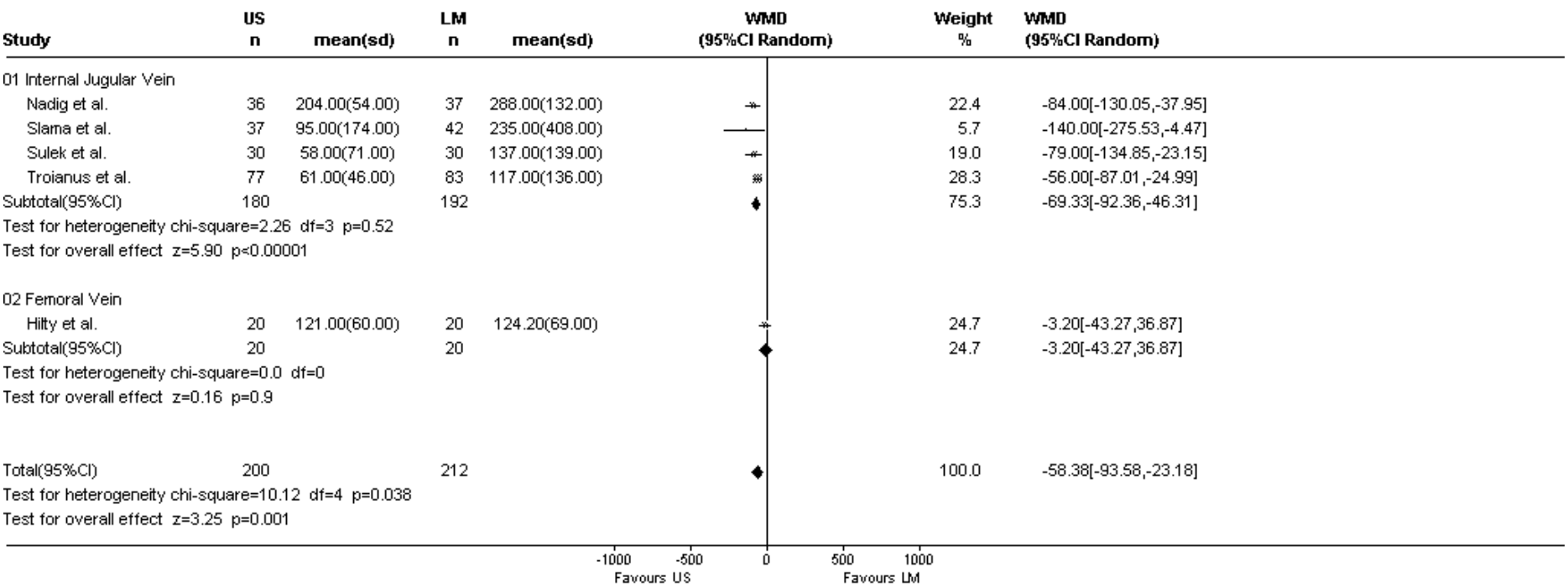


Figure 9. Effect of ultrasound (US) guidance on number of failed catheter placements (infants)

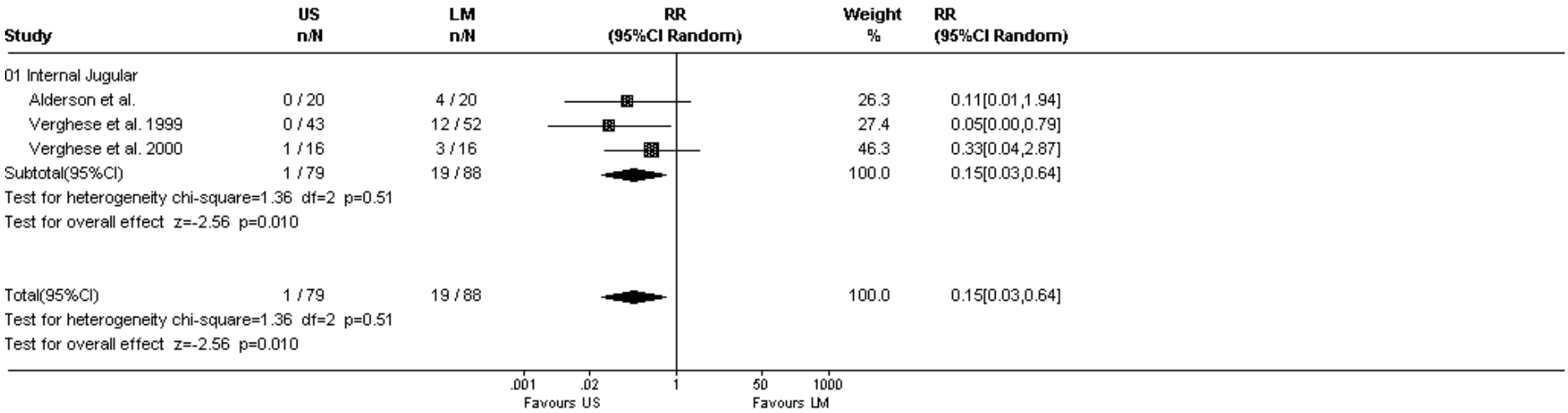


Figure 10. Effect of ultrasound (US) guidance on the number of catheter placement complications (infants)

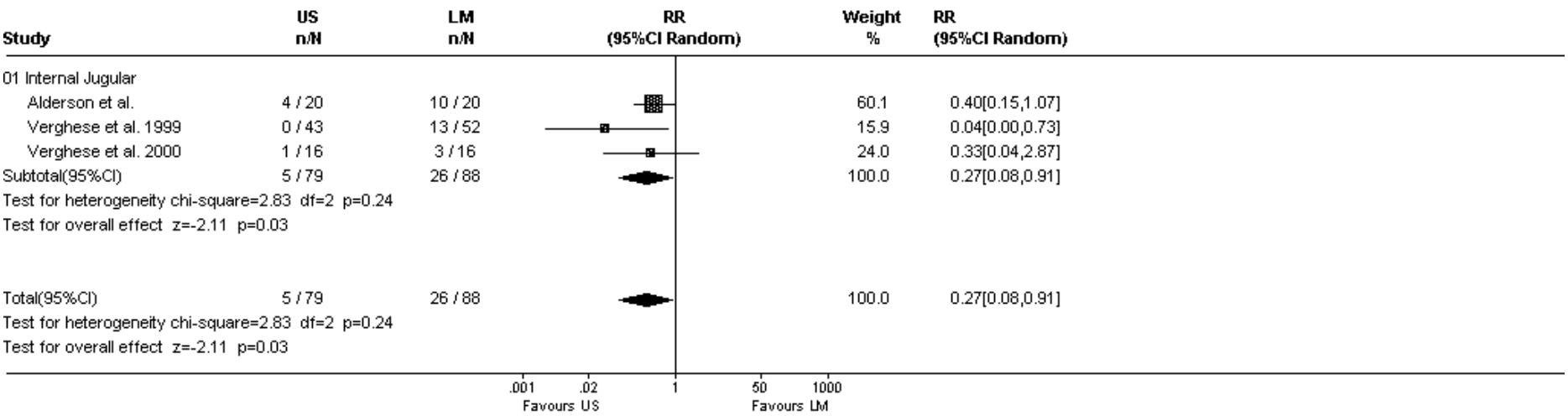


Figure 11. Effect of ultrasound (US) guidance on the number of attempts to successful catheterisation (infants)

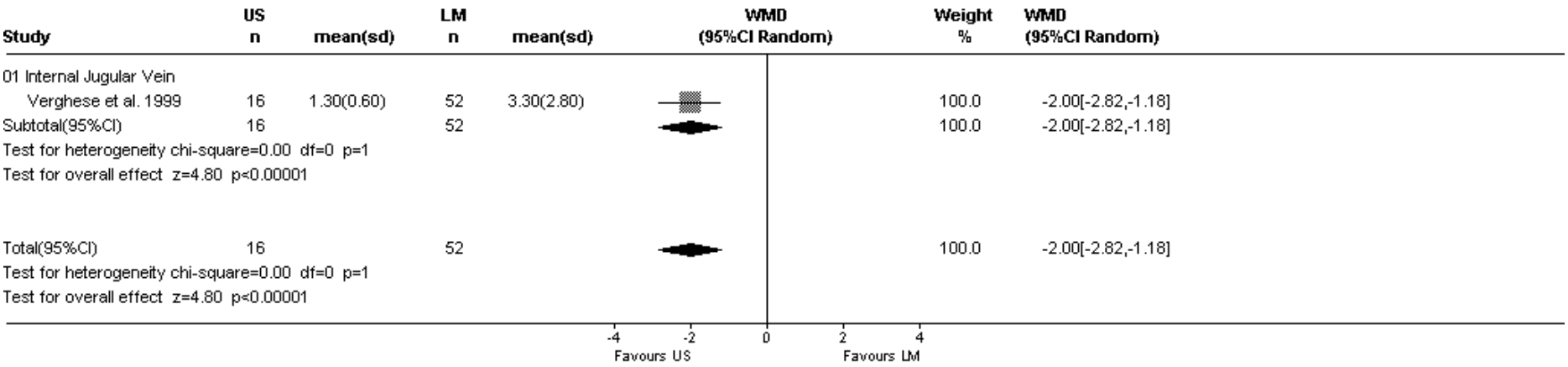


Figure 12. Effect of ultrasound (US) guidance on the number of seconds to successful catheterisation (infants)

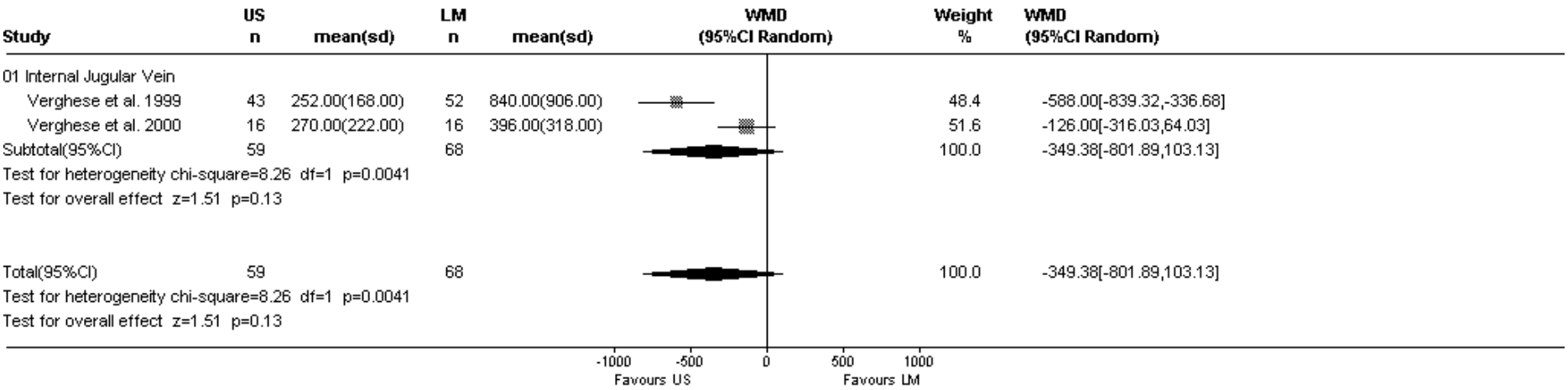


Figure 13. Effect of DUS guidance on number of failed catheter placements (adults)

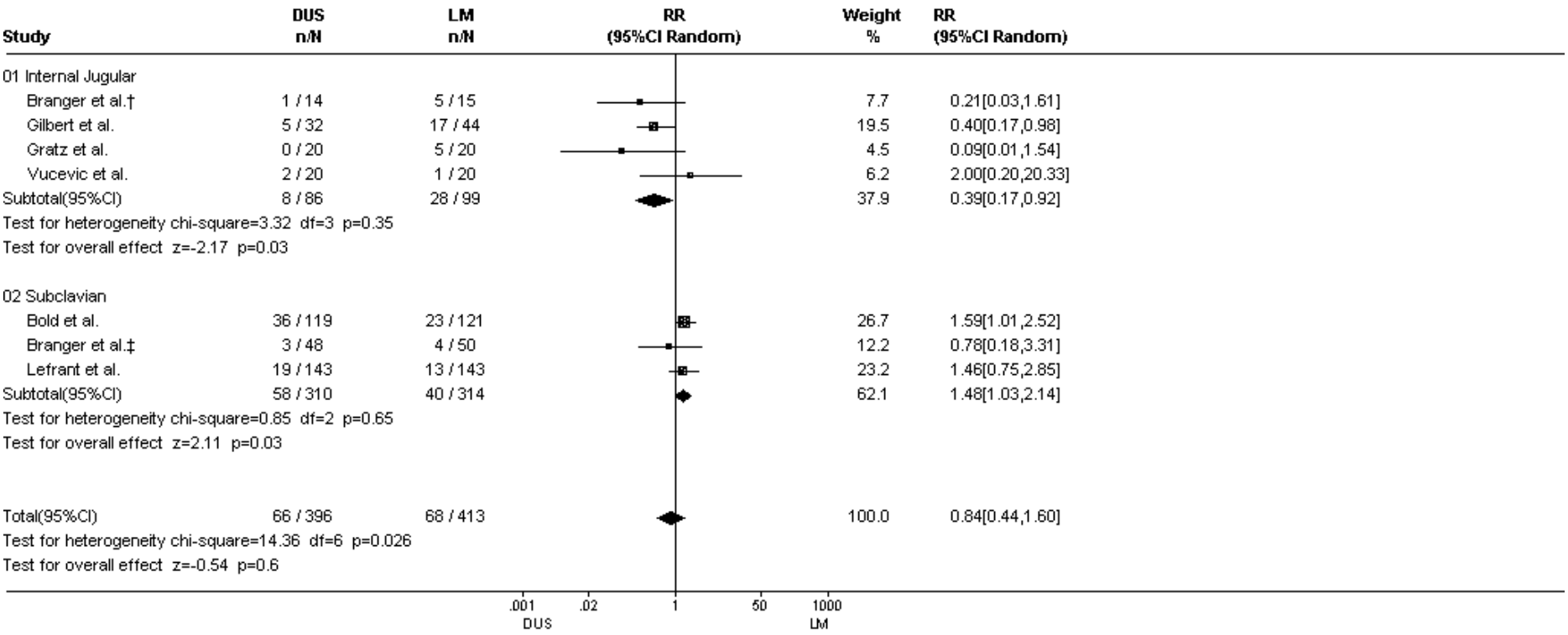


Figure 14. Effect of DUS guidance on the number of catheter placement complications (adults)

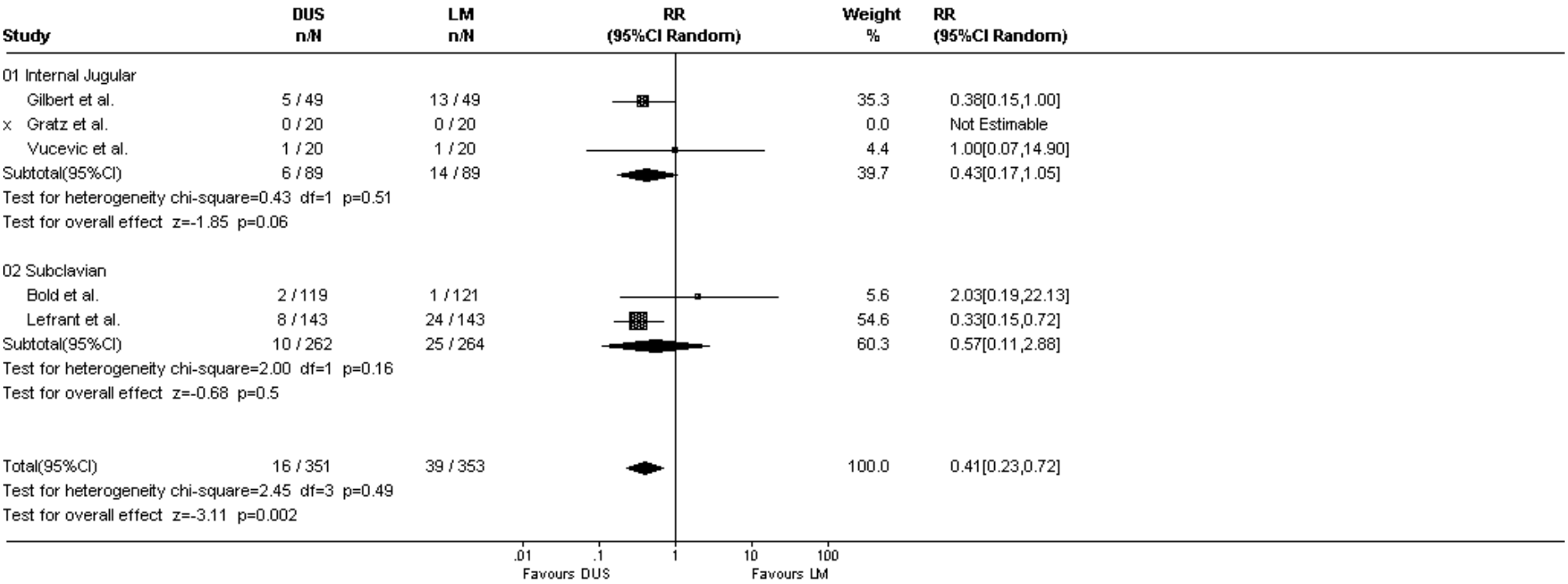


Figure 15. Effect of DUS guidance on the risk of failure on first catheter placement attempt (adults)

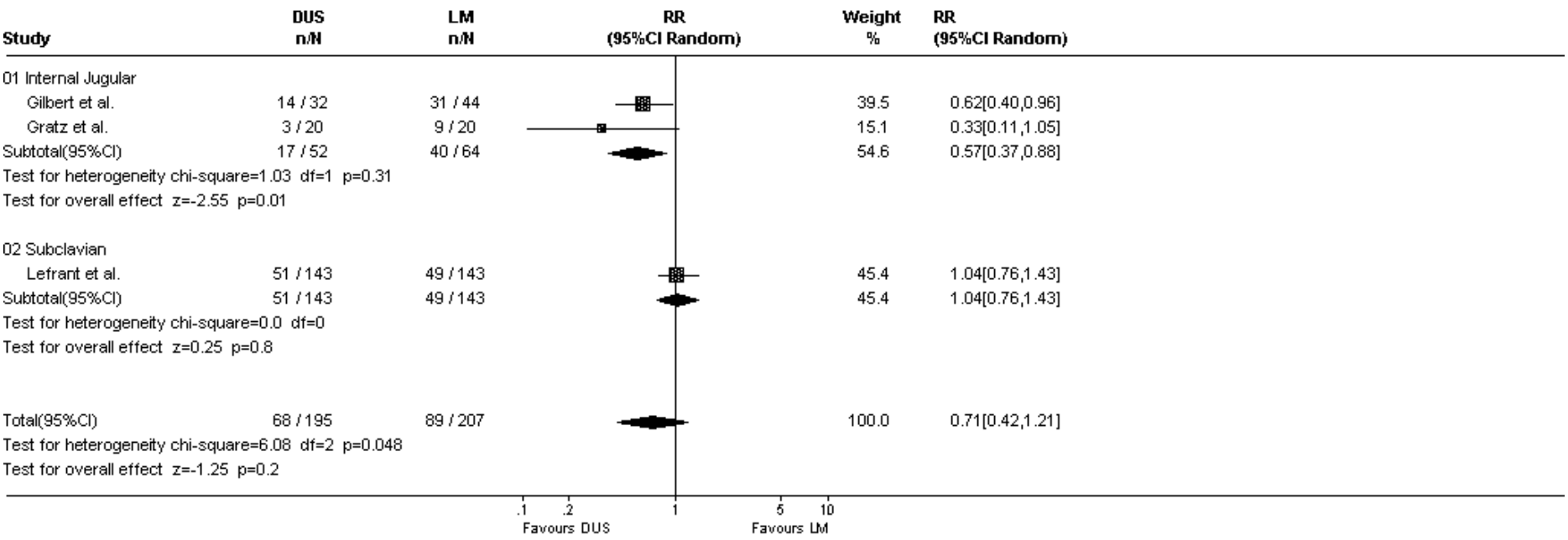


Figure 16. Effect of DUS guidance on the number of attempts to successful catheterisation (adults)

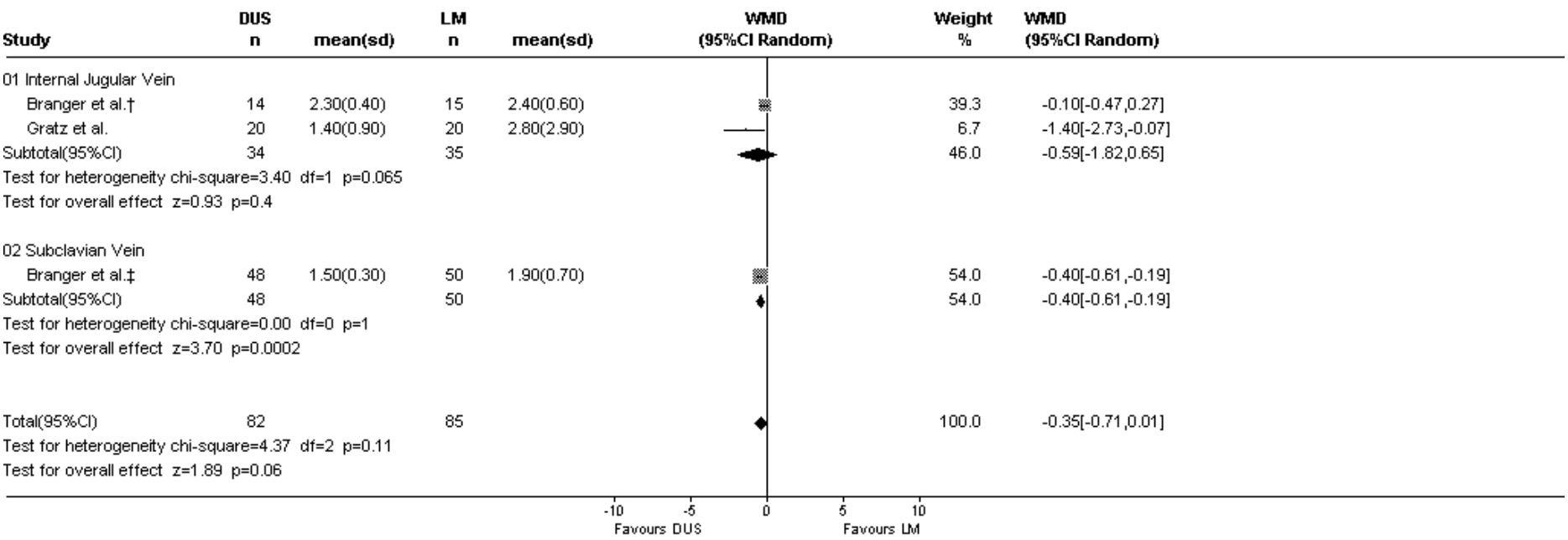


Figure 17. Effect of DUS guidance on the number of seconds to successful catheterisation (adults)

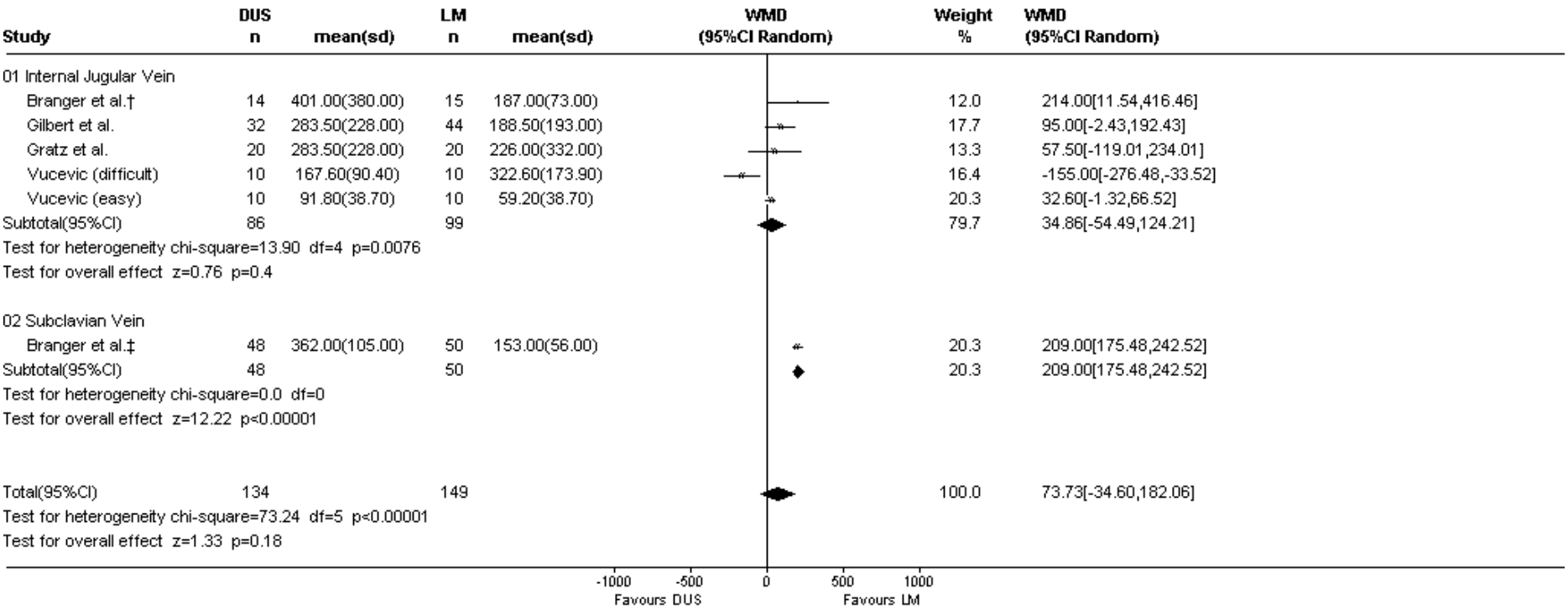


Figure 18. Effect of DUS guidance on number of failed catheter placements (infants)

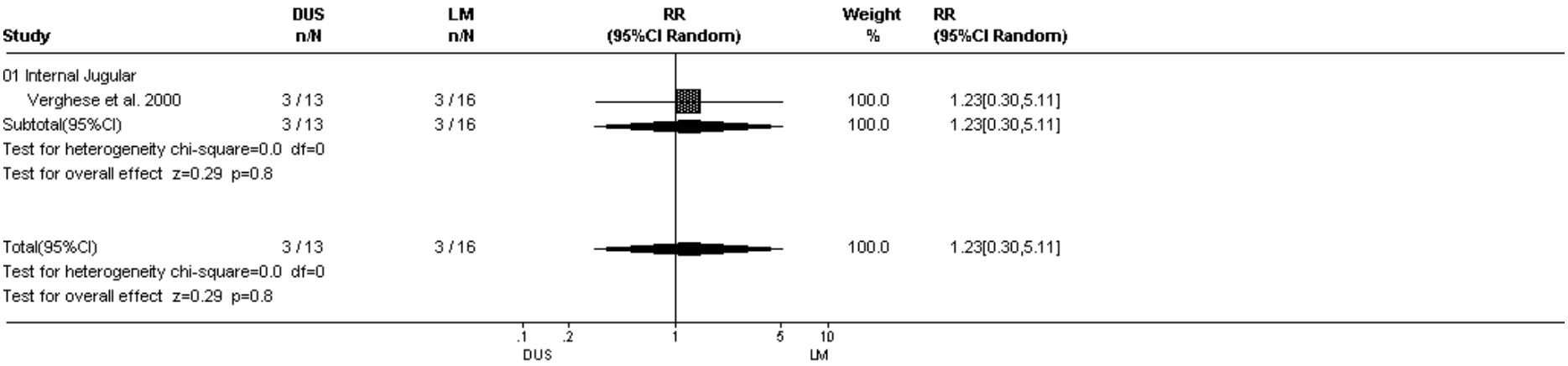


Figure 19. Effect of DUS guidance on the number of catheter placement complications (infants)

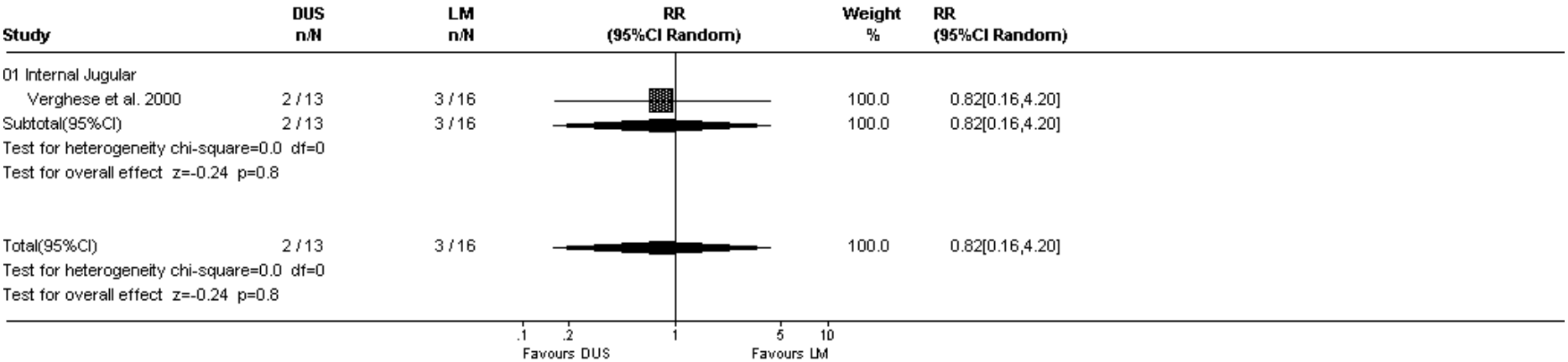
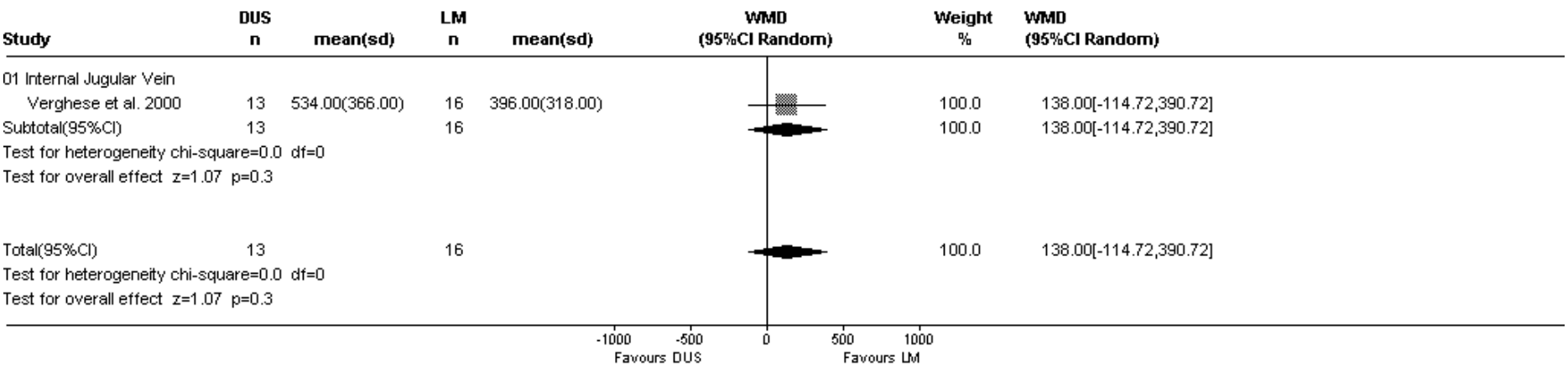


Figure 20. Effect of DUS guidance on the number of seconds to successful catheterisation (infants)


Study
DUS n
mean(sd)
LM n
mean(sd)
WMD (95%CI Random)
Weight %
WMD (95%CI Random)
01 Internal Jugular Vein
Verghese et al. 2000 13 534.00(366.00) 16 396.00(318.00) 100.0 138.00[-114.72,390.72]
Subtotal(95%CI) 13 16 100.0 138.00[-114.72,390.72]
Test for heterogeneity chi-square=0.0 df=0
Test for overall effect z=1.07 p=0.3
Total(95%CI) 13 16 100.0 138.00[-114.72,390.72]
Test for heterogeneity chi-square=0.0 df=0
Test for overall effect z=1.07 p=0.3
-1000
-500
0
500
1000
Favours DUS
Favours LM

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