NETSCC, HTA

21st July 2011

Protocol for Technology Assessment Report 09/01/25 commissioned by the NIHR HTA Programme March 2011

1. Title of the project

A systematic review and economic evaluation of the effectiveness and generality of educational interventions for preventing catheter-related bloodstream infections in critical care

2. Protocol version: 2

This version of the protocol was amended on 14th April 2011. The inclusion criteria for participants in Table 1 were slightly modified and the updated criteria were applied to all titles and abstracts.

3. Project team

Geoff Frampton[1*] – Research Fellow, Evidence Synthesis
Petra Harris[1] – Research Fellow, Evidence Synthesis
Olatunde Aremu[1] – Research Fellow, Health Economics
Keith Cooper[1] – Senior Research Fellow, Health Economics
Jonathan Shepherd[1] – Principal Research Fellow, Evidence Synthesis
Andrew Clegg[1] – Professor of Health Services Research and Director of SHTAC
Jeremy Jones[1] – Principal Research Fellow, Health Economics
Karen Welch[1] – Information specialist
Jennifer Cleland[2] – Senior Clinical Lecturer in Medical Education
Nick Graves[3] – Associate Professor of Health Economics
Tracey Cooper[4] – Consultant Nurse in Infection Prevention
Brian Cuthbertson[5] – Professor of Critical Care

* Project lead investigator
1 Southampton Health Technology Assessments Centre (SHTAC)
School of Medicine, University of Southampton
Epsilon House, Southampton Science Park,
Chilworth, Southampton SO16 7PX

2 Division of Medical and Dental Education, School of Medicine, University of Aberdeen

3 Institute of Health and Biomedical Innovation, Queensland University of Technology, Australia

4 Department of Infection Prevention and Control, South London Healthcare NHS Trust

5 Department of Critical Care Medicine, Sunnybrook Health Sciences Centre, Toronto, Canada

4. Plain English summary

Catheters are very important for the treatment of patients in critical care but provide a route of entry for bacteria and other micro-organisms into the bloodstream, and are frequently associated with serious infections. These infections increase patients' discomfort, length of stay in hospital, the cost of their treatment and risk of death.

Education is important for ensuring that hospital staff understand how to maintain hygiene and follow practices that reduce the risk of infections. Education may be part of a "care bundle", alongside other activities designed to reduce infections. Types of education are very diverse, ranging from simple leaflets or posters to seminars and group discussions and complex strategies designed to encourage staff to follow more hygienic procedures. Although some of these education strategies can prevent infections and potentially save lives, the effectiveness of most has not been evaluated in detail, especially whether infection prevention can be maintained in the longer term, and whether education carried out in one critical care setting is applicable to other settings.

This project (an evidence synthesis) will rigorously and systematically assess the evidence to determine which types of educational intervention can help prevent infections in critical care patients who have a vascular catheter, whether they can maintain long-term prevention of infections, and whether they are cost effective. To address the difficulty of evaluating complex educational strategies, the project will employ an evidence mapping technique that can help to visualise the different parts of complex strategies and enable them to be assessed and compared. A decrease in the frequency of catheter-related bloodstream infections will be the key measure of the effectiveness of education. Where available, information will also be collected on the extent to which education strategies are followed and implemented by nurses and doctors.

This project will help the NHS to implement educational procedures for reducing infections that are the most effective and the best value for money. The project is particularly relevant to a strategy that was implemented during 2009-2011 in critical care units in some NHS trusts in England. The strategy, known as 'Matching Michigan', was originally developed in the USA and has not previously been evaluated to see if it has similar findings in the UK. The project will link to the Matching Michigan team in England to ensure that the assessment of cost-effectiveness is directly relevant to NHS trusts in England. The findings of this project could assist future planning of infection prevention strategies related to Matching Michigan.

5. Decision problem

The aim of this health technology assessment project is to assess the clinical effectiveness and cost effectiveness of different educational schemes for preventing catheter-related bloodstream infections (CRBSI) in patients in critical care. Initial scoping searches for this project suggest that research on educational interventions for preventing CRBSI appears to be mostly from studies that may not have optimal study designs and may not be representative of critical care settings and practices in the UK. Uncertainty remains about the extent of the evidence and effectiveness of interventions. There is therefore a need to systematically synthesise all relevant evidence about these educational interventions to clarify their effectiveness, strengths and limitations, and their relevance to the NHS. Results of this evidence synthesis will help to inform future research and policy for implementing educational infection prevention schemes.

6. Background

6.1 Catheter-related bloodstream infections (CRBSI) in critical care

Intravascular catheter placement is an important cause of bloodstream infections (BSI) [1][2], and is the commonest source of hospital-acquired bacteraemia in hospitals in England [3]. Catheter-related bloodstream infections (CRBSI) are a particular problem in critical care due to the high frequency of intravascular catheter placement and increased susceptibility to infections among critical care patients. CRBSI are associated with morbidity and, especially in paediatric critical care, also mortality [4]. Estimates of the additional length of stay per CRBSI episode in UK critical care units have ranged from 1.9 days [5] to 11 days [6]. Due to a lag in the publication of infection rates, there is uncertainty as to whether these published data are representative of current rates of CRBSI in UK critical care units.[1]

CRBSI result from inadequate hygiene and suboptimal catheter management procedures. These include among others inadequate hand hygiene of hospital staff, inadequate skin hygiene at the site of patients' catheter insertion, suboptimal location of catheters, and unnecessary placement of catheters. CRBSI are believed to be largely preventable following work in the UK that has successfully reduced the number of cases of MRSA BSI. It has been proposed that the majority of CRBSI could be prevented using evidence-based educational interventions to ensure that doctors and nurses are committed to a culture of safety and follow best practice to achieve this [7][8].

6.1.1 Definitions of CRBSI

Various definitions and terms are used, and sometimes confused, in the literature to describe a bloodstream infection that has developed as a consequence of an indwelling intra-vascular catheter. To define CRBSI (sometimes also referred to as CRBI), both a percutaneously-drawn blood culture, and a catheter tip culture (or blood drawn through the catheter itself) should quantitatively or semiquantitatively confirm the same organism up to 48 hours after removal of the catheter, together with clinical manifestations of systemic infection (e.g., fever, chills, hypotension) [9, 10].

Catheter-associated BSI (CABSI), sometimes also referred to as CABI or central line associated bacteraemia (CLAB), are defined as all BSI in patients with central venous catheters (CVC) after excluding other sites of infection by medical review [9, 10]. CLAB means a bloodstream infection with no other apparent focus of infection where a central line (i.e. CVC) has been in situ within 48 hours of the event.

According to these strict definitions, CABSI overestimates the true incidence of CRBSI. However, these definitions are not always rigidly adhered to.

These various definitions make direct comparison of rates of infection difficult and at times misleading, and care will be taken when reviewing studies that report rates of infection based upon the different definitions. The Matching Michigan project provides clear quantitative criteria for defining CABSI, CRBSI, and catheter-suspected BSI; these may assist classification of infections in the current work.

[1] Recent unpublished data from UK critical care units suggest that CRBSI rates may in some cases be much lower than those reported in the published literature (Dr D. Wyncoll, personal communication). In the current project, as indicated in section 8.2, the most relevant data to UK critical care units will be used to evaluate cost-effectiveness of educational interventions.

6.1.2 Diagnosis of CRBSI

Diagnosis of CRBSI is made in various ways, depending upon both local clinical practice and, for infection surveillance purposes, the definition of infection in use. Diagnostic criteria for surveillance purposes are rigorously applied and take account of multiple factors including:

- The number of blood culture specimens performed, and whether these cultures are percutaneously-drawn, or drawn via the CVC
- Whether the CVC has been removed, and if so whether culture of the line tip demonstrates significant quantities of the same micro-organism as is detected in percutaneously-drawn blood
- Identification of a known pathogen in a single blood culture, or a common skin organism identified in two or more sets of blood cultures
- Presentation of identified signs of systemic infection in a patient, linked to one or more positive blood cultures

Use of different definitions of infections can dramatically alter the reported infection rate unless they are aligned with clinical practice. For example, if clinical practice is not to send a CVC line tip to the laboratory for culture, or to draw only a single set of percutaneous cultures, then any definition requiring catheter-tip culture or more than one set of cultures will never be met, potentially giving an artificially low infection rate. However, provided that an infection definition is applied consistently over time, then the impact of interventions aimed at improving practice and reducing infection rates should still be reliably demonstrated. Care will be taken when reviewing studies to ensure that infection definitions have been applied consistently.

6.1.3 Impact of CRBSI on patients and health services

CRBSI increases patients' discomfort and length of stay in hospital [6] and their risk of health complications and death [4]. Complications include acute respiratory distress syndrome, disseminated intravascular coagulation, acute renal failure, and shock [7]. However, data on mortality, quality of life and long-term prognosis specifically related to CRBSI are not available for the UK. Recent estimates of the mortality rates of patients with CRBSI in critical care units in France, Germany and Italy ranged from 11% to 17.1% [5]. The most recent (2009) estimate of the financial impact for the NHS suggests that annual costs related to CRBSI in intensive care units are £19.1 to £36.2 million [5].

6.2 Educational interventions for preventing CRBSI

6.2.1 Definition of educational interventions

In general, educational interventions involve the communication of information to a specific target group for one or more of the following purposes: to raise awareness; to enhance or improve knowledge; or to change behaviour [11]. Educational interventions for preventing CRBSI ideally should include behaviour modification components underpinned by relevant theory [12]. For the purposes of this project our working definition of an educational intervention is any intervention that aims to prevent CRBSI and: (a) includes at least an element of factual information provision related to that aim; (b) is described by the authors as educational; or (c) is described by the authors as behavioural. Project scoping searches indicated that behaviour-modifying interventions to prevent CRBSI are often called "educational" rather than "behavioural" interventions, and behaviour modification components of interventions are not always mentioned in the titles and

abstracts of studies. We define educational interventions broadly in this project to ensure that relevant behavioural interventions are not missed at the study selection step.

6.2.2 Types of intervention

Educational interventions for preventing CRBSI have been trialled in critical care settings in many countries and vary considerably in their content and complexity. They range from the provision of simple fact sheets and posters [13] to complex interventions comprising multiple behavioural components [14]. Interventions differ in the number and duration of education components, whether they are didactic or interactive, and whether surveillance and performance feedback are also present. Interventions that contain several different elements which together aim to achieve a particular outcome are referred to as 'multi-faceted', 'multi-component', or 'bundled' interventions [15]. Multi-faceted educational interventions that have been developed for preventing CRBSI include the Michigan project in the USA [16] and the NHS Central Venous Catheter Care Bundle [17]. These include, among others, specific components for ensuring staff hand hygiene, patient skin hygiene, appropriate choice of catheter type and insertion site, and appropriate ongoing catheter care.

6.2.3 Current usage in the NHS

To address the prevention of CRBSI, the NHS has recently developed 'Saving Lives' tools [18] which include the 'High-Impact' care bundles for central venous catheters and peripheral intravenous cannula [17]. These bundles are based on 'EPIC-2' guidelines [19], which stress the importance of education of hospital staff for successful implementation of infection control programmes. However, in the EPIC-2 guidelines there is a lack of evidence on the types of educational interventions that are most appropriate and effective, and the guidelines do not make any recommendations that specifically relate to critical care settings. EPIC-2 guidelines are also inconsistent with US guidelines [9] in interpreting the quality of evidence. Following a recommendation in the Darzi Report [20], during 2009-2011 the UK National Patient Safety Agency implemented an initiative known as 'Matching Michigan' [8, 21] to reduce CRBSI, based on a care bundle that has successfully reduced CRBSI in over 100 intensive care units (ICU) in the Michigan study in the USA [16]. However, the original study in the USA was not randomised and did not assess the importance of the education strategy in the effectiveness of the overall care bundle [16]. Guidance is needed from the wider literature on how to implement educational strategies to optimise the clinical effectiveness and cost effectiveness of this and other related bundled interventions, but the evidence to support such guidance has not been critically synthesised.

7. Planned investigation

7.1 Existing research

7.1.1 Clinical effectiveness of educational interventions

Studies have suggested that the introduction of interventions involving staff education alone or in combination with performance feedback can reduce the frequency of CRBSI in ICU by 40% to 89% [16, 22-29]. Various multi-faceted interventions involving staff education alongside other strategies have also been shown to reduce the frequency of CRBSI in ICU [e.g. 30-32]. However, most of the evidence has not been critically appraised and appears to be mainly from non-randomised studies of relatively short duration. These may give an over optimistic picture of infection control, as they do not consider longer-term attenuation of the effectiveness of interventions. Some multi-component bundled interventions involving staff education in critical care may provide sustained (3-year) reductions in infections [33], whereas other bundled interventions appear to have had no effect [34]. Although prevention of infections in some critical care units may be enhanced using staff

interventions with education reinforcement, surveillance, performance feedback and process control [e.g. 23], the cost effectiveness and wider generalisability of these is unclear. Strategies that combine both education and behaviour change stimuli would be expected to have greater impact, by providing a paradigm in which education includes components to target change in the knowledge, beliefs and skills which influence practice [35, 36]. However, health agencies also have to consider how to avoid overwhelming staff with new initiatives and deal with competing demands for safer care with higher throughput [9], particularly as increased staff workload negatively affects the care of critically ill patients [37]. The most complex interventions might not therefore necessarily be the most clinically and cost effective [38].

7.1.2 Cost effectiveness of educational interventions

Based on the estimated annual costs of CRBSI to the NHS above [5], the potential cost reduction to the NHS that could be made by preventing CRBSI would clearly be substantial. The costs of implementing educational interventions to achieve this however are rather unclear. The Michigan intervention [16] could prevent up to 15 deaths and save around $2 million annually in one intensive care unit (ICU) based on rates of CRBSI in the USA [39] (which might not be representative of current rates of CRBSI in the UK – section 6.1), but there are many uncertainties about how to transfer this type of intervention to UK practice. For example, it is unclear whether interventions tested in ICU in specific localities are generalisable to different geographic regions and healthcare systems, and whether education reinforcement works in situations of high staff turnover and staff shortage as often occur in the UK. The purported simplicity and cost of some interventions is also questionable, for example the Michigan intervention was described as simple and inexpensive but appears to require the delivery of at least 16 lectures by trained staff [39], the overall cost of which has not been explored.

7.1.3 Evidence scoping

Scoping searches for this proposal (which are likely to underestimate the true extent of the evidence) identified more than 20 prospective cohort studies of potentially relevant educational interventions (some of which are cited above) but no randomised controlled trials (RCTs). Eight potentially relevant narrative reviews were identified in scoping, but no systematic reviews have directly assessed the clinical effectiveness of educational strategies for preventing CRBSI in critical care. The most relevant systematic reviews in related areas have investigated: the effectiveness of bundled behavioural interventions to control healthcare associated infections (not limited to education, CRBSI or critical care) [14]; the effectiveness of interventions for preventing CRBSI in critical care (not limited to education or behavioural interventions) [40]; and educational interventions for preventing healthcare associated infections (not limited to educational or behavioural interventions, CRBSI, or critical care) [41].

None of these systematic reviews included economic analyses. Most of the available information on the economic impact of CRBSI in critical care is from work conducted in the USA [22, 42]. A recent brief narrative review of epidemiological studies, referred to above [5], provides an insight into the economic burden of CRBSI in critical care in European countries including the UK but, due to a shortage of information on costs, its findings are based on numerous assumptions and uncertainties.

The scoping search highlights the need for an evidence synthesis assessing both the clinical and cost effectiveness of educational interventions for preventing CRBSI in critical care, to assist decision making in the NHS.

7.2 Research objectives

The aim of this project is to conduct an evidence synthesis of the clinical and cost effectiveness of educational interventions aimed at hospital staff in critical care (doctors and nurses) for preventing CRBSI. An economic model will be devised by adapting an existing cost effectiveness model or constructing a new one using the best available evidence to determine cost effectiveness in a UK critical care setting. The project aims also to provide recommendations that will be sufficiently specific to be of use to those implementing infection-prevention strategies in the NHS and for further research.

The main objectives will be as follows:

1. To systematically review: (a) the clinical effectiveness; and (b) the cost effectiveness of educational interventions for the prevention of CRBSI.

2. To use an evidence mapping approach to describe the scope of the clinical effectiveness evidence base in terms of the different types of educational interventions, critical care settings, study designs and their theoretical basis, types and duration of education reinforcement, and outcomes reported including evidence of sustainability of effect. The evidence map would: (a) provide an overview, classification and characterisation of relevant educational interventions to enable complex interventions to be visualised and, where appropriate, compared; (b) provide a classification and report of other key study attributes, for example illustrating how CRBSI and CABSI are defined and applied in the studies; and (c) use recognised criteria to screen studies in terms of their relevance to the NHS.

3. To apply the evidence mapping exercise results to prioritise a subset of studies of highest relevance for detailed appraisal in the systematic review of clinical effectiveness.

4. To develop a decision analytic model to determine and compare cost effectiveness of relevant groups of interventions and settings identified through evidence mapping, either by adapting an existing economic model or constructing a model for the UK de novo.

5. To identify future research needs and make specific recommendations about the implementation of educational interventions for preventing CRBSI that are relevant to service users in the NHS.

8. Research methods

The project will involve a systematic review of the clinical effectiveness (section 8.1) and a systematic review and economic evaluation of the cost effectiveness (section 8.2) of educational interventions for preventing CRBSI in critical care (Fig. 1). The purpose of the cost effectiveness systematic review will be twofold: to assess whether an appropriate economic evaluation has been undertaken and, if not, to provide evidence to develop and populate a de novo economic evaluation.

8.1 Systematic review of clinical effectiveness

8.1.1 Literature search

Literature will be identified from several sources including:

1. General health and biomedical databases including BIOSIS, the British Nursing Index, CINAHL, EMBASE, MEDLINE, the Science Citation Index, and the Social Sciences Citation Index (also others if considered relevant);

2. Specialist electronic databases (e.g. the Cochrane Library; Database of Abstracts and Reviews of Effectiveness);

3. Unpublished literature and conference proceedings;

4. Contact with individuals with expertise in the field;

5. Checking of reference lists;

6. Research in progress databases (e.g. the UKClinical Research Network website, Current Controlled Trials, and Clinical trials.gov);

7. Relevant websites identified by the project team and Advisory Group.

All databases will be searched from their inception to the current date. Hand searching will focus on key journals and meeting abstracts published in the past two years, with the key journals identified in consultation with experts and from analyses of search results. Based on the scoping searches, we do not envisage that many non-English-language studies will be found (studies conducted in other countries were usually reported in English). We will include relevant non-English language as well as English language studies in the project, irrespective of their geographical location. The search strategy will be developed and applied by an experienced information specialist to ensure that as many relevant foreign language studies as possible are identified. Where required, translation will be done by native speakers of the language within the project team's research institutions. If an excessive number of foreign language studies requires translation, we will contact the HTA Programme to advise of the situation, in case provision of additional resources is considered appropriate.

A comprehensive database of relevant published and unpublished articles will be constructed using Reference Manager bibliographic software.

8.1.2 Inclusion criteria and search strategy

Inclusion criteria for the systematic review of clinical effectiveness will be based on the PICOD scheme (Population, Intervention, Outcome, Comparator, Design) and are shown in Table 1. Inclusion criteria for the systematic review of cost effectiveness are reported below (section 8.2). Note that although the target for educational interventions is critical care staff (doctors and nurses), it is the patients that are the relevant population for inclusion in evidence synthesis. This is because the relevant primary outcomes (CRBSI) are reported for patients.

Care will be taken to ensure that the search strategy can adequately capture educational interventions, given that these may be very diverse, inconsistently or poorly reported, or that education may make up a relatively small component of multi-faceted interventions. The search strategy will also be developed to capture the different possible variants, acronyms, synonyms and definitions of catheter-related bloodstream infections (including CRBSI, CABSI), taking into consideration that these might not have been used consistently and correctly in the literature. A search strategy for studies of cost effectiveness will also be developed, following standard procedures (section 8.2).

Understanding how and why interventions work is an integral part of the appraisal of complex interventions [43]. Process evaluations and secondary outcomes (e.g. knowledge, behaviour, attitudes or compliance of staff) may help to explain intervention mechanisms. Process evaluations and secondary outcomes will be included provided that relevant primary (infection) outcomes are also reported (Table 1). If reported in sufficient detail, process evaluations will be assessed following a systematic approach, to be agreed by the project team (e.g. an approach employed in a recent synthesis of evidence on sexually transmitted infections [44] may be suitable).

Table 1 Inclusion criteria for the systematic review of clinical effectiveness

Participants (P)	Patients in any critical care units who receive vascular catheters of any type whilst in critical care (including tunnelled and non-tunnelled catheters, subcutaneous catheter ports, peripherally inserted central catheters and cannula) for any medical purposes.
Intervention (I)	Any educational interventions for preventing CRBSI in critical care as defined in section 6.2.1. Studies that do not explicitly state an aim to prevent infections, but which report educational interventions that could prevent CRBSI in critical care, will be included if they meet the other inclusion criteria and report relevant outcomes.
Comparator (C)	Relevant comparators are: usual care (no active intervention) or any educational intervention that differs from the primary intervention in one or more educational components.
Outcomes (O)	Primary outcomes will be used for study selection decisions. Primary outcomes: (1) The frequency of catheter-related bloodstream infections, expressed as infection rates per device-days (usually expressed as BSI per 1000 catheter-days), per hospital-days, as a proportion of the study population, or relative to a comparator. Any related infection definitions will be accepted for inclusion screening (e.g. CRBSI, CABSI) as the accuracy and appropriateness of these will be scrutinised at the evidence mapping step. (2) Mortality due to CRBSI. Secondary outcomes: These will be assessed if relevant primary outcomes are reported, and may include: knowledge; attitudes; behaviour; and compliance of critical care staff. Process evaluations: These will be assessed if relevant primary outcomes are reported.
Design (D)	Interventional studies only. Randomised controlled trials, non-randomised or quasi-randomised controlled clinical trials, prospective cohort studies, retrospective cohort studies, controlled before-after studies, and interrupted time series studies will be included if they evaluate a relevant intervention. Case-control studies, case series, cross-sectional studies, and descriptive studies will be excluded. Where there is evidence from different types of study design for a specific intervention, only those studies with the most rigorous designs will be included and data extracted.

The study designs which will be included are not limited to controlled trials (Table 1). This is because in a scoping exercise much of the evidence found was from cohort studies. For the systematic review of cost-effectiveness, studies will only be included if they report the results of full economic evaluations [cost-effectiveness, cost-utility, cost-benefit or cost-consequence analyses].

8.1.3 Study selection

Studies will be selected for inclusion through a two-stage process using the pre-defined and explicit criteria outlined in Table 1. The full literature search results will be screened by two reviewers to identify all citations that may meet the inclusion criteria. Full manuscripts of all selected citations will be retrieved and assessed by two reviewers against the inclusion criteria. Studies published as abstracts or conference presentations will only be included if sufficient details are presented to allow an appraisal of the methodology and the assessment of results to be undertaken. To ensure that studies are screened consistently, an inclusion decision checklist will be developed and used for each manuscript assessed. Any disagreements over study inclusion will be resolved by consensus or if necessary by arbitration by a third reviewer.

8.1.4 Evidence mapping

All studies that meet the inclusion criteria will be entered into a mapping exercise in order to clarify the structure of educational interventions and identify those that are potentially of most relevance to the NHS.

The mapping exercise is summarised in Fig. 2 and will follow principles developed by the Global Evidence Mapping Initiative [45] to classify and summarise the evidence base as well as guidance from the Medical Research Council [43] and the National Institute for Health and Clinical Excellence (NICE) [46] on the reporting and evaluation of complex interventions. The key objectives of this step will be to: (a) provide an overview, classification and characterisation of relevant educational interventions to enable complex interventions to be visualised and, where appropriate, compared; (b) provide a classification and report of other key study attributes, for example illustrating how CRBSI and CABSI are defined and applied in the studies, and whether studies included process evaluations, information on potential facilitators or barriers to implementation, or other secondary outcomes; and (c) identify studies that are of most relevance to the NHS which should be prioritised for full evidence synthesis. The mapping exercise will be conducted as follows (Fig. 2):

1. With assistance from the Project Advisory Group (section 10), the characteristics of studies to be included in the descriptive map will be determined and made into a list;

2. In a pilot exercise involving two researchers, keywords will be developed that reliably and reproducibly describe each of the study characteristics in the list;

3. Each included study will be mapped by one researcher and the agreed keywords relevant to describe the characteristics of each study will be entered into a Microsoft Excel or Access database such that study interventions and keywords can be cross-tabulated;

4. Keyword assignments and database entries for each study will be checked by a second researcher;

5. Entries in the database will be used to concisely summarise the structure and composition of the study interventions using numerical, graphical and/or narrative methods where appropriate.

Depending upon the overall quality and quantity of evidence available, the evidence mapping exercise could include a preliminary appraisal of methodological quality to help decide which studies are prioritised for detailed full evidence synthesis (e.g. based on study design and sample size). A thorough appraisal of methodological quality, using risk of bias criteria, will be applied

later to those studies that are identified as being of most relevance to the NHS and which proceed for full data extraction (section 8.1.5).

8.1.5 Data extraction and quality assessment

The extraction of studies' findings will be conducted by one reviewer and independently checked by a second reviewer using a pre-designed and piloted data extraction form to avoid any errors. The data extraction form will be based on the PICOD scheme to clearly record and report all relevant aspects of the populations (P), interventions (I), comparators (C) outcomes (O), as well as methodological aspects of the study designs (D). Any disagreements between reviewers will be resolved by consensus or if necessary by arbitration involving a third reviewer. This process will be applied to those studies identified in the mapping exercise (section 8.1.4) as being of highest relevance in the context of current practice in the NHS. The methodological quality of these included studies, including their internal and external validity, will be appraised using established criteria for studies of clinical effectiveness [47] and recognised quality assessment approaches for studies of cost effectiveness and economic models (section 8.2). Missing information will be obtained from investigators of the primary studies if possible, so as to maximise the information about the educational interventions that can be extracted from each study.

8.1.6 Data synthesis

Studies will be synthesised through a narrative review with tabulation of results of included studies. If feasible, the results from individual studies will be synthesised through meta-analysis using established methods [47], with causes of heterogeneity of results examined.

8.2 Economic evaluation

The cost effectiveness of educational interventions in preventing CRBSI in critical care will be assessed in two stages: a systematic review of cost effectiveness and development of a decision analytic economic model (Fig. 1).

8.2.1 Systematic review of cost effectiveness

Searches of general health and biomedical databases (as listed in section 8.1.1), specialist electronic databases (e.g. the NHS Economic Evaluation Database; the Cochrane Library), and unpublished literature and conference proceedings will be carried out to identify relevant studies. The systematic review will focus on economic evaluations of educational interventions to prevent CRBSI. To inform development of our economic evaluation we will also include any studies that report model-based economic evaluations of other (non-educational) interventions, if they were published since a 2007 review of the economics of preventing CRBSI [48]. Experts will be contacted to ask if they know of any relevant published or unpublished studies that we have not identified. Studies will be included in the systematic review if they are full economic evaluations (cost utility or cost effectiveness studies) that report both measures of costs and consequences, and include outcomes expressed as CRBSI cases avoided, or life years or quality-adjusted life years gained. The methodological quality of included cost effectiveness studies will be appraised using accepted criteria for appraising economic evaluations [49, 50]. Studies will be synthesised through a narrative review that includes: a clear explanation of the assessment process; a detailed critical appraisal of study methods; tabulation of the results of the included studies; a summary indicating which data are used in the economic model; and an explanation of any knowledge gaps and assumptions.

Fig. 1 Overview of the project approach

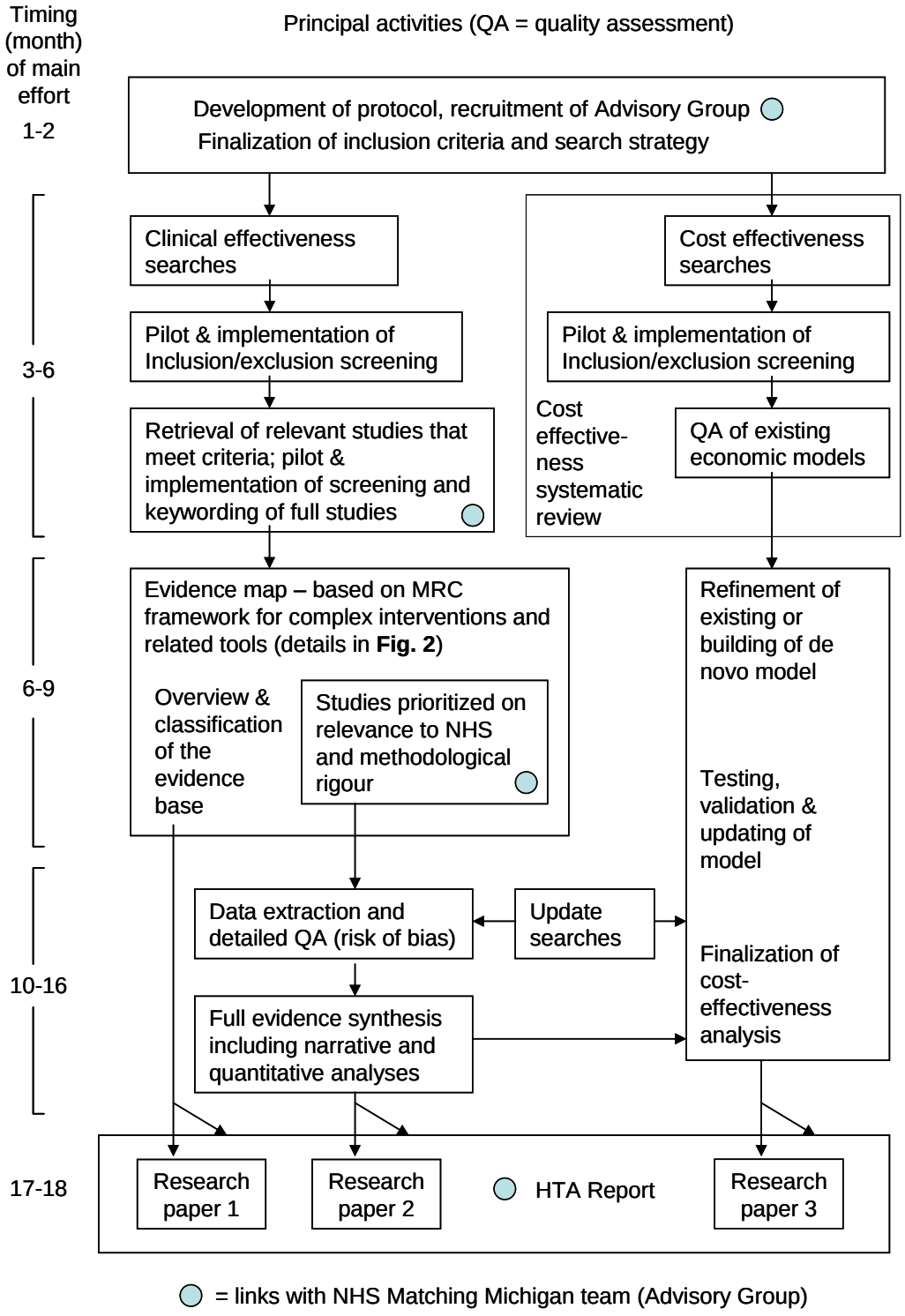
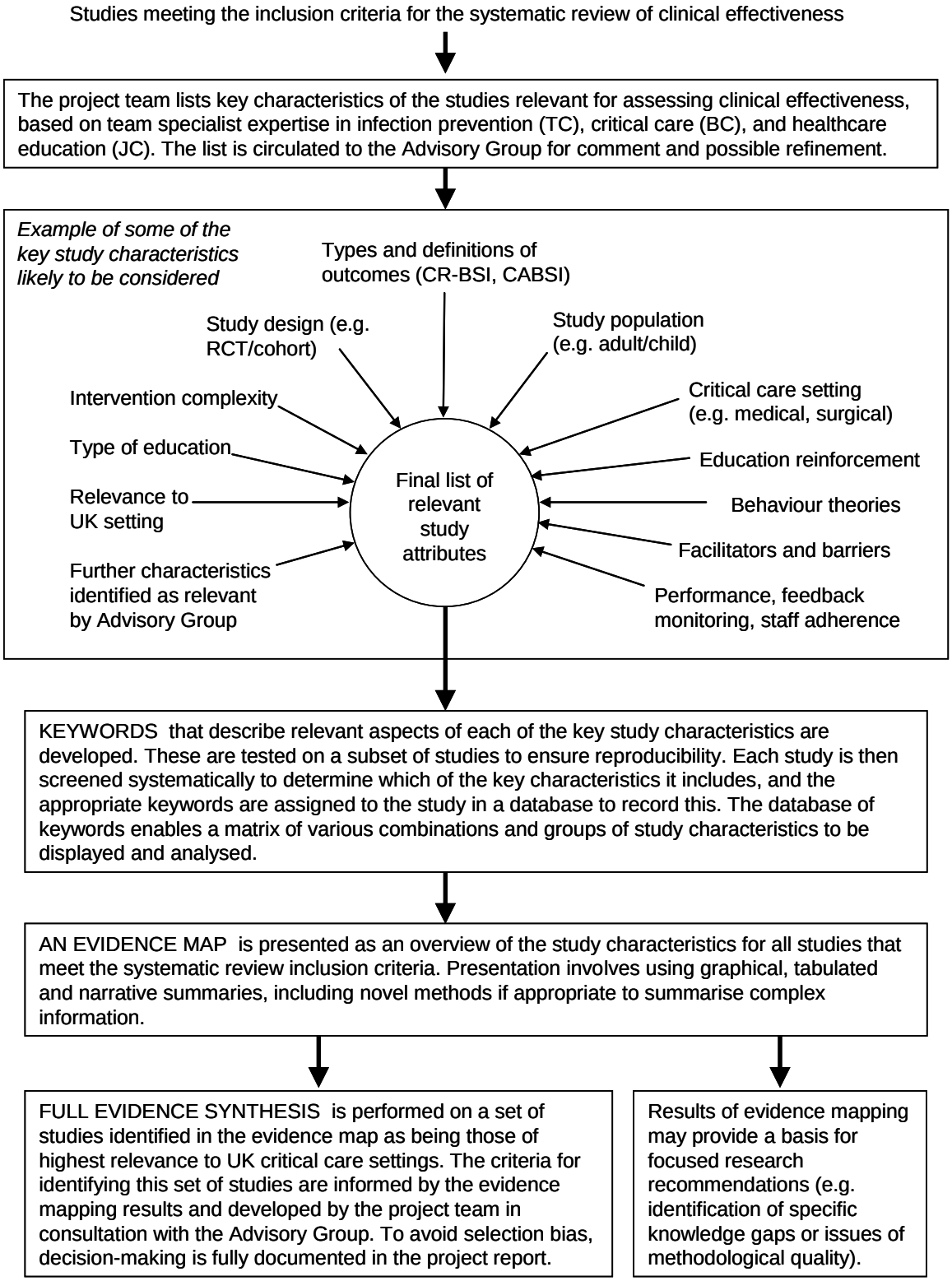


Fig. 2 Overview of the evidence mapping procedure for studies of clinical effectiveness



8.2.2 Decision analytic model

Evidence from both the systematic review of cost effectiveness and the systematic review of clinical effectiveness (section 8.1) will be used to develop the economic model. Existing economic models of interventions to prevent CRBSI identified in the systematic review of economic evaluations will be assessed for their relevance and quality. If these are not suitable, a *de novo* decision analytic model will be developed. Development of model structure will be informed by previously published models (such as that developed by one of the applicants [51]) and validated through discussion with clinical and methodological advisors. Accepted guidelines for good practice in decision-analytic modelling [52] and the general principles outlined in the NICE 'reference case'[53] will be followed. Clinical effectiveness parameters in the model will be taken from the systematic review of clinical effectiveness. Additional targeted literature searches will be required to populate other parameters in the model, such as the baseline risk of CRBSI. Expert opinion will be used where suitable data to populate the model cannot be identified from the literature. Where expert opinion has been used, this will be clearly identified in the report of the model.

The model will provide a cost-consequences analysis, reporting the costs of alternative educational interventions (broken down by key components, such as staff training, administration, consumables etc. where possible) and their consequences in terms of patient outcomes, principally any effect on the risk of CRBSI. The outcome of the model will be presented as the incremental cost per CRBSI avoided. We will consider the feasibility of developing also a cost-utility analysis model incorporating final outcomes (life expectancy or quality-adjusted life expectancy – i.e. QALYs). This will require estimating excess mortality attributable to CRBSI in patients admitted to ICU and the impact of such infections on patients' quality of life. The model will adopt a UK NHS and Personal Social Services perspective.

The resources necessary for providing the educational interventions will be estimated from studies included in the systematic review of effectiveness (section 8.1), and from discussion with expert advisors. The costing will concentrate on costing studies that were conducted in health systems with similar institutional arrangements to the NHS, and those including educational interventions that are similar to those being introduced in the NHS (for example, 'Matching Michigan'). Unit costs will be developed based on published evidence, official sources such as NHS Reference Costs [54] and Unit Costs of Health and Social Care [55], and from the Costing Unit at Southampton General Hospital. Costs will be inflated to current prices as necessary. If no published data on resource use are available, estimates will be based on information from expert advisors.

Uncertainty relating to key parameters will be explored using deterministic and, where appropriate, probabilistic sensitivity analyses. If it is feasible to develop a full cost-utility model, probabilistic sensitivity analyses will be conducted and the results expressed using cost effectiveness acceptability curves (CEACs). The key variables to be explored will include: effectiveness of educational interventions, baseline risk of CRBSI, cost and duration of CRBSI, mortality attributable to CRBSI, and QALYs.

The model will be developed using standard software including Excel and TreeAge Pro to ensure transparency and would be flexible in terms of permitting different estimates to be used for key input parameters. Any structural assumptions underlying the model would be transparently reported. The model could therefore be updated in response to new information about critical care (intensive care) practices. We propose to consult the project's Advisory Group, which will include clinicians working in critical care, to identify which of the possible changes in critical care practices are likely to be most relevant. This will ensure that appropriate, modifiable, input parameters and structural assumptions are included in the model.

9. Project timetable and milestones

The project will take 18 months, commencing 4th January 2011. Twelve milestones and three proposed research publications arising from the project are detailed in the full project proposal (see also Fig 1). Interim reports will be prepared and submitted at dates to be confirmed by the HTA Programme. A final project report will be completed and disseminated by 30 June 2012.

10. Advisory Group

Julian Bion – Professor of Critical Care; clinical lead of Matching Michigan project
Andrew Jackson – Consultant Nurse IV Therapy & Care; Infection Prevention Society
Annette Richardson – Nurse Consultant Critical Care; British Association of Critical Care Nurses
Trudie Roberts – Professor of Medical Education; Association for the Study of Medical Education
Katie Scales – Consultant Nurse Critical care; National Infusion and Vascular Access Society
Barry Williams – Critical Care Patient Liaison Committee (CritPal)
Duncan Wyncoll – Consultant Intensivist; Intensive Care Society

11. References

1. Penne K. Using evidence in central catheter care. Seminars in Oncology Nursing 2002;18:66-70.
2. Hospital Infection Society. The third prevalence survey of healthcare associated infections in acute hospitals in England 2006. Department of Health, England; 2007.
3. Nosocomial Infection National Surveillance Service (NINSS). Surveillance of hospital-acquired bacteraemia in English hospitals 1997-2002. Public Health Laboratory Service; 2003. http://www.library.nhs.uk/HEALTHMANAGEMENT/ViewResource.aspx?resID=264523
4. Armenian SH, Arrieta AC, Singh J. Risk factors for mortality resulting from bloodstream infections in a pediatric intensive care unit. Pediatric Infectious Disease 2005;24:309-314.
5. Tacconelli E, Smith G, Hieke K, Lafuma A, Bastide P. Epidemiology, medical outcomes and costs of catheter-related bloodstream infections in intensive care units of four European countries: literature and registry-based estimates. Journal of Hospital Infection 2009;72:97-103.
6. Plowman R, Graves N, Griffin M, Roberts JA, Swan AV, Cookson B, et al. The socio-economic burden of hospital acquired infection. London, School of Hygiene and Tropical Medicine: Public Health Laboratory Service; 1999.
7. Wenzel RP, Edmond MB. Team-based prevention of catheter-related infections. New England Journal of Medicine 2006; 355:2781-2783.
8. Richardson A. Minimising central venous catheter-associated bloodstream infections – 'Matching Michigan' in England. Nursing in Critical Care 2009;14:105-106.
9. O'Grady NP, Alexander M, Dellinger EP, Gerberding JL, Heard SO, Maki DG, et al. Guidelines for the prevention of intravascular catheter-related infections. Morbidity and Mortality Weekly Report 2002;51 (RR 10):1-26.
10. Mermel LA, Farr BM, Sherertz RJ, Raad II, O'Grady N, Harris JS, et al. Guidelines for the management of intravascular catheter-related infections. Clinical Infectious Diseases 2001; 32:1249–1272.
11. Griesbach D. Educational interventions to prevent hepatitis C: A review of the literature and expert opinion. NHS Health Scotland 2009.

12. Reed D, Price EG, Windish DM, Wright SM, Gozu A, Hsu EB, et al. Challenges in systematic reviews of educational intervention studies. Annals of Internal Medicine 2005; 142: 1080-1090.
13. Atherton SL, Tjoelker RC. Evidence based fact sheet: An effective method for implementing change. American Journal of Infection Control 2006;34(5):E51.
14. Aboelela SW, Stone PW, Larson EL. Effectiveness of bundled behavioural interventions to control healthcare-associated infections: a systematic review of the literature. Journal of Hospital Infection 2007;66:101-108.
15. Conn VS, Rantz MJ, Wipke-Tevis DD, Maas ML. Designing effective nursing interventions. Research in Nursing and Health 2001;24:433-442.
16. Pronovost P, Needham D, Berenholtz S, Sinopoli D, Chu H, Cosgrove S, et al. An intervention to decrease catheter-related bloodstream infections in the ICU. New England Journal of Medicine 2006;355:2725-2732.
17. Department of Health. High Impact Intervention No. 1 Central Venous Catheter Care Bundle. Department of Health; 2008. http://www.clean-safe-care.nhs.uk/toolfiles/14_SL_HII_1_v2.pdf
18. Department of Health. Clean, Safe Care: Reducing Infections and Saving Lives. Department of Health; 2008. http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_081650
19. Pratt RJ, Pellowe CM, Wilson JA, Loveday HP, Harper PJ, Jones SRLJ, et al. epic2: National evidence-based guidelines for preventing healthcare-associated infections in NHS hospitals in England. Journal of Hospital Infection 2007;65S:S1-S64.
20. Department of Health. High Quality Care for All. Department of Health; 2008. http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_085825
21. National Patient Safety Agency. Minimising central venous catheter associated bloodstream infections: Matching Michigan. National Patient Safety Agency; April 2009. http://www.npsa.nhs.uk/nrls/improvingpatientsafety/anaesthesia-and-surgery/matching-michigan/
22. Warren DK, Zack JE, Mayfield JL, Chen A, Prentice D, Fraser VJ, et al. The effect of an education program on the incidence of central venous catheter-associated bloodstream infection in a medical ICU. Chest 2004;126:1612-1618.
23. Rosenthal VD, Guzman S, Pezzotto SM, Crnich CJ. Effect of an infection control program using education and performance feedback on rates of intravascular device-associated bloodstream infections in intensive care units in Argentina. American Journal of Infection Control 2003;31:405-409.
24. Yilmaz G, Caylan R, Aydin K, Topbas M, Koksal I. Effect of education on the rate of and the understanding of risk factors for intravascular catheter-related infections. Infection Control and Hospital Epidemiology 2007; 28:689-94.
25. Salomao R, Blecher S, Da Silva M, Villins M, Da Silva EH. Education and performance feedback effect on rates of central vascular catheter-associated bloodstream infections in adult intensive care units in one hospital in Sao Paulo, Brazil. American Journal of Infection Control 2005; 33(5): E58.
26. Gómez WV, Vergara GR, Pertuz AM, Rosenthal VD. Education and performance feedback effect on rates of central vascular catheter-associated bloodstream infections in newborn intensive care units in a private hospital in Colombia. American Journal of Infection Control 2005; 33(5): E76-E77.

27. Ozgultekin A, Rosenthal VD, Turan G, Akgun N. Education and performance feedback effect on rates of central vascular catheter -associated bloodstream infections in adult intensive care units of one Turkish hospital. American Journal of Infection Control 2006; 34(5): E23.
28. Higuera F, Rosenthal VD, Duarte P, Ruiz J, Franco G, Safdar N. The effect of process control on the incidence of central venous catheter-associated bloodstream infections and mortality in intensive care units in Mexico. Critical Care Medicine 2005; 33(9): 2022-2027.
29. Maas A, Flament P, Pardou A, Deplano A, Dramaix M, Struelens MJ. Central venous catheter-related bacteraemia in critically ill neonates: risk factors and impact of a prevention programme. Journal of Hospital Infection 1998;40: 211-24.
30. Eggimann P, Harbarth S, Constantin M-N, Touveneau S, Chevrolet J-C, Pittet D. Impact of a prevention strategy targeted at vascular-access care on incidence of infections acquired in intensive care. Lancet 2000;355:1864-1868.
31. Karali V, Stefanopoulou P, Bitzani M, Ambatzidou F, Vassiliadou G, Riggos D. Effects of an education: prevention strategy on decreasing catheter-related infections in intensive care. Critical Care 2003;7 (suppl 2):123.
32. Lobo RD, Levin AS, Brasileiro Gomes LM, Cursino R, Park M, Figueiredo VB, et al. Impact of an educational program and policy changes on decreasing catheter-associated bloodstream infections in a medical intensive care unit in Brazil. American Journal of Infection Control 2005;33:83-87.
33. Schelonka RL, Scruggs S, Nichols K, Dimmitt RA, Carlo WA. Sustained reductions in neonatal nosocomial infection rates following a comprehensive infection control intervention. Journal of Perinatology 2009;26:176-179.
34. Cohran J, Larson E, Roach H, Blane C, Pierce P. Effect of intravascular surveillance and education program on rates of nosocomial bloodstream infections. Heart and Lung 1996;25:161-164.
35. Bonetti D, Eccles M, Johnston M, Steen M, Grimshaw J, Baker R, Walker A, Pitts N. Guiding the design and selection of interventions to influence the implementation of evidence-based practice: An experimental simulation of a complex intervention trial. Social Science and Medicine 2005; 60:2135-2147.
36. The Improved Clinical Effectiveness through Behavioural Research Group. Designing theoretically-informed implementation interventions. Implementation Science 2006;1:4.
37. Hugonnet S, Chevrolet J-C, Pittet D. The effect of workload on infection risk in critically ill patients. Critical Care Medicine 2007;35(1):76-81.
38. Collins LM, Murphy SA, Nair, VN, Strecher VJ. A strategy for optimizing and evaluating behavioural interventions. Annals of Behavioral Medicine 2005;30:65-73.
39. Berenholtz SM, Pronovost PJ, Lipsett PA, Hobson D, Earsing K, Farley JE, et al. Eliminating catheter-related bloodstream infections in the intensive care unit. Critical Care Medicine 2004;32:2014-2020.
40. Ramritu P, Halton K, Cook D, Whitby M, Graves N. Catheter-related bloodstream infections in intensive care units: a systematic review with meta-analysis. Journal of Advanced Nursing 2008;62:3-21.
41. Safdar N, Abad C. Educational interventions for prevention of healthcare-associated infection: A systematic review. Critical Care Medicine 2008;36:933-940.
42. Coopersmith CM, Rebmann TL, Zack JE, Ward MR, Corcoran RM, Schallom ME, et al. Effect of an education program on decreasing catheter-related bloodstream infections in the surgical intensive care unit. Critical Care Medicine.2002;30(1):59-64.
43. Medical Research Council. Developing and evaluating complex interventions: New guidance. MRC; September 2008. http://www.mrc.ac.uk/complexinterventionsguidance

44. Shepherd J, Kavanagh J, Picot J, Cooper K, Harden A, Barnett-Page E, Jones J, Clegg A, Hartwell D, Frampton GK, Price A (2010). The effectiveness and cost-effectiveness of behavioural interventions for the prevention of sexually transmitted infections in young people aged 13-19: a systematic review and economic evaluation. Health Technology Assessment 14 (7) 1-230.
45. Global Evidence Mapping (GEM) Initiative. http://www.evidencemap.org/
46. National Institute for Health and Clinical Excellence. Behaviour change at population, community and individual levels. NICE Public Health Guidance 6; October 2007. http://www.nice.org.uk/PH006
47. Higgins JPT, Green S (eds). The Cochrane Handbook for Systematic Reviews of Interventions. Version 5.0.1 (updated September 2008). http://www.cochrane-handbook.org/
48. Halton K, Graves N. Economics of preventing catheter-related bloodstream infection? Emerging Infectious Diseases 2007;13(6):815-23.
49. Evers S, Goossens M, de Vet H, van Tulder M, Ament A. Criteria list for assessment of methodological quality of economic evaluations: Consensus on Health Economic Criteria. International Journal of Technology Assessment in Health Care 2005;21(2):240-245.
50. Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. Methods for the economic evaluation of health care programmes. Oxford: Oxford University Press; 2005.
51. Halton KA, Cook DA, Whitby M, Paterson DL, Graves N. Cost effectiveness of antimicrobial catheters in the intensive care unit: addressing uncertainty in the decision. Critical Care 2009;13:R35.
52. Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R. Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technology Assessment 2004;8(36).
53. National Institute for Health and Clinical Excellence. Guide to the methods of technology appraisal. NICE; 2008. http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf
54. Department of Health. NHS reference costs 2008/09. Department of Health; 2009. http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_095859
55. Curtis L. Unit Costs of Health and Social Care. Canterbury: University of Kent; 2008.