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Identification of evidence for key parameters in decision-analytic models of cost-effectiveness : a description of sources and a recommended minimum search requirement

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Abstract

The paper proposes recommendations for a minimum level of searching for data for key parameters in decision-analytic models of cost-effectiveness and describes sources of evidence relevant to each parameter type. Key parameters are defined as treatment effects, adverse effects, costs, resource use, health state utility values (HSUVs) and baseline risk of events. The recommended minimum requirement for treatment effects is comprehensive searching according to available methodological guidance. For other parameter types the minimum is the searching of one bibliographic database plus, where appropriate, specialist sources and non-research based and non-standard format sources. The recommendations draw on the search methods literature and on existing analyses of how evidence is used to support decision-analytic models. They take account of the range of research and non-research based sources of evidence used in cost-effectiveness models and of the need for efficient searching. Consideration is given to what constitutes best evidence for the different parameter types in terms of design and scientific quality and to making transparent the judgments that underpin the selection of evidence from the options available. Methodological issues are discussed including the differences between decision-analytic models of cost-effectiveness and systematic reviews when searching and selecting evidence and comprehensive versus sufficient searching. Areas are highlighted where further methodological research is required.

Key points for decision makers

- Procedural guidance on how to search for evidence for key model parameters does not exist resulting in inconsistent search practice and a lack of transparency
- A minimum search requirement across all key model parameters is proposed

- Important considerations are taken into account including the diverse range of evidence used in models and the need for efficient searching

1.   Introduction

The use of decision-analytic models to assess the cost-effectiveness of healthcare interventions requires the assembly of a broad range of evidence. An analysis on the use of evidence in models identified fourteen types of information drawing on research and non-research based sources [1]. A feasibility study of systematic searching for cost-effectiveness models identified forty-two search questions arising from a typical model [2]. Key model parameters, common to most decision-analytic models of cost-effectiveness, have been identified by a number of sources as treatment effects, including adverse events, costs, resource use, utilities and baseline risk of events [3-6]. Whilst authoritative search methods exist for evidence on treatment effects [7, 8], equivalent methods for other types of evidence are not as well established. Procedural guidance on how to search for evidence across all the main model parameter types does not exist. As a result the process by which evidence is identified can lack transparency.

An analysis of published cost-effectiveness models revealed that only 52% of models referenced clearly the sources of data inputs and that search strategies were rarely reported [5]. A recent analysis of the critiques of sponsors' searches submitted to NICE (National Institute for Health and Care Excellence) found that substantially more critical comments related to clinical-effectiveness searches than to searches supporting the cost-effectiveness analysis. This figure probably points to the lack of systematic criteria by which cost-effectiveness searches for models can be assessed [9].

The need to improve the rigour and transparency by which evidence is identified therefore is recognised in the methodological literature. Increasingly reimbursement agencies and peer reviewed journals require more explicit reporting, including the reporting of search strategies, of how key data inputs are identified [10]. Despite this, detailed guidance on how to implement a more systematic approach to searching within a decision-analytic modelling framework does not exist. In the absence of such guidance this paper proposes a required, minimum level of searching for the systematic identification of evidence for key model parameters. The focus is on bringing together in one place a description of relevant sources and recommendations for a minimum level of searching in order to encourage a consistent, transparent and systematic approach to searching across all the main parameter types for decision-analytic models of cost-effectiveness.

2.   Identification of data inputs

For the purposes of this paper, key data inputs are defined as treatment effects, adverse effects, costs, resource use, utilities and risk of baseline events. This corresponds with the definition of key data inputs in a number existing sources on the review of evidence for model parameters. [3-6] Recommendations are presented for a minimum level of searching for each of the main data inputs. The minimum level of searching considers the range of the types of evidence that should be sought for each parameter type. It also considers the scope of the evidence that should be sought in order

that evidence requirements relating to all relevant health states within the model pathway are systematically addressed.

The recommendations suggest how much searching constitutes a minimum level of searching. The merits of comprehensive versus sufficient evidence retrieval is a topic of methodological debate, with some studies questioning the value of searching a large number of databases [3, 11, 12]. This debate is particularly pertinent in the context of cost-effectiveness models and is considered in the discussion section. The recommendations presented here emphasise efficiency over exhaustive searching. However, it is important to note that the minimum level of searching will not necessarily be considered sufficient for all parameter types for all models in all circumstances. It is a starting point for encouraging a consistent approach across all parameter types. Guidance is given on where the minimum level of searching might not be considered sufficient and where the level of searching should be extended.

In terms of sources of evidence, the recommendations cover bibliographic databases, such as Medline [13]. Medline is suggested as the prime example of a bibliographic database due to its wide availability and importance as a source of evidence relevant to health technology assessment (HTA). Other databases exist, such as EMBASE, and where it is considered appropriate, these are considered alongside Medline.

For general bibliographic databases, the use of search filters is recommended. Filters are combinations of keywords incorporated into search strategies to restrict results to a specific study design or type of information (e.g. costs). Filters are designed to optimise results in terms of sensitivity (to maximise the retrieval of relevant evidence) or precision (to minimise the retrieval of irrelevant evidence). A large collection of filters has been compiled by the InterTASC Information Specialists' Subgroup (ISSG) in the United Kingdom (UK). Filters referred to in the paper can be located via the ISSG Search Filter Resource [14].

The recommendations for searching also include specialist bibliographic databases and non-database searching. This reflects the broad range of evidence types and formats used to inform model parameter estimates. Various analyses demonstrate that a wide range of research study designs and non-research evidence is used [1, 4, 10]. The recommendations presented here categorise evidence into research-based and non-research based sources. Non-research based sources include a range of types of evidence including compilations of routinely collected statistics, information collected for administrative purposes (such as prescription rates) and reference sources (e.g. classifications of disease or drug formularies). Non-research based sources are also described as being of non-standard format as typically they do not follow the standardised, structured reporting of published research.

The recommendations for searching for each parameter type are presented below and are summarised in Table 1. They include a description of the types of evidence used for each parameter type, the sources where the evidence might be located and the factors to consider in defining the scope of the searches to be undertaken. Issues relating to the implementation of the recommendations, particularly with regard to searching beyond the minimum required level of searching are presented later in the paper.

2.1   Treatment effects

Randomised controlled trials and meta-analyses of RCTs are the main sources of evidence used to inform estimates of treatment effects [1, 10]. This is consistent with the view that RCTs are the best source of clinical effectiveness evidence. A hierarchy of evidence for model data inputs defines best evidence as meta-analyses of RCTs and single RCTs that include head to head comparisons and final outcomes [4].

Health technology assessment and modelling guidelines recommend that estimates of treatment effects should be based on a full systematic review [6, 15]. Systematic review guidelines developed by organisations such as Cochrane and CRD (Centre for Reviews and Dissemination) provide detailed guidance on how to search for effectiveness evidence and this paper would recommend their guidance for this type of data input [7, 8].

The methods include searching multiple bibliographic databases (e.g. Medline and Embase) using a systematic reviews filter or RCTs filter. The Cochrane Highly Sensitive Search Strategy (HSSS) has been developed and validated for the identification of RCTs in Medline [7]. The HEDGES Project at McMaster University in Canada has developed relevant filters aimed at maximising sensitivity and precision [16].

Specialist databases focussing on systematic reviews and RCTs also exist. The Cochrane Library provides full-text access to Cochrane systematic reviews and to bibliographic records on CENTRAL, the Cochrane trials register [17]. The CRD DARE (Database of Reviews of Effects) database, which is no longer being updated, remains a valuable source of structured systematic review abstracts dating from 1994 to March 2015 [18].

Systematic review guidelines recommend other search techniques, in addition to bibliographic database searching, to optimise the completeness of searches [7, 8]. These include consulting trials registers for ongoing and unpublished trials, handsearching, citation searching, grey literature searching and consultation with experts.

In order to identify the full range of treatment effects data relevant to a model a number of factors should be considered in determining the scope of searches [19]. In addition to searches on the

intervention of interest, comparator searches are required to inform an indirect comparison if head-to-head trials do not exist. For network meta-analyses searches are required on a whole range of interventions. Effectiveness searches beyond the interventions and comparators of interest are required if they form an important part of the disease management pathway. These could include, for example, companion diagnostics to target treatment at patient subgroups or downstream interventions such as later stage treatment options in models of cancer treatment.

2.2   Adverse effects

The hierarchy of evidence for model inputs suggests RCTs and meta-analyses of RCTs as the highest quality adverse effect evidence [4]. However, adverse effect evidence from RCTs is not always available or sufficient for a number of reasons. The assessment of adverse effects as a secondary outcome within a trial might not be reported in detail. Adverse events might occur in the long term or be too uncommon to be captured in the relatively short-term design of trials. The selection criteria for trial participants can exclude vulnerable groups who are more likely to be susceptible to adverse effects such as children, pregnant women and older people. Adverse effects can impact on the ability to tolerate treatment, on health related quality of life (HRQoL) or on the costs of managing the condition. If these impacts are significant, assessment might require searches beyond RCT evidence even where this is available.

Cochrane and CRD provide guidance on adverse effect searching [7, 8]. They cite non-randomised observational studies and non-research based information as relevant sources of evidence.

Evidence can be identified via general bibliographic databases such as Medline. It should be noted that whilst Medline is recommended here due to its availability, EMBASE and the Science Citation Index (SCI) might produce higher yields of adverse effects evidence [20]. A search filter for adverse effects has been developed and validated [21]. The filter focusses on drug adverse events and a different approach might be required for non-drug interventions[22]. A systematic review of the sensitivity and precision of a range of filters has been published [23]The available filters contain generic terms including, for example, *'adverse effects'*, *'complications'*, *'safety'*. It might also be necessary, where specific adverse effects are of particular importance, to include more specific terms (for example *'nausea and vomiting'*, *'gastrointestinal bleeding'*).

Specialist databases include TOXLINE [24] and pharmaceutical subscription sources such as the Derwent Drug File [25] and International Pharmaceutical Abstracts (IPA) [26]. Whilst early research suggests that the Derwent Drug File may have some value [27] more recent research suggests that generic bibliographic databases as described above may provide the highest yield [20].

Non-research based evidence accessed via the internet includes summaries of adverse effects evidence and adverse event reporting systems. These are provided by pharmacovigilance and post-

market surveillance systems such as the United States Food and Drug Administration (US FDA) MedWatch and Postmarket Drug Safety Information, the United Kingdom Medicines and Healthcare products Regulatory Agency (MHRA), the European Medicines Agency (EMA) Pharmacovigilance system and VigiAccess™, a search interface for VigiBase, the adverse drug reactions database of the World Health Organization [28-32]. A study of pharmaceutical regulation in the BRIC countries (Brazil, Russia, India and China) provides details of pharmacovigilance systems in emerging markets [33].

In order to identify the full range of adverse effect data a number of factors should be considered in determining the scope of searches. Some adverse effects, such as nausea and vomiting, kidney failure, hair loss, are common across interventions. In assessing the impact of these on costs and HRQL it might be useful to broaden the search to seek indirect evidence on these specific adverse effects, beyond the interventions and comparators of interest. Consideration should be given to where in the disease pathway adverse effects might impact on the cost-effectiveness of the intervention of interest. For example, a comparison of early interventions might take into account a change in the risk of progressing to more aggressive or invasive treatment options later in the disease pathway.

2.3   Costs

Research-based and non-research-based sources are used for costs. Within each category a wide range of evidence types exist making it difficult to specify the best source of evidence [1]. Research-based sources include primary economic evaluations, where costs data are collected prospectively as part of an RCT or observational study, secondary economic evaluations where data are derived from existing published and unpublished sources and costing studies. Non-research-based sources include drug tariffs, administrative information such as prescription costs and routinely collected statistics. The importance of 'real world' non-research based sources is often highlighted to support the external validity of cost estimates. The Coyle and Lee hierarchy recommends estimates based on reliable administrative databases or costs collected prospectively within RCTs [4]. The hierarchy places these above unsourced data from previous economic evaluations and emphasises the importance of using evidence from the same geographical or political jurisdiction as the analysis.

Cochrane and CRD provide guidance on searching for cost-effectiveness evidence but this is restricted to the identification of existing economic evaluations [7, 8, 34]. Guidance on searching for individual cost components and estimates of unit costs is not provided.

Evidence to inform costs estimates can be identified via bibliographic databases such as Medline. Filters have been developed to identify costs information. The CRD website provides economics filters for Medline and other bibliographic databases [35]. The HEDGES project has developed costs filters aimed at maximising sensitivity and precision [16].

Specialist databases exist for the identification of economic evaluations. The CRD website hosts the HTA database with details of assessments undertaken by INAHTA (International Network of Agencies for Health Technology Assessment) members and the NHS EED database which is no longer being updated but continues to provide quality assessed abstracts of economic evaluations up to March 2015 [18]. The Tufts CEA (Cost-Effectiveness Analyses) Registry provides free level access to bibliographic details of over 4000 published cost-utility analyses (CUAs) [36].

A wide range of non-standard format and non-research based sources can inform cost estimates. Many are accessed via the internet although expertise or familiarity with their non-standard format might be required to exploit them fully. This type of information covers statistical data collected for routine administrative purposes, including health service prescription costs or claims databases or compilations of information specific to a given jurisdiction. The latter types include drug tariffs or health service salary scales. Many sources are generic in that they are not specific to a particular disease or intervention and therefore will be of relevance to many cost-effectiveness analyses within the relevant jurisdiction. For example, in England, three core sources are the annual NHS Reference Costs, [37] the British National Formulary (BNF) [38] and the PSSRU unit costs, [39] a compilation of unit costs produced by the Personal Social Services Research Unit, University of Kent.

The curation of sources for different countries and jurisdictions would provide a valuable resource to support the identification of costs evidence. A pre-determined set of core sources, however, might be restrictive and the exploration of alternative or additional sources specific to the decision problem should also be undertaken. Search techniques aimed at identifying such sources include reference checking in published economic evaluations, consulting with experts or organisations (e.g. charities, professional organisations) and speculative searches using web-based search engines.

In planning searches several important considerations should be taken into account [19]. The scope of searches should not be restricted to the intervention of interest as costs relating to the disease area more generally will be relevant and costs information beyond the immediate condition of interest may well be applicable. For example, in a type II diabetes model, long term complications which incur costs would include cardiovascular disease, blindness, kidney disease and lower limb amputation. The cost of managing adverse effects, including, possibly, those associated with downstream treatments might be relevant. The scope of information required therefore is dictated by all events and health states that have a cost implication within the time horizon of the model. The model perspective might restrict the scope to direct health and social services costs but a broader perspective could take account of carer or societal costs.

A final consideration is the granularity of the costs information [19]. Some costs will require a detailed specification, comprising multiple cost components. For example the costs of managing type II diabetes would require treatment acquisition costs but also monitoring costs including health service appointments and tests. A complete picture might require evidence from many sources. Other cost

specifications could require a more parsimonious approach to avoid an overly complicated model. For example, downstream health states, such as 'blindness' might be represented by a single, overall cost drawn from a single source. In such cases, consideration should be given to the methods used, in the originating source, to arrive at a single, overall cost estimate.

2.4   Resource use

Methodological guidelines do not always differentiate between evidence on costs and resource use [10]. Cost components comprise two elements; unit costs (e.g. cost of an outpatient appointment) combined with typical resource use in a given context (e.g. number of outpatient appointments). The two types of information are closely associated and the recommendations on costs searching are important in locating information on resource use. However it is important to consider the two separately as estimates won't necessarily be derived from the same sources.

Resource use estimates are taken from both research-based and non-research based sources. Administrative data, claims databases, RCTs, guidelines and observational studies have all been identified as options [1]. Information on practice, such as clinical guidelines, is useful although consideration should be given to the gap between recommended practice and actual real world practice. Prospective, study-based data collection and analyses of administrative data are both at the top of the hierarchy of evidence on resource use [4]. The hierarchy highlights the jurisdiction of interest as the most important criterion by which evidence should be judged.

Evidence can be identified via searches of bibliographic databases such as Medline. No published search filter exists for resource use. An unvalidated filter used locally in conjunction with costs filters incorporates MeSH (Medical Subject Headings) and freetext terms. (Figure 1 (Anthea Sutton, personal communication, 29 July 2014)).

<INSERT FIGURE 1 HERE>

The filter could be supplemented with terms relating to current practice (e.g. audit, current practice, care pathway). An unvalidated filter for clinical guidelines provides a list of potentially useful search terms [40].

Specialist bibliographic databases specific to resource use do not exist. In addition to the cost-effectiveness databases described above, clinical practice guideline databases, such as the AHRQ (Agency for Healthcare Research and Quality) National Guideline Clearinghouse (NGC) in the US might be useful [41].

Non-research based and non-standard format sources can be located using the same methods described above for costs. Core sources specific to the jurisdiction of interest should be available. In

England and Wales these include health service statistics produced by the ONS (Office for National Statistics), [42] HRG data (Health Resource Groups) [43] and HES data (Hospital Episode Statistics) [44] although the latter may be subject to a Data Access Request [45]. Judgements should be made about how well the data classification matches the definitions used in the model. Other current practice information includes that produced by professional bodies (e.g. Royal Colleges in the UK) and health policy-related organisations (e.g. the King's Fund organisation in the UK) [46, 47].

As with other types of model parameter, the scope of searches should be guided by all important elements within the time horizon and perspective of the model that have a resource use implication.

2.5 Health state utility values (HSUVs)

Evidence on treatment-related utility gains should be derived from RCTs but might not be available [48]. An analysis of models found that baseline HSUV estimates were sourced mainly from cross-sectional observational studies [1]. Evidence might be drawn from cost-utility analyses although it is important to ascertain how estimates from originating utilities sources have been derived and incorporated. The evidence hierarchy for models places direct evidence collected for the specific study above indirect evidence from the literature [4].

Advice on how to search and review HSUVs evidence has been produced by ScHARR (School of Health and Related Research), Sheffield University for the NICE Decision Support Unit (NICE DSU) and the Campbell and Cochrane Economic Methods Group [48, 49].

Studies can be identified using bibliographic databases such as Medline. There is no validated search filter for the identification of studies, although the ScHARR guidance contains MeSH and free-text terms frequently used to index and describe relevant studies [48]. The absence and inconsistent application of HSUV terminology is a recognised search problem. A large proportion of studies are indexed under 'quality of life'. However, this retrieves a high number of irrelevant studies with a broader interpretation of quality of life, beyond that of preference-based health state valuation. A search restricted to HSUV terminology, including the names of relevant instruments, (e.g. EQ-5D) will minimise the retrieval of irrelevant evidence but risks missing evidence if terms do not appear in study titles, abstracts or indexing. There is, therefore a trade-off in the sensitivity and efficiency of the search. The extent of this trade-off is an important area for empirical research.

In terms of specialist sources, the Tufts CEA Registry indexes cost-utility studies and provides searchable files of utility weights [36]. ScHARRHUD, (ScHARR Health Utilities Database) a developmental database, indexes the bibliographic details of studies that contain utilities estimates using generic preference-based measures [50]. Some of the main instruments used to measure utilities have their own website.

In defining the scope of searches all the health states which impact on health related quality of life should be taken into account [1]. This includes baseline HSUVs for the health states which form the model pathway. For example, in a diabetes model, utility estimates relating to downstream events such as stroke and myocardial infarction are relevant. It also includes estimates relating to the benefits or disbenefits associated with interventions and comparators of interest and with treatment options at other stages of the pathway. This can include the impact of adverse events and factors such as the delivery of treatment (for example home versus hospital management or oral versus intravenous administration). Where HSUVs are derived using mapping techniques, searches might be required to identify a relationship between an available quality of life instrument and a generic preference-based utility measure.

2.6   Baseline risks of clinical events

Evidence is required to assess the risks of experiencing the main clinical events associated with a condition to estimate the transition rates between model health states. Epidemiological evidence in both research-based and non-research based formats is used [1, 10] although it is difficult to define the characteristics of the types of evidence that should be sought [4, 10]. Descriptions of research-based sources include observational studies, particularly longitudinal cohort studies and case-series [1]. Non-research based sources are characterised as nationally collected or compiled statistics or routinely collected administrative data. Disease registers, epidemiological databases and health surveys are difficult to classify as being research or non-research based. These types of epidemiological evidence are recommended above clinical event data from RCTs due to the controlled selection criteria for trial populations [4]. Variation in risks is attributed to various factors, including geographical location and, therefore, evidence relevant to the jurisdiction of interest is recommended [4].

Bibliographic databases such as Medline can be searched to inform baseline estimates of clinical events although validated search filters aimed specifically at identifying epidemiological studies do not exist. Search filters are available for the identification of observational studies [14] although these are problematic given the variation in terminology relating to observational study design and the wide range of purposes, beyond epidemiology, for which such studies are conducted. Available filters for observational studies are largely unvalidated and none has been tested for the specific purpose of identifying epidemiological evidence for informing models parameter estimates. MeSH headings and subheadings exist which, combined with terms relating to the condition or decision problem of interest, may be useful in the identification of evidence on baseline risks. (Figure 2) The names of specific epidemiological databases or registries can also be included as freetext search terms.

<INSERT FIGURE 2 HERE>

The subscription Incidence and Prevalence Database (IPD) [51] indexes epidemiological studies and reports. It was considered useful in a study of searching to inform model parameter inputs but the added value of searching IPD for models has not been formally assessed [2].

Non-research and non-standard format sources include nationally collected statistics on mortality (including life tables for all-cause mortality), morbidity and health surveys. The ONS for England and Wales and the Centers for Disease Control and Prevention (CDC) in the US are two examples of national collections [42, 52]. Other possible sources include WHO [53] and clinical and professional organisations and charities. Large epidemiological studies and registries sometimes have dedicated websites.

The combination of standard and non-standard format sources together with a lack of consistent terminology with which to describe evidence makes this a difficult area to search. Expert advice and a degree of iteration are useful in identifying the names of epidemiological sources relevant to a specific decision problem. The curation of non-standard format epidemiological sources, both by geographical location and by disease area would be a useful resource.

<INSERT TABLE 1 HERE>

3.   Implementing the minimum search requirement

A minimum requirement for searching is recommended..Recommendations for each parameter type are summarised in table 1. For treatment effect parameters the minimum requirement is comprehensive searching according to methodological guidance such as that of Cochrane and CRD. For other parameter types the recommended minimum level is the searching of one bibliographic database, such as Medline, specialist sources where these are easily accessible and consultation or exploration of non-research based and non-standard format sources where appropriate to the parameter type.

The recommended minimum search requirement draws on experience and existing methodological literature on searching for specific types of evidence and on searching for cost-effectiveness models more generally. It should be noted that the impact of the minimum level of searching on model outputs has not been tested empirically, neither in terms of implications of not searching comprehensively nor in terms of the added value of searching more databases. There appears to be general consensus that, with the exception of treatment effects, comprehensive searching to inform parameter estimates is not considered an efficient use of resources [3, 6]. However, it should be noted that fulfilling the recommended minimum level of searching presented in this paper will not necessarily be considered sufficient in all circumstances. Consideration should be given to the impact on bias and uncertainty within model parameters and on the overall outputs of the model. Where it is felt that additional searching would add value, the level of searching should be extended to include additional search

resources and techniques such as reference checking. Reasons for extending the search might include; a judgment that this would produce a sufficiently increased yield of relevant information (i.e. if each stage of the minimum requirement uncovers a large proportion of new material), knowledge that model results are sensitive to certain parameter estimates or that an issue (e.g. adverse effects) is of particular importance to decision-makers or that reimbursement agencies or journal policies state their own standard search requirements.

4.   Reporting searches

The main sources searched should be reported together with brief details of the scope of the search strategies and any restrictions including search filters and date and language limits. Full keyword strategies, including the database name, the software platform used and the dates the searches were undertaken should also be reported, usually as an appendix. Reporting levels might be restricted by space limitations in the main body of the report and consideration should be given to the further use of appendices or to providing information as supplementary material.

5.   Discussion

This is the first paper, to the author's knowledge, that provides, in one place, procedural guidance on searching across all key model parameters. Papers exist that describe search methods for specific types of information and other papers consider issues relating to searching for models more generally. These have been referred to in the text and all are useful in supporting the guidance.

A frequent question, and one which is considered in the paper, is how much searching should be undertaken [3]? In systematic reviews comprehensive searching in order to minimise the risk of bias is the methodological requirement, but even this is qualified by considerations of available resources [7]. In models of cost-effectiveness, the bringing together, within a single framework, information from a broad range of diverse sources generates inevitable uncertainty which cannot be eradicated by comprehensive searching for each individual parameter. The frequent absence of relevant evidence is also important in considering how much effort should be spent in identifying the next best, yet limited, available source.

Value of information is potentially a useful concept in defining sufficient evidence in that it identifies the aspects of the analysis to which the outputs of the model and, ultimately, the decision are most sensitive [3]. It could therefore be useful in prioritising the areas of the model where search efforts should focus. Here, the process would be to demonstrate sufficient searching rather than comprehensive searching, such that further evidence would add nothing to the analysis. It is important to bear in mind however, the emergent nature of model development, whereby a parameter which appears unimportant in the early stages is found to be significant over the course of the analysis.

Whilst the focus of this paper has been on the main data inputs common to most cost-effectiveness models, it is important to acknowledge that estimates may be required for a range of additional parameters depending on the topic being modelled and that the use of evidence in modelling is not restricted to the derivation of values for model parameters [19]. There are a large number of structural and analytical activities all of which have to be supported by evidence of some form in order that the model can be judged a credible and acceptable representation of the decision problem. The identification of information is required to support transparent, evidence-based judgments relating to, for example, the design of model structure, the definition of the disease pathway and analytical approaches such as the extrapolation of short term and surrogate outcomes evidence into long term, clinically meaningful estimates. The development of procedural guidance on how to search systematically for these types of information need is an important area of methodological development.

The paper has dealt with each parameter type separately. Whilst separate searches, at some level, should be conducted to inform each parameter type, this does not fully reflect how the large number of information needs, arising from the modelling process, present themselves nor how all the evidence used to inform the model is identified [19]. The modelling process begins with a clearly structured cost-effectiveness question but this does not translate easily into a complete set of predefined, discrete and sequential search questions. Model development is an iterative and dynamic process and evidence is encountered and assembled at all stages of the process [19, 54]. Although some information needs will be known at the outset, exact information requirements are clarified as the understanding of the decision problem and the specification of the model design unfolds. It is useful to think of evidence acquisition as an iterative, gathering process comprising both direct and indirect information retrieval. For example reports of trials identified through clinical effectiveness searches might uncover references to important epidemiological evidence or discussion with a clinical expert might provide leads to evidence sources covering a wide range of the diverse information needs arising from the model. All of these information seeking processes are important in a systematic exploration of evidence considered relevant to a decision problem. In terms of reporting, all direct searches, including search strategies should be reported but equally important, in order that the whole process of information acquisition is transparent, is an audit of how all evidence cited in support of a model came to be part of the modelling process. The appendices of two published cost-effectiveness models provide examples of how this can be presented [55, 56].

The paper focusses on searching but the identification and selection of evidence are very closely associated in the iterative modelling process. The evidence hierarchy referred to in the paper is a guide to the strengths and limitations of the types of evidence that can inform the different parameter types. However its usefulness as a selection tool is limited as it only describes evidence according to type and does not account for the quality of individual sources [4]. It perhaps oversimplifies the diversity of evidence where, beyond the use of RCTS for treatment effects, the relationship between best evidence type and parameter type is relatively complex. The non-standard format of some

sources, such as compiled statistics, makes it difficult to define individual sources according to the hierarchical categories.

The selection of evidence of an appropriate design and of high internal validity is important in minimising the risk of bias. For the assessment of individual sources there exists a wide range of quality assessment tools [8]. The generic GRADE tool has been identified as being potentially relevant to the selection of evidence for model parameters [57]. Most quality assessment tools however, have been designed to support the rigour of systematic reviews, which select evidence according to pre-specified binary criteria, categorising evidence as relevant or not relevant. This is limited in supporting the equivalent process in modelling, where selection is multidimensional, balancing scientific rigour with real-world issues that are of relevance to decision makers, weighing up the attributes of a number of sources all of which might be candidates for inclusion for different reasons, or identifying the least worst option where there is a dearth of evidence [19]. The rigour of the selection process in modelling lies not in adherence to pre-defined criteria but in justifying, testing and making transparent the judgments underlying selection decisions. This can be achieved by describing the main candidate sources available, explaining why selected options are considered preferable to alternatives, stating strengths and inadequacies in the best available sources and exploring, through sensitivity analysis, the selected options and important alternatives.

This paper defines and recommends a minimum level of searching for each parameter type and that the minimum level should be extended if it is thought that further searching would add value. It should be acknowledged that the minimum level has not been tested empirically. This and the definition of sufficient evidence are important areas of future methodological research. Nonetheless, in an area where there is a lack of procedural guidance and where there is widespread inconsistency in search practice, the minimum requirement offers a systematic and transparent approach to searching, which draws on a wide range of research on search methods and authoritative HTA and modelling guidance.

6.   Conclusion

The paper is the first to provide procedural guidance to searching across all the main data input types in cost-effectiveness models. It summarises the factors relating to the identification and selection of evidence that are specific to decision-analytic modelling and provides guidance on reporting in order that the processes of searching and of making selection judgments are transparent and justified. The paper highlights issues of methodological debate and defines areas where future methodological research would be useful. Importantly, the paper highlights the methodological differences between decision-analytic models of cost-effectiveness and systematic reviews in order to provide recommendations that focus on the specific requirements of decision-analytic models.

Compliance with Ethical Standards

Figure 1:   **Unvalidated search filter for resource use[a,b]**

1	resource allocation/
2	health care rationing/
3	(resource$ adj2 (allocat$ or utili$ or usage or use$)).tw.
4	or/1-3

a. Anthea Sutton, personal communication, 29 July 2014 b. Search syntax for Medline, OvidSP

Figure 2:   MeSH terms for baseline risks

Databases, Factual/
ep (epidemiology as subheading)
Epidemiologic methods/
Epidemiologic studies/
Epidemiology/
Health Surveys/
Incidence/
Pharmacoepidemiology/
Prevalence/
Registries/
Risk/
Risk assessment/
Risk Factors/

Table 1: **Summary of minimum search requirements**

	Existing guidance	Minimum search recommended	Bibliographic databases	Specialist databases	Non-database searching	Other considerations
Treatment effects	Cochrane CRD	Full systematic review search as recommended by Cochrane and CRD guidance	Medline, EMBASE etc.[a]	Cochrane Library (CDSR and CENTRAL) CRD DARE[a]	Trials registers, handsearching, grey literature, contact with experts[a]	Scope of searches might be required to include terms for comparators (including for networked meta-analysis) and companion and downstream interventions.
Adverse effects	Cochrane CRD	1 bibliographic database[b] Specialist databases if accessible Non-research and non-standard format sources	Medline using adverse effects filters[c]	e.g. TOXLINE Derwent Drug File International Pharmaceutical Abstracts	e.g. US FDA Medwatch and Postmarket Drug Safety Information UK MHRA EMA	RCT adverse effect evidence might also be retrieved from treatment effects searches. Scope of searches might include generic (e.g. adverse effects) and specific terms (e.g. nausea and vomiting) Scope of searches might include adverse effects associated with interventions at other stages of the disease pathway where these might impact of cost-effectiveness
Costs	None	1 bibliographic database[b] Specialist databases if accessible Non-research and non-standard format sources	Medline using economics filters[c]	INAHTA HTA database NHS EED Tufts CEA Registry	e.g. NHS Reference Costs BNF PSSRU Unit Costs	Wide range of research and non-research evidence types used. Search scope should focus on whole disease, not just intervention of interest. Search scope will be dictated by model time horizon and perspective. Cost estimates at different levels of granularity might be required in the same model. Evidence relevant to jurisdiction of interest is a key consideration.
Resource use	None	1 bibliographic database[b] Specialist databases if accessible Non-research and non-standard format sources	Medline using unvalidated resource use filter and clinical guidelines filter[c]	e.g. AHRQ National Guideline Clearinghouse	e.g. HES data HRG data ONS data Professional and policy-related organisations	Evidence will also be identified through costs searches. Scope of searches might include term relating to current clinical practice. Search scope will be dictated by model time horizon and perspective. Evidence relevant to jurisdiction of interest is a key consideration.
Health state utility values	ScHARR, University of Sheffield	1 bibliographic database[b]	Medline incorporating terms	Tufts CEA Registry	None	Absence and inconsistent application of HSUV terminology is a recognised search problem

Identification of evidence for key model parameters

		Specialist databases if accessible	recommended in ScHARR guidance	ScHARRHUD Instruments (e.g. EQ-5D) may have dedicated website	Scope of searches should take into account all health states which impact on health related quality of life.
Baseline risk of clinical events	None	1 bibliographic database[b] Specialist databases if accessible Non-research and non-standard format sources	Medline incorporating selected epidemiological terms and names of specific sources if known (e.g. disease registries)	Incidence and Prevalence Database	e.g. ONS US CDC WHO	Difficult to define characteristics of relevant research and non-research based epidemiological evidence. Evidence relevant to jurisdiction of interest is a key consideration.

a. Refer to Cochrane or CRD guidance for full details [7, 8]. b. Additional databases should be searched if it is judged this would increase yield. c. Filters referred to in text can be accessed via the ISSG Search Filter Resource [14]. d. Whilst Medline is recommended due to its availability, EMBASE and the Science Citation Index (SCI) might produce higher yields of evidence
AHRQ=Agency for Healthcare Research and Quality, BNF=British National Formulary, CDSR=Cochrane Datatabase of Systematic Reviews, CEA=cost-effectiveness analyses, CENTRAL=Cochrane Central Register of Controlled Trials, CRD=Centre for Reviews and Dissemination, DARE=Database of Reviews of Effects, EMA=European Medicines Agency, EQ-5D=European Quality of Life-5 Dimensions, HES=Hospital Episodes Statistics, HRG=Health Resource Group, HSUV=health state utility value, INAHTA HTA=International Network of Agencies for Health Technology Assessment, NHS EED=National Health Service Economic Evaluation Database, ONS=Office for National Statistics, PSSRU=Personal Social Services Research Unit, RCT=randomised controlled trial, ScHARR=School of Health and Related Research, ScHARRHUD=ScHARR Health Utilities Database, UK MHRA=United Kingdom Medicines and Healthcare products Regulatory Agency, US CDC=United States Centers for Disease Control and Prevention, US FDA=United States Food and Drug Administration, WHO=World Health Organisation

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