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Position paper on how to best formulate research recommendations for primary research arising from HTA reports

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Position paper on how to best formulate research recommendations

for primary research arising from HTA reports

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Institute for Quality and Efficiency in Health Care

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This position paper is a deliverable of EUnetHTA Joint Action 2 Work package 7 Subgroup 2.

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Stakeholder involvement

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Public consultation

No further comments were received during public consultation.

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Executive Summary

This Position Paper is one of the two deliverable of EUnetHTA Joint Action 2, Work package 7 Subgroup 2. The expected output is that of a greater harmonization among HTA agencies in the formulation of needs for Additional Evidence Generation.

Health Technology Assessment relies on the availability of scientific information and insufficient data leads to incomplete assessment. To overcome this, the HTA community needs to:

- communicate its own information requirements to the developers and research community;
- deal proactively with research gaps to inform future research.

The main objective of this position paper is, therefore, to provide a structured approach to identify gaps and formulate research recommendations. Its content stems from the in depth analysis of the relevant scientific literature and is divided in two sections.

The first section addresses the formulation of research recommendations targeted at resolving uncertainties related to the safety and clinical effectiveness of a health technology (answerable with biomedical research).

On the basis of the common and prevalent themes identified through the literature overview the following three step approach is proposed, to best identify critical uncertainties which can feed into recommendations for Additional Evidence Generation:

- selection of all comparative assessment questions necessary to establish the safety and effectiveness of the health technology of interest through definition of the *Evidence Profile* of the technology;
- analysis of results of the HTA report against the *Evidence Profile* and highlight of evidence gaps;
- identification of pivotal evidence gaps for Additional Evidence Generation and formulation of research recommendations using the PICO structure integrated by a brief explanation on why the uncertainty is considered critical.

The second section addresses the formulation of research recommendations targeted at resolving uncertainties related to the effective adoption and implementation of a health technology in real world practice (answerable with post-adoption surveillance and data gathering).

Considerations that should be taken into account, in order to determine when it might be recommendable to collect additional observational data after coverage include:

- appropriateness in diffusion and utilizations;
- variations in effectiveness and safety;
- real impact on the health care system;
- relative effectiveness and safety.

The identified and described common steps to formulate recommendations for real world data collection are:

- identification of uncertainties;
- translating uncertainties into research questions;
- refinement and consensus of key research questions;
- prioritization of outcomes.

A transparent and harmonized approach for communicating knowledge requirements should contribute to avoid delay in development of effective and safe health technologies, while increasing efficiency in use of resources in research.

Glossary

Term	Definition
ADC	Additional Data Collection
AEG	Additional Evidence Generation
AGREE	Appraisal of Guidelines for Research and Evaluation
AHRQ	Agency for Healthcare Research and Quality
Assessment question	Question addressed within HTA/Systematic Reviews
ASSR-RER	Agenzia Sanitaria e Sociale Regionale - Regione Emilia-Romagna http://asr.regione.emilia-romagna.it
avalia-t	Axencia de Avaliación de Teconoloxìas Sanitarias de Galicia http://avalia-t.sergas.es
CAD	Coverage with Appropriate Determination
CED	Coverage with Evidence Development
CMS	Centers for Medicare & Medicaid Services
CSP	Coverage with evidence participation
EPICOT	Evidence, Population, Intervention, Control, Outcome, Time
EUnetHTA	The European Network for Health Technology Assessment, http://www.eunethta.eu
GRADE	Grading of Recommendations Assessment, Development and Evaluation, a tool for grading the quality of healthcare evidence http://www.gradeworkinggroup.org
HAS	Haute Autorité de Santé, a Health Technology Assessment agency in Paris, France. http://www.has-sante.fr
HTA	Health Technology Assessment
IGRT	Image Guided Radiation Treatment
IMRT	Intensity Modulated Radiation Treatment
NIHR-NETSCC	National Institute for Health Research - Evaluation Trials and Studies Coordinating Centre
OIR	Only in Research Option
PICO	Population, Intervention, Comparison, Outcome
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses http://www.prisma-statement.org
Research question	Question addressed through primary research
Research recommendation	Recommended research questions for primary research
RCT	Randomised Controlled Trial
SBU	Swedish Council on Health Technology Assessment, a Health Technology Assessment Agency in Stockholm, Sweden. http://www.sbu.se
SG 2	Subgroup 2
TAVI	Transcatheter Aortic Valve Implantation
WP7	Work Package 7 of EUnetHTA Joint Action 2.

Background

Within EUnetHTA Joint Action 2, Subgroup 2 of Work Package 7 is dedicated to Additional Evidence Generation (AEG). The objective is to develop and test a methodological basis for the European cooperation on HTA to improve quality of Additional Evidence Generation for HTA.

Two deliverables are associated with the work of the WP7 Subgroup 2:

1. Methodological documents, aiming to improve the methodological aspects of AEG:
   - Position paper on how to best formulate a research recommendation (this paper)
   - Position paper on how to decide on the appropriate study design (companion paper developed by NETSCC)
2. Pilot of a core protocol for AEG, aiming to agree on core elements of a study protocol for AEG and to test it on an example technology.

The expected output of this work is that of a greater harmonization among HTA agencies in the formulation of recommendations for Additional Evidence Generation, in order to both guide decision makers on the evidence they should expect to support their decisions, and better inform technologies developers and researchers on the evidence that is required to complete or finalize health technology assessments.

It does not address prioritization of health technologies that should undergo an HTA process, nor prioritization of research recommendations between different intended uses of a technology or between technologies competing for health systems' resources.

The lead for the present position paper has been assigned by WP7 to ASSR- RER and avalia-t with the contribution and coordination of HAS.

1. Introduction

Detecting unresolved factual uncertainty is important in supporting decisions on health technologies' adoption. Consequences of waiting for more robust information – carrying the risk of delaying introduction of effective interventions - must be weighed against the consequences of premature diffusion. This could result in harms or unnecessary costs. While policy-makers are used to making decisions with an incomplete body of evidence, they nevertheless need to clearly recognize when the uncertainty is substantial. Policy options - such as Coverage with Evidence Development (CED) or Only in Research options (OIR) - try to combine early use in clinical practice with the development of the further research needed. When further research can resolve uncertainty on the adoption of new technologies, formulating the relevant and useful research recommendations (stating specific requirement for the generation of additional evidence) becomes decisive to complete the development of health technologies and, ultimately, for their adoption in clinical practice.

Formulating recommendations for research within HTA is also considered of increasing importance, in order to shorten the time lag between technologies' development and patients' access to innovations. By informing both pre-adoption primary clinical research and post-adoption evaluation of real impact of health interventions, HTA is able to contribute dynamically to the development and diffusion of health innovations.

In summary, establishing key principles for formulating recommendations for research can:

- help to align the research agenda with that of decision-makers - increasing the likelihood of evidence based decision making;
- improve the quality and relevance of the additional evidence produced;
- contribute to quicken decision-making on technology's adoption and access for patients.

2. Objectives

The present position paper is aimed at improving presentation of research recommendations by providing a structured approach to identify research gaps and to formulate research recommendations targeted at:

- resolving uncertainties related to the safety and clinical effectiveness of a health technology, answerable with biomedical research (developed in Section A);

- resolving uncertainties that may arise when the technology is adopted and implemented in real world practice (answerable with post-adoption surveillance and data gathering, developed in Section B).

3. Methods

3.1. Search of the relevant literature

A search of the literature was carried out by HAS to retrieve and select most relevant articles and papers that provide a discussion and/ or propose a methodology on how to formulate recommendations for research, arising from systematic reviews type HTA reports.

A structured search strategy that combines Medical Subject Heading (MeSH) terms and free-text terms related to formulating research recommendations in the specific context of Additional Evidence Generation was developed (see Annex B). The Medline database was searched in March 2014 with no time limits and without restrictions on type of publication. An update was performed in September 2014.

The search in PubMed was supplemented by a manual internet search of:

- websites of main international governmental and HTA agencies;
- other organizations of interest such as European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP)
- Google and Google scholar.

The manual internet search was performed in March 2014. Only the websites available in English and French (or with an English version of publications) were examined. First, the 'publication' tab (when available) was searched for relevant reports and documents related to formulating a research question, recommendation or dealing with uncertainty. As a second step, a manual search in the search box was conducted using terms following keywords "question", "recommendations", "methodology", "gaps".

WP7 SG2 partners were also contacted in order to provide any documentation of interest from their agencies.

Finally, manual review of the bibliographic references of the selected references was undertaken.

3.2. Content analysis

All included relevant articles and publications underwent an initial reading for familiarization and identification of prevalent and common themes. The themes of interest for this position

paper were identified as follows: a) formulating the assessment questions, b) identifying evidence gaps and dealing with uncertainty, c) going from research gaps to research needs and formulating recommendations for research. A data extraction form was set up and a content analysis was carried out to extract text blocks related to the main themes from the original articles. Through a third in depth reading and comparison of content related to the main themes we were able to identify common approaches, which are the basis of this position paper.

4. Results

The initial Medline search resulted in 342 articles and 44 additional articles were identified by the September update, for a total of 386 records. After screening titles and abstracts for papers dealing with formulating the research questions (recommendations) or with identifying evidence gaps and dealing with uncertainty, nine articles were retained for full text analysis. Papers dealing with research design, statistics, setting research priorities as well as different study reports were excluded. Twenty one publications were retrieved through additional hand search and thirteen papers were provided by WP7 SG2 partners. Handbooks focusing on formulating research questions for systematic reviews were excluded.

From the full text screening of the 43 papers, five additional publications were excluded because not pertinent to the topic, and a total of 38 publications were included in the overview.

A flowchart representing the process of inclusion of publications is reported in Annex B.

Annex C reports tables of data extraction for included articles and publications.

This position paper is divided in two sections:

- the first section – developed by ASSR-RER addresses the formulation of research recommendations targeted at resolving uncertainties related to the safety and clinical effectiveness of a health technology (answerable with biomedical research);
- the second section – developed by avalia-t addresses the formulation of research recommendations targeted at resolving uncertainties related to the effective adoption and implementation of a health technology in real world practice (answerable with post-adoption surveillance and data gathering).

Examples of practical applications are provided in Annex D.

4.1. Section A - How to formulate research recommendations to complete the safety and effectiveness profile of a health technology

OBJECTIVE

Describe a structured and transparent process for formulating research recommendations targeted at resolving key uncertainties related to the safety and clinical effectiveness of a health technology

4.1.1. Introduction

Health Technology Assessment (HTA) reports based on systematic review synthesize the available scientific evidence on the relative effectiveness, benefits and harms for a variety of diagnostic, treatment and health care delivery decisions. They provide syntheses of relevant evidence to inform real world health care decisions for consumers, clinicians and policymakers. It follows that HTA reports provide the basis for describing the state of development of research on a given technology and to identify possible evidence gaps, some of which could hinder final decisions on adoption and diffusion of the technology. As stated by Scott et al (Scott 2008) "by systematically summarizing the available evidence in response to policy-driven questions, HTAs routinely identify evidence gaps that are relevant to policy makers" and that need to be addressed by primary research.

Although identification and discussion of evidence gaps is common within HTA reports, recommendations for additional research tend to be non-specific and in many cases of little help to decision makers, researchers and technology developers.

As not all evidence gaps are relevant to inform decision making and research resources are finite, recommendations for Additional Evidence Generation should concern answerable research questions expected to demonstrate health benefits or improvements in the quality of the healthcare services. In other words, evidence gaps are translated into research requirements when there are reasonable grounds for believing that a technology will bring substantial benefits, but there is persisting uncertainty regarding the real impact of the technology.

4.1.2. Process for the development of recommendations for research

From the literature overview several step-wise approaches have been identified for the formulation of recommendations for research following the finalization of an HTA report or other types of evidence synthesis and interpretation (NICE 2013; Scott 2008; James Lind Alliance 2010; AHRQ 2014; NICE 2011; Choudhury 2010; Ballini 2010). Majority of these approaches insist on the necessity to a) detect uncertainties resulting from the systematic review of the available evidence, b) establish which - among those - are key uncertainties and c) translate the key uncertainties into research recommendations.

On the basis of the above common and prevalent themes identified through the literature overview, a three step approach is proposed to best identify critical uncertainties which can feed into recommendations for Additional Evidence Generation:

- selection of all comparative assessment questions necessary to establish the safety and effectiveness of the health technology of interest through definition of the *Evidence Profile* of the technology;
- analysis of results of the HTA report against the *Evidence Profile* and highlight of evidence gaps;
- identification of pivotal evidence gaps for Additional Evidence Generation and formulation of research recommendations.

4.1.2.1. Evidence Profile of the technology

- ***An evidence profile of the technology is developed as a synopsis of pivotal comparative assessment questions stating: population, intervention, comparators, relevant patients-health outcome ranked for importance and - when possible- setting, timing, study design, outcome measurement and size of desired effect.***

Innovative health technology can be proposed for a single or a variety of intended clinical use and published studies might report on different clinical conditions, patients and outcomes. To address this, HTA reports contain extensive information on the description of the health problem addressed by the technology and on the management of the health problem. The scoping carried out by HTA reports' developers contributes to the definition of the rationale supporting the technology's potential clinical role and its hypothetical added benefits. Through

scoping, main uncertainties regarding the role of a technology within the health care process are expressed in the form of questions - i.e. assessment questions - that guide the search for information and data that can provide answers. Analysis and interpretation of the retrieved information say whether and to what extent expressed uncertainties have been solved or are still pending.

The evidence profile of a health technology consists therefore in the synopsis of all assessment questions, stated within the HTA report, necessary to prove the theoretical rationale of the technology for its intended clinical use. When possible the evidence profile of the technology should state the quality of evidence and the level of certainty necessary to inform a decision.

Most guidance recommends that the assessment questions related to the safety, efficacy and effectiveness are formulated according to the Population, Intervention, Comparator, Outcome format (NICE 2011; AHRQ 2014; James Lind Alliance 2010). Some suggest to include Timing and Setting as additional optional variables. Particular emphasis is put on the selection of the most appropriate comparator and of the patient important outcomes which have a potential relationship with the intervention (AHRQ 2013). Definition of relevant outcomes, prior to reviewing the scientific literature, ensures that evaluation of the published research and subsequent development of recommendations are made explicit and unbiased by the search results (Fenton 2010; Berger 2009; Ballini 2010a; Ballini 2010b; Guyatt 2011; James Lind Alliance 2010).

Some handbooks also recommend to indicate the type of study design necessary to obtain robust information, as this ensures transparency of the assessment of the quality and robustness of retrieved data (Moher 2008; NICE 2013; Berger 2009). As highlighted by the ISPOR guidance "the practice of a priori specification of the research question and study design ... is strongly advised to assure end-users that the results were not the product of data-mining" (Berger 2009). When relevant and possible, the direction and size of the expected effect on the most relevant outcomes are also specified.

The process for the development of recommendations for research can be carried out prospectively, while developing an HTA report, or retrospectively, using a completed HTA report. Both approaches involve the expression, at the start of the process, of the evidence profile of the technology highlighting pivotal assessment questions. The evidence profile indicates the questions that need to be answered in order to take a decision and, consequently, states the uncertainty which might be responsible for withholding the decision. In order to complete the subsequent steps of the process, level of importance to the listed outcomes of each assessment question's PICO, is also required to have them in a ranking order.

Development of the technology's evidence profile needs to be carried out following a structured and transparent process. As already stated, it can be easily extracted from the HTA report of reference, especially if experts and stakeholders have been involved in the scoping process of the HTA report. In fact most guidance, handbooks and articles emphasize the need to involve experts and stakeholders in the process, especially patients, carers and health professionals. Their involvement is considered crucial to agree on the theoretical rationale and potential benefits of the new technology and to outline the investigational pathway necessary to prove safety and effectiveness of the technology (AHRQ 2014; AHRQ 2013; Scott 2008; Carey 2012; Berger 2009; James Lind Alliance 2010; NICE 2013; NICE 2011; Fenton 2010; Chalkidou 2007; Ballini 2010a; Ballini 2010b). This involvement is further sustained by the fact that literature on innovative or emerging technologies is often limited and focused on surrogate outcomes, overlooking questions and outcomes that are important to patients and clinicians (Fenton 2010). In fact in its 2011 guidance, NICE states that the "process of identification/prioritising key uncertainties should be led by the advisory committees, with input from clinicians, researchers, patients and carers, service users or the target population, reviewers, health economists and Institute technical staff" (NICE 2011).

If it is not feasible to have such a structured open consultation, a comparative reading of international clinical practice guidelines of good methodological quality, according to the AGREE evaluation check list (Brouwers 2010), developed for the target condition, can assist in the refinement and integration of the technology's evidence profile.

The resulting evidence profile provides a sort of blue print of the ideal investigational pathway necessary to demonstrate safety and effectiveness of the technology.

Table 1: Step 1 - Evidence profile of a technology.

1. EVIDENCE PROFILE OF THE TECHNOLOGY					
Rationale					
Clear statement on rationale supporting the use of technology explaining how its intrinsic characteristics can lead to improvement on patient-important outcomes compared to current management					
Indication : state the clinical indication					
Population	**Intervention**	**Comparator**			
Health status, disease, inclusion criteria	Technology and setting of use	Relevant comparator technologies and setting of use			
Domains: Safety + Effectiveness					
Study Designs (types of study design which can produce robust and transferrable results)					
Outcome - level of importance 1	**Outcome - level of importance 2**	**Outcome - level of importance 3**	**Outcome - level of importance 4**	**Outcome - level of importance 5**	
For each outcome: measurement tool + desired effect size and quality of evidence					

4.1.2.2. Evidence gaps - HTA report results vis a vis the evidence profile

- ***Results from the Health Technology Assessment report are transferred into the technology's evidence profile, stating level of confidence in estimates provided. Absence of studies or low/very low confidence in estimate of effect for selected important outcomes indicate the presence of evidence gaps responsible for main uncertainty.***

Evidence gaps can be defined as all the evidence missing from a body of research on a particular topic that would otherwise potentially answer the questions of decision-makers, including clinicians, patients, administrators and policy makers (Scott 2008).

In order to highlight evidence gaps, assessment results reported in the Health Technology Assessment report - or produced while developing the report - are transferred within the evidence profile and matched with predefined PICOs of assessment questions.

Information regarding appropriateness of study design, risk of bias and quality are reported for the data and estimates extracted from studies retrieved and included in the Health Technology Assessment report. The critical assessment carried out in the HTA report will indicate the quality of the retrieved evidence and support the judgment on how robustly the assessment questions have been answered. EUnetHTA methodological publications provide guidance on how to assess quality of clinical studies for different types of technologies (http://www.eunethta.eu/eunethta-guidelines). Overall quality of evidence for each outcome is also assessed and level of confidence on the estimate provided for each outcome is reported, as described by the GRADE approach (Guyatt 2008b).

The NICE research recommendations process and methods guidance provides a detailed list of different reasons for uncertainties (NICE 2011), differentiating between situations in which evidence is not available from situations in which evidence is available but insufficient, unreliable or not transferable. The UK Database of Uncertainties about the Effects of Treatments (UK DUETs http://www.library.nhs.uk/duets), which publishes treatment uncertainties, reports evidence gaps occurring when systematic reviews reveal that a health technology has uncertain medical effects or when there is no systematic literature review available. Similarly AHRQ suggests to identify main uncertainties through addressing a list of questions related to the type, quality and amount of evidence deemed necessary to make a decision (AHRQ 2013).

Within this process for the formulation of recommendations for research, the assessment of results available from the Health Technology Assessment report against the evidence profile (Table 2) allows to highlight existing key uncertainties and evidence gaps in terms of:

- absence of studies evaluating any of the predefined PICOs;
- low or very low level of confidence on the estimates provided.

In other words, when there is no available data or the available data provide estimates that would most probably be challenged by further research, an evidence gap related to substantial uncertainty is highlighted.

A graphical representation of results from this exercise can provide an immediate sense of the stage of development of research on safety and effectiveness on a given health technology (see examples in Annex D).

Table 2: Step2 - Evidence profile of a technology and evidence gaps

1. EVIDENCE PROFILE OF THE TECHNOLOGY				
Rationale				
Clear statement on rationale supporting the use of technology explaining how its intrinsic characteristics can lead to improvement on patient-important outcomes compared to current management				
Indication : state the clinical indication				
Population	**Intervention**	**Comparator**		
Health status, disease, inclusion criteria	Technology and setting of use	Relevant comparator technologies and setting		
Domains: Safety + Effectiveness				
Study Designs (types of study design which can produce robust and transferrable results)				
Outcome - level of importance 1	**Outcome - level of importance 2**	**Outcome - level of importance 3**	**Outcome - level of importance 4**	**Outcome - level of importance 5**
For each outcome: measurement tool + desired effect size and quality of evidence				
2. EVIDENCE GAPS				
Assessment results				
Outcome - level of importance 1	**Outcome - level of importance 2**	**Outcome - level of importance 3**	**Outcome - level of importance 4**	**Outcome - level of importance 5**
For each outcome: Number of studies; type of studies; estimate of effect size Quality of evidence and level of confidence in estimate				

4.1.2.3. Formulation of recommendations for research

- ***Key comparative assessment questions unanswered or inadequately answered by available evidence represent main uncertainties and are translated into recommendations for research, in the format of a clear question - using the PICO structure - integrated by a brief explanation on why the uncertainty is considered critical***.

Recommendations for research are aimed at reducing uncertainty in coverage decisions through generating additional evidence on health technologies.

There will often be cases, where the available evidence is insufficient to support a positive or a negative recommendation, and issuing recommendations for use of the intervention only in the context of research can represent a rational way for addressing uncertainty (Chalkidou 2007), provided clear recommendations for research are given.

Possession of complete knowledge on the safety and effectiveness of a technology is unrealistic. Although it is wise to be aware of all knowledge gaps, Additional Evidence Generation should be considered mainly for research questions targeted at resolving the uncertainties which are the main source for doubt and indecision (i.e pivotal research questions related to most important safety and effectiveness outcomes). Scott et al provide a clear way of differentiating between evidence and research gaps: "while it would be nice to know everything (the evidence gap), most of the time decision-makers must be content with picking a few aspects of the evidence gap that would be the most useful for informing decisions and the most practicable to answer within the time and resource constraints of the research environment (the research gap)" (Scott 2008).

The formulation of research recommendations has been an issue for many years. In 2005, representatives of organizations commissioning and summarizing research, including the BMJ Publishing Group, the Centre for Reviews and Dissemination, the National Coordinating Centre for Health Technology Assessment, NICE, the Scottish Intercollegiate Guidelines Network, and UK Cochrane Centre, met as members of the DUETs development group to discuss the state of research recommendations and improve the presentations of proposals for further research (Brown 2006). After a review of different research recommendations models they proposed the EPICOT format for framing the research questions. This framework requires to consider the following core elements:

E - Evidence : What is the current state of the evidence?

P - Population: What is the population of interest?

I - Intervention : What are the interventions of interest?

C - Comparison : What are the comparisons of interest?

O - Outcome: What are the outcomes of interest?

T - Time stamp : Date of recommendation

Some additional optional elements, that can be particularly relevant, are the disease burden or relevance and the appropriate study type.

In line with the EPICOT framework, the final step of the proposed process foresees that the PICOs' structure defined in the evidence profile of the technology, integrated with the results from the available evidence are used to formulate recommendations for research (see Table 3 for an overview of the three steps).

The level of importance assigned to the listed outcomes, as well as the quality of evidence and level of certainty required, direct the identification of main uncertainties, which - if addressed by poor quality studies or not addressed at all - represent relevant evidence gaps that need translating into recommendations for Additional Evidence Generation (Table 3). Research on clinical benefits or harms judged of limited value or importance, would not be recommended.

The actual formulation of the recommendations for research should maintain the original PICO structure of the evidence profile of the technology, integrated - when feasible - with a recommended study design (See position paper on study design http://www.eunethta.eu/outputs/wp7-sg2-position-paper-how-decide-appropriate-study-design-aeg-available) and the desired or expected size of effect (Brown 2006; NICE 2011).

A recommendation for research should be structured as a "stand-alone statement" (NICE 2011) that sets out:

- the question that needs to be answered using the PICO format,
- the explanation of the rationale in support of the question, describing the potential relationships between the intervention/technology and important health outcomes
- the state of the available evidence.

An explanation of why the uncertainty has been identified as being key and a brief description of the process and outputs of the three steps outlined in this position paper, should also be provided.

Most of the publications reviewed for the present position paper recommend or advise to present key recommendations for research to experts and stakeholders to receive inputs and suggestions (Chalkidou 2009; NICE 2011; AHRQ 2014; AHRQ 2013b; Aslam 2010; Thabane 2009).

Open consultation might not always be feasible; however attention should be paid to ensure that selection of recommendations for research reflects the importance attributed to the PICOs in relation to the stage of development of the technology. For example, if safety questions are not sufficiently answered, then evidence gaps related to safety will be considered most important and urgent.

Each uncertainty needs to be verified as a true uncertainty (James Lind Alliance 2010), and once the list of relevant evidence gaps is compiled and before finalizing the recommendations the following actions must be undertaken:

- check whether the HTA report needs updating: if the date of the literature search is not recent, an update of the literature search will need to be carried out to retrieve, assess and include in the analysis any newly found published study;
- check international databases of ongoing studies: protocols of relevant ongoing studies should be evaluated to assess whether identified evidence gaps are being addressed by ongoing studies and when results are likely to become available. If ongoing studies appear as finished, but have not yet been published, principal investigators might be contacted to inquire about likelihood and timing of data release.

Table 3: from evidence profile of the technology to recommendations for research

1. EVIDENCE PROFILE OF THE TECHNOLOGY					
Rationale					
Clear statement on rationale supporting the use of technology explaining how its intrinsic characteristics can lead to improvement on patient-important outcomes compared to current management					
Indication : state the clinical indication					
Population		**Intervention**		**Comparator(s)**	
Health status, disease, inclusion/ exclusion criteria		Technology and setting of use		Relevant comparator(s) and setting of use	
Domains: Safety + Effectiveness					
Study Designs **(types of study design which can produce robust and transferrable results)**					
Outcome - level of importance 1	**Outcome - level of importance 2**	**Outcome - level of importance 3**	**Outcome - level of importance 4**	**Outcome - level of importance 5**	
For each outcome: measurement tool + desired effect size and quality of evidence					
2. EVIDENCE GAPS					
Assessment results					
Outcome - level of importance 1	**Outcome - level of importance 2**	**Outcome - level of importance 3**	**Outcome - level of importance 4**	**Outcome - level of importance 5**	
For each outcome: Number of studies; type of studies; estimate of effect size Quality of evidence and level of confidence in estimate					
3. RECOMMENDATIONS FOR RESEARCH					
Questions with clear rationale: potential relationship between intervention and important outcomes (optional information: burden of disease and study type)					
Evidence	**Population**	**Intervention**	**Comparator**	**Outcome(s)**	**Time stamp**
Current state of the evidence available / reasons for uncertainty	Population or sub/population of interest	The technology / intervention and setting of use	Relevant Comparator and setting of use	Outcome(s) of interest	Date

4.2. Section B - How to formulate research recommendations in the framework of observational data collection to recover real world data to support decision making

OBJECTIVE

Provide a brief overview of the considerations that might be taken into account to determine when it might be recommendable to collect additional observational data after coverage and establish how to proceed to identify key research recommendations

4.2.1. Introduction

In some countries, conditional coverage frameworks differentiate two scenarios:

- Promising technologies that present insufficient evidence and are covered only in controlled research conditions, restricting access to specific conditions (selected centers, highly experienced centers, specific indications, patient subgroups, etc.) and linking reimbursement to research studies rigorously designed to obtain data that can be essential for coverage decision making.
- Technologies that present sufficient evidence to conclude that they are beneficial and are covered for approved indications but the reimbursement is linked to the collection of observational data to oversee that technologies are appropriately provided and that results in real world conditions conform to what was anticipated from the evidence base.

In this part of the paper we will focus on the formulation of research recommendations regarding additional observational real world data after coverage. Taking into account that currently HTA reports do not tend to focus on real world uncertainties (See position paper on study design http://www.eunethta.eu/outputs/wp7-sg2-position-paper-how-decide-appropriate-study-design-aeg-available), the methodology proposed is based on the Centers for Medicare & Medicaid Services (CMS), AHRQ and avalia-t´s experiences and feedback from this Position Paper draft working group. It must be acknowledged that the paper might not cover all key questions that could inform additional observational research or take into

account the different regulatory scenarios in Europe. This is designed as a starting point for gathering feedback and stimulating thoughtful discussion, ultimately leading to a future approach and framework for observation of technologies after coverage, that can meet the expectations and needs of the different health care systems and decision makers. Supplemented by Section 4.2.4.3. on defining a research question, it sets out a thought process for the systematic reviewer to follow when defining his or her research recommendations.

4.2.2. Contextualization

In the past decade, the exponential growth in technological innovations -within a scenario of limited budgets and more educated patients that demand rapid access to promising technologies - has prompted the interest in research frameworks that can provide decision makers with additional information on health technologies, while providing timely access to the new treatments. To this end, many countries have implemented different policy frameworks to facilitate the controlled approval of insufficiently evaluated innovations, restricting access to specific conditions (selected centers, specific indications, patient subgroups, etc.) and linking reimbursement to rigorously designed research studies.

However, while it is commonly accepted that frameworks that restrict research to controlled settings are key to address specific effectiveness and safety research gaps, it has been acknowledged that the benefits and harms of some technologies might greatly depend on how they are used and if they are provided to appropriate patients once they are diffused in real world settings (Eisenberg 1999). Research studies restricted to pre-specified conditions and patients do not account for real world use confounders, misuse or the evolution of medical procedures, to the point that the trial's findings might be of diminished relevance to assess the real impact on the health care system (Hannon 2008). In addition, these research studies might exclude patients that could probably benefit from the treatment; the same is true for patients that are not attended in the assigned centers (Eisenberg 1999). In line with these concerns, many experts are beginning to consider that collecting observational data after general coverage could be an option to evaluate the appropriateness and quality of care and determine the real impact in the health system, without denying key therapy to patients when uncertainties are not dealing with essential effectiveness or safety issues. However, within the European Union (EU), the collection of observational data after coverage seems to have been mainly restricted to safety surveillance.

From the review performed (section 1.3.) it can be presumed that in the European context, only Spain (Galician Health Care System) has in place a policy framework that contemplates the systematic collection and analysis of observational data as a means to provide appropriate information regarding the real world application of the new technologies in order to re-inform decision making regarding requirements for reimbursement and final conditions or indications approved (Varela Lema 2014). This framework is contemplated for technologies that have demonstrated to be effective and safe in the short term and are presumed to be highly beneficial but present uncertainties regarding the application (modes of delivery, optimal service design, misuse, acceptability, interactions, etc.), net health benefits (specific patient group effectiveness or patient susceptibility groups, rare adverse events, specific patient reported outcomes, etc.), long term outcomes or impact on the healthcare system (economic, organization, structure). The recommendations made in the HTA reports provide guidance on the indications and conditions, specifying the uncertainties and possible evaluative scenario (observational studies; only in research). The establishment of post-introduction observation recommendations is based on the Spanish NHS post-introduction observation methodological guidelines (Varela Lema 2012; Varela Lema 2007).

Within the United States, Medicare also contemplates that the national coverage determination process may result in coverage conditioned to the submission of additional data to demonstrate that the process was provided as specified, produce evidence for future changes, improve the evidence base or inform medical decision making (CMS 2006). When technologies are viewed to have adequate evidence to support coverage but additional data is required to ensure that new technologies are provided appropriately to patient meeting specific characteristics (*coverage with appropriate determination*-CAD), technologies are covered and for the most part, providers are requested to submit extra data to databases or registries. In the same way as in Spain, when evidence is considered promising but insufficient to support coverage, the technology may be covered only while evidence is being developed and additional clinical data can be required to clarify the impact of these technologies on the health of Medicare beneficiaries "*coverage with evidence participation*" (CSP). In the specific case of CSP, observational data registries can be also considered for many CSP. Similarly to what happens in Spain, HTA reports delivered by AHRQ can provide specific considerations regarding indications and conditions, research questions, evaluative scenarios and possible data collection instruments (databases, registries). The AHRQ, authority responsible for assuring that the research priorities appropriately reflect the needs and priorities of the Medicare Programme, has developed a user guide that puts through the research questions that are appropriate for observational registries (Glicklich 2010).

4.2.3. Considerations for recommending additional observational real world data after coverage to support decision making

The Centers for Medicare & Medicaid Services (CMS 2006) and Spanish NHS post-introduction observation guidelines (Valera-Lema 2012), establish that additional real world data can be useful for evaluating appropriateness in diffusion and utilization, variation of effectiveness and safety outcomes among institutions/patients, unexpected complications in net health benefits, comparative effectiveness or impact on the health care system.

4.2.3.1. Appropriateness in diffusion and utilization

Observational data gathered from registries or databases may be essential, if it is recognized that the technology presents great uncertainties regarding the diffusion, adoption, implementation or utilization. Tables 4-6 summarize the specific issues that may be considered to determine the need for additional real world data collection.

Table 4. Considerations[1] regarding diffusion, adoption, implementation and utilization

Issue	Considerations
Adequacy of diffusion	The adoption and implementation of the technology requires important financial, organizational, structural, technical or personal resources and can be prone to inadequate uptake and diffusion.
Adequacy of adoption	The technology is recommended only for use by healthcare institutions or professionals with specific credentials or training or maintenance quality assurance processes and can be prone to inappropriate adoption.
Adequacy of implementation	The use of the technology can requires important organizational or management changes (creation of multidisciplinary groups, new units, coordination among groups) and can be prone to inappropriate implementation.
Off-label use	The technology is only recommended for patients with specific conditions and criteria and can be prone to off label indications.
Adequacy of use	The technology is considered to be highly prone to off-label deviations from evidence-based guidelines.
Acceptability	The technology might be less accepted by patients/clinicians than existing alternative (more demanding, aggressive, etc.).

[1] The considerations with respect to diffusion, adoption and implementation are only applicable to medical devices (diagnostic and therapeutic), procedures (medical or surgical) and organizational systems.

4.2.3.2. Variations in effectiveness and safety

Observational real world data may also be considered for evaluating variations in effectiveness and safety outcomes when it is determined that real world applicability could differ from

pivotal trials and further experimental research is not considered feasible, practical or ethical. The following issues might be considered to value the relevance of additional observational data collection.

Table 5. Considerations regarding real world effectiveness and safety outcomes

Issue	Considerations
Different applications	The technology can be susceptible to different applications in real world practice (different protocols, combination with other technologies, drugs) unforeseen in preliminary studies that could lead to deviations in effectiveness and safety outcomes.
Different experience	Clinician training and experience could lead to differences in effectiveness and/or safety outcomes.
Subgroup effectiveness	Specific trademarks or specific subgroups of patients are liable of presenting differences in effectiveness and/or safety.
Patient susceptibility groups	Especially sensitive groups (elderly patients, patient with co-morbidities, children, etc.) are liable of presenting higher complication or adverse event rates.
Patient reported outcomes	Specific patient reported outcomes - considered important for measuring the net health care value or quality of care - are not adequately evaluated in available studies.
Unexpected adverse events	Insufficient size or follow up to evaluate potentially rare or long term adverse events.
Risks to health professionals or environment	Potential harms to health care professionals (for example, radiation) or to the environment (dangerous waste) are not adequately covered in available studies.

4.2.3.3. Real impact on the health care system

Observational real world data can be highly appropriate when there are important uncertainties regarding the real impact on the health care system (organizational, financial and other).

Table 6. Considerations regarding impact on the health care system

Issue	Considerations
Organizational or structural impact	The adoption of the technology requires important organizational changes (creation of multidisciplinary groups, new units, coordination among groups) and there is uncertainty regarding the real impact on the health care service (length of stay, waiting list, etc.)
Financial impact	The adoption of the technology could require an important investment in infrastructure, equipment, fungible costs, maintenance or human resources and there is uncertainties regarding the real financial impact on the health care system.
Ethical, social or legal impact	The technology can have an ethical, social or legal impact and this has not been adequately covered in the available studies.

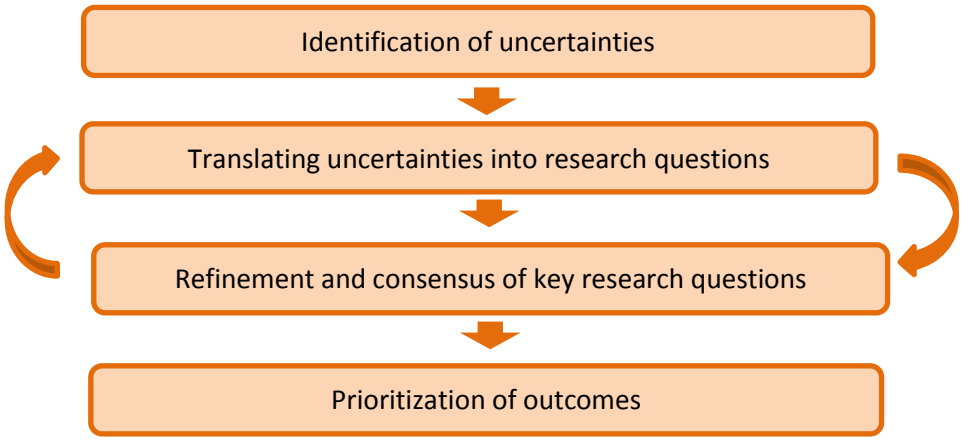
4.2.3.4. Relative effectiveness and safety

Observational real world data could also be reasonable to ascertain relative effectiveness and safety when it is established that the technology has a very important potential to provide significant benefits and there can be important barriers for conducting clinical trials. However, it must be acknowledged that in the majority of hierarchies of evidence, observational studies, although rigorously conducted are viewed to provide lower quality evidence than RCT. Despite recognition of the value of observational trials for evaluating relative effectiveness, there are no specific criteria for deciding when it would be most appropriate to carry out an observational study versus a RCT. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group has proposed that randomized trials are not always feasible and, in some instances, observational studies may provide better evidence, as is generally the case for rare adverse effects. The AHRQ user´s guideline also highlights that observational registries can offer the ability to evaluate patient outcomes when clinical trials are not practical (e.g. very rare diseases, long term outcomes), and they may be the only option when clinical trials are not ethically acceptable or when there is no established or recommended management procedures.

4.2.4. Steps for formulating recommendations for real world data collection

The explicit identification of uncertainty is perceived as the first step to formulating research recommendations. Uncertainties related to real world use, like other research uncertainties, are derived through the process of systematic reviewing and economic modelling (NICE 2011). However, the approaches previously described for the identification of key clinical/cost-effectiveness or safety uncertainties that arise due to insufficient or imprecise information, biased information, inconsistency or unknown consistency or not the right information (such as not the appropriate outcome measured or the population assessed) might not be fit to cover other types of uncertainties that could be context dependent or related to the application in real practice. In many cases high quality evidence is available but there is uncertainty regarding the net benefits, which could be context dependent.

Figure 1. Common steps to formulate research recommendations (AHRQ, avalia-t, NICE, FRN)



The prioritization of outcomes and questions regarding financing is out of the scope of this paper.

4.2.4.1. Identification of uncertainties

The identification of research uncertainties related to use in real world practice requires reliable and exhaustive information on the health problem and current use of the technology, technical characteristics of the technology and an in depth knowledge of the health care system. This information is not derived directly from the evidence base but may be obtained from manufacturers of the technology, clinical experts, patients associations or grey literature. The available literature must be critically synthesized and analyzed in the light of this background information, requiring for this task expertise and practice.

The HTA Core Model® Online (http://www.eunethta.eu/hta-core-model) produced within Work Package 8 of EUnetHTA Joint Action 2, contains an extensive list of generic questions in the health problem and current use of the technology domain, description and technical characteristics of the technology domain, organizational domain, cost domain, legal and ethical domain that are highly relevant for identifying real world uncertainties regarding diffusion, adoption, implementation and utilization of technologies. Below we summarize the HTA Core Model® questions that are considered by avalia-t to be key for identifying real world uncertainties. These questions, considered in the light of the particular health care system and organizational setting provide the basis for anticipating which technologies will present problems when they are applied in real practice.

Preliminary results can provide an overall picture of the technology that can serve to reconsider the scope of the project if problems are anticipated. In such case, an exhaustive collection of general background data may be required for understanding the implications of applying and implementing a technology in a particular context.

Issue	HTA core model questions that may be taken into account for identifying uncertainties related to the diffusion, adoption, implementation and utilization of the technology.
Adequacy of diffusion	○ What material investments are needed to use this technology? ○ What kind of special premises are needed to use the technology and the comparator?
Adequacy of adoption	○ Who administers the technology and the comparators and in what context and level of care are they provided? ○ What kind of qualification and quality assurance processes are needed for the use or maintenance of the technology? ○ What kind of training and information is needed for the personnel/carer using this technology?
Adequacy of implementation	○ Is the technology a new, innovative mode of care or replacement, and add-on to or modification of a standard mode of care or replacement of a standard mode of care? ○ Who administers the technology and the comparators and in what context and level of care are they provided?
Off-label use	○ For which health conditions and populations, and for what purposes is the technology used? ○ For which indications has the technology received marketing authorization or CE marking? ○ What is the reimbursement status of the technology?
	○
Adequacy of use	○ How is the disease or health condition currently diagnosed according to published guidelines and in practice? ○ For which health conditions and populations, and for what purposes is the technology used? ○ What kind of variations in use are there across countries/regions/settings? ○ Who decides which people are eligible for the technology and on what basis? ○ Who administers the technology and the comparators and in what context and level of care are they provided?
Acceptability	○ What are other typical or common alternatives to the current technology? ○ How the disease or health condition currently diagnosed according to published guidelines and in practice? ○ How much are the technologies utilized? ○ What are other typical or common alternatives to the current technology? ○ Who administers the technology and the comparators and in what context and level of care are they provided? ○ Is the patient willing to use the technology again?

Issue	HTA core questions that may be taken into account to assess uncertainties related to real world effectiveness and safety outcomes
Different	○ What are the differences in the management for different stages of the

	applications	disease or health condition? o How the disease or health condition currently diagnosed according to published guidelines and in practice? o For which health conditions and populations, and for what purposes is the technology used? o What kind of variations in use are there across countries/regions/settings o Who decides which people are eligible for the technology and on what basis? o Who administers the technology and the comparators and in what context and level of care are they provided? o Are the reference values or cut off-points clearly established? o What equipment and supplies are needed to use the technology and the comparator? o What kind of qualification and quality assurance processes are needed for the use or maintenance of the technology? o What kind of training and information is needed for the personnel/carer using this technology? o What kind of training and information should be provided for the patient who uses the technology, or for his family? o How does test accuracy vary in different settings?
	Different experience	o Who administers the technology and the comparators and in what context and level of care are they provided? o What kind of qualification and quality assurance processes are needed for the use or maintenance of the technology? o What kind of training and information is needed for the personnel/carer using this technology? o What kind of training and information should be provided for the patient who uses the technology, or for his family?
	Subgroup effectiveness	o For which health conditions and populations, and for what purposes is the technology used? o What is the target population in this assessment? o What is the disease or health condition in the scope of this assessment?
	Patient susceptibility groups	o For which health conditions and populations, and for what purposes is the technology used? o What are the susceptible patient groups that are more likely to be harmed through the use of the technology?
	Patient reported outcomes	o What is the natural course of the disease or health condition? o What are the symptoms and the burden of disease or health condition for the patient? o What are the consequences of the disease or health condition for the society? o What aspects of the consequences/burden of the disease are targeted by the technology? o What is the claimed benefit of the technology in relation to the comparator? o What are the measured and/or estimated health related outcomes of the assessed technology and its comparators?
	Unexpected adverse events	o What is the phase of development and implementation of the technology and the comparators? o Is the technology a new, innovative mode of care or replacement, and add-on to or modification of a standard mode of care or replacement of a standard mode of care? o What is the technology and the comparator(s)? o Who administers the technology and the comparators and in what context and level of care are they provided? o Are the reference values or cut off-points clearly established?

	○ Are harms related to dosage or frequency of applying the technology? ○ How does the frequency or severity of harms change over time or in different settings? ○ What are the consequences of false positives, false negative and incidental findings generated by using the technology from the point of view of patients? ○ Are the technology and comparator associated with user dependent harms? ○ How does the safety profile of the technology vary between different generations, approved versions or products? ○ Can different organizational settings increase or decrease harms? ○ How can one reduce safety risks for patients? ○ What is known about the intra- and inter-observer variation in test interpretation?
Risks to health professionals or environment	○ What kind of occupational harms can occur when using the technology? ○ What kind of risks for public and environment may occur when using the technology? ○ How can one reduce safety risks for professionals? ○ How can one reduce safety risks for environment?

Issue	**HTA core model questions that may be taken into account to determine uncertainties in real world impact**
Organizational or structural impact	○ How does the technology affect the current work processes? ○ What kind of patient/participant flow is associated with the new technology? ○ What kind of involvement has to be mobilized for patients/participants and others? ○ What kind of cooperation and communication of activities have to be mobilized? ○ How is the quality assurance and monitoring system of the new technology going to be organized? ○ How does centralisation or centralisation requirements influence the implementation of the technology? ○ What are the processes ensuring access to care of the new technology for patients/participants? ○ What are the processes related to purchasing and setting up the new technologies? ○ What management problems and opportunities are attached to the technology? ○ Who decides which people are eligible for the technology and on what basis?
Financial impact	○ What type of resources are used when delivering the assessed technology and its comparator(s)? ○ What were the measured and/or estimated costs of the assessed technology and its comparator(s)? ○ What are the estimated differences in costs and outcomes between the technology and its comparator(s)? ○ What are the uncertainties surrounding the costs and economic evaluation of the technology and its comparator(s)? ○ To what extent can differences in costs, outcomes or cost effectiveness be explained by variations between any subgroups using the technology and its comparator(s)? ○ To what extent can the estimates of costs, outcomes or economic evaluations be considered as providing a valid description of the technology and its comparator(s)?

	○ What are the likely budget impacts of implementing the technologies being compared?
Ethical, social or legal impact	○ Does the implementation or use of the technology affect the patient´s capability and possibility to exercise autonomy? ○ Is there a need for specific interventions or supportive actions concerning information in order to respect patient autonomy when the technology is used? ○ Does the implementation or withdrawal of the technology challenge or change professional values, ethics or traditional roles? ○ How does implementation or withdrawal of the technology affect the distribution of health care resources?

4.2.4.2. Translating uncertainties into research questions

The PICO classical structure is not appropriate for formulating research questions that are aimed at assessing if technologies are appropriately provided and that results in real world conditions conform to what was anticipated from the evidence base. In the majority of cases, there is no specific population, comparator or control and the research questions would simply imply the translation of key uncertainty gaps into specific measurable outcomes. The HTA Core Model® (http://www.eunethta.eu/hta-core-model) can provide some help regarding how information in each of the domains relates to specific measurable outcomes. Please refer to the clarification section of each of the result cards and the general description of why the domain is important and of its relation to other domains.

4.2.4.3. Refinement and consensus of research questions

The critical synthesis of the literature will often identify many uncertainties and gaps in the evidence base. It is acknowledged that not all evidence gaps are relevant to inform decision making and taking into account that the implementation of observational studies can be very demanding, it is important that future research questions only address answerable evidence gaps and among these, those that are expected to result in net health benefits or improvements in the quality of the healthcare services (Varela-Lema 2012; NICE 2011: Stone 2002; Carey 2012). Establishing the key principles of what assessments are really needed can improve the quality and appropriateness of data produced and can ultimately lead to more efficient process and quicker access to market. Determining the value of the clinical research question requires balancing the benefits gained diminishing uncertainties against the resources, feasibility, timeliness of information and risk of introducing technologies that present uncertainty. From various monitoring experiences it can be deduced that it is

important that only data related to key questions are collected; data should be considered sufficiently important for clinicians and stakeholders and whenever possible should not lead to an increased number of procedures or tests performed to the patient.

There are few organizations that have in place structured methods for refinement of evidence gaps. Evidence comes mainly from the US (AHRQ CSP program), Italy, Spain and the UK (Varela- Lema 2014; Ballini 2010a; Carey 2012; Bennett 2012). With independence of the policy or research framework, all agree on the need to involve different stakeholders (payers, clinicians, researchers, patients or patients representatives, health economics and organization's technical staff, etc.) in the formulation of key research questions, yet tackle the refinement and consensus of key research questions from different approaches and the involvement of stakeholders to define key questions/needs takes place at different timeframes. The processes are more or less structured and do not always differentiate between identification of key research questions/gaps or prioritization of research questions/needs. AHRQ Future Research Needs projects (Carey 2012) have developed different methods to identify research needs, most involving the following steps:

1) identification of research gaps from systematic review;

2) orientation of stakeholders to questions, FRN process and prioritization criteria;

3) elaboration and consolidation of research gaps through and iterative process with stakeholders;

4) priority ranking of research gaps;

5) transformation of research gaps into needs;

6) refinement and re-ranking of priorities and

7) addition of study design considerations.

For identifying research needs in the management of gestational diabetes mellitus they have included 2 additional steps before the final prioritization of outcomes by national stakeholders: 1) a refinement and ranking of questions by institutionally based local stakeholders with expertise (9 point Likert scale) and 2) a consensus development by national leaders and experts about research questions clinical/benefit importance (Delphi method). Within the Spanish framework of post-introduction observation (Galician Health Care System), the summarized list of research recommendations with the underlying considerations is reviewed by the Regional Advisory Committee in order to determine their potential added value and feasibility. A prioritization tool, named PriTec (PriTectools www.pritectools.es/) has been

developed to help establish the clinical benefit/relevancy of addressing each of the issues. The tool allows for scoring from 1 to 9, automatically calculating a score for each domain (population/end users, technology characteristics, effectiveness/safety, organization/costs and other implications), furnishing the absolute and weighted score. The prioritization tool can also be used by national/regional stakeholders to prioritize the research which will be selected for funding purpose since the tool allows for comparing up to 9 technologies based on the frequency and severity of disease. Regional experts representing the different areas of interest are identified for consensus development, refinement and elaboration of the list of final key research recommendations.

5. Conclusions

To be effective Health Technology Assessment relies on the availability of scientific information. Insufficient data leads to incomplete assessment and to overcome this, the HTA community needs to:

- communicate its own information requirements to the developers and research community;
- deal proactively with research gaps to inform future research.

As the HTA community has started to assess technologies increasingly closer, or even prior, to their time of marketing authorisation, there is the realisation that there are evidence gaps that are a "natural" consequence of the newness of the innovation. Consequently there is a need for a transparent and harmonized way of communicating knowledge requirements to technology developers, researchers and decision makers. This will help to: avoid loss or delay in development of effective health technologies; increase efficiency and reduce waste of resources in research that does not address relevant questions, is redundant or methodologically poor; adequately invest in post marketing additional data collection.

While some of the evidence gaps may be addressed by using increased Real World Evidence prior to authorisation, there is also a growing realisation of the importance of post marketing research.

Health Technology Assessment can play a significant role in the process of knowledge generation, and this position paper is meant to provide a common basis for developing recommendations for Additional Evidence Generation. Through the sharing of common criteria and methods for Additional Evidence Generation, the EUnetHTA collaboration intends being proactive and supportive towards an efficient and rapid production of research results and prompt access of patients to effective health interventions.

In this position paper explicit processes have been proposed for the formulation and development of recommendations for research targeted at:

- resolving uncertainties related to the safety and clinical effectiveness of a health technology, answerable with biomedical research;
- resolving uncertainties that may arise when the technology is adopted and implemented in real world practice (answerable with post-adoption surveillance and data gathering).

Main recommendations for resolving uncertainties answerable with primary biomedical research are as follows:

- An evidence profile of the technology is developed as a synopsis of pivotal comparative assessment questions stating: population, intervention, comparators, relevant patients-health outcome ranked for importance and - when possible- setting, timing, study design, outcome measurement and size of desired effect.

- Results from the Health Technology Assessment report are transferred into the technology's evidence profile, stating level of confidence in estimates provided. Absence of studies or low/very low confidence in estimate of effect for selected important outcomes indicate the presence of uncertainty and of evidence gaps.

- Key assessment questions unanswered or inadequately answered by available evidence represent main uncertainties and are translated into recommendations for research, using the PICO structure - integrated by a brief explanation on why the uncertainty is considered critical.

Main recommendations for resolving uncertainties answerable with post-adoption surveillance and data gathering are as follows:

- The identification of research uncertainties related to use in real world practice requires a reliable and exhaustive information on the health problem and current use of the technology, technical characteristics of the technology and an in depth knowledge of the health care system. In many cases high quality evidence is available but there is uncertainty regarding the net benefits, which could be context dependent.
- Research recommendation would imply the translation of key uncertainty gaps into specific measurable outcomes, with the help of the HTA Core Model® (http://www.eunethta.eu/hta-core-model).

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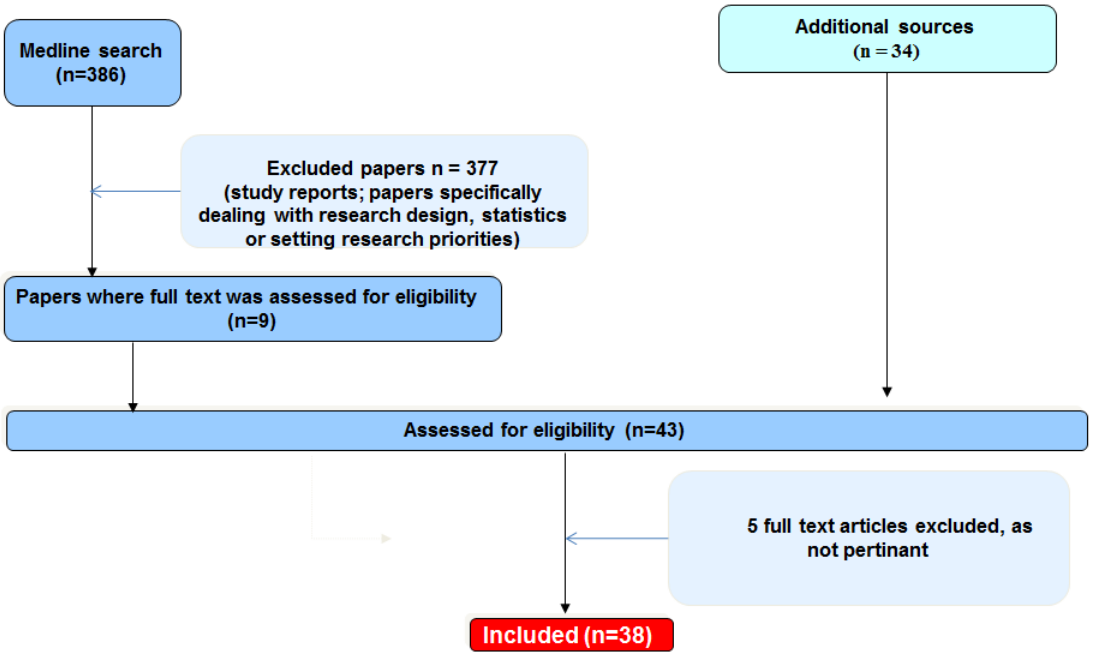
Annex B
Literature search: strategy and flow-chart

Search strategy

Table Annex B.1.: Search strategy

	Terms used	Number of hits
Step 1	(post-authorization[Title/Abstract] OR post authorization [Title/Abstract] OR postauthorization[Title/Abstract] OR post-marketing[Title/Abstract] OR post marketing[Title/Abstract] OR postmarketing[Title/Abstract] OR product surveillance, postmarketing[MeSH Terms] OR additional data[Title/Abstract] OR additional studies[Title/Abstract] OR additional study[Title/Abstract] OR evidence gaps[Title/Abstract] OR research gaps[Title/Abstract] OR observational[Title/Abstract] OR non interventional[Title/Abstract] OR non-interventional[Title/Abstract] OR real life[Title/Abstract] OR real world[Title/Abstract])	386
AND		
Step 2	(research question[Title/Abstract] OR research questions[Title/Abstract] OR researchable question[Title/Abstract] OR researchable questions[Title/Abstract] OR (formulate[title/abstract] OR formulating[title/abstract]) AND (question[title/abstract] OR questions[title/abstract] OR research[title/abstract])	

Flowchart of literature search



Annex C
Tables of data extraction for included articles and publications

Record ID	1 AHRQ 2013
Document type	Power point presentation
Document feature	Sixteen slide presentation “Prepared for: Agency for Healthcare Research and Quality (AHRQ)” on best practices on writing study protocol for CER.
Agency	AHRQ
Authors	
Title	Study Objectives and Questions for Observational Comparative Effectiveness Research - 2013
Formulating Assessment Question	A study’s objectives and questions form the foundation for research protocols Defining and Refining Study Questions Using the PICOTS Framework [slide 8]
Identifying research gaps	The following are suggested questions to discuss with stakeholders to help elicit the amount of uncertainty that is acceptable to them. What level of new scientific evidence is needed by the decision maker to make a decision or to take action? What quality of evidence is needed for the decision maker to act? What level of certainty of the outcome is needed by the decision maker(s)? How specific does the evidence need to be? Will decisions require the consensus of multiple parties?
From Research Gaps to Research Needs	
Main documents cited	1. Smith SR. Study objectives and questions. In: Velentgas P and Dreyer NA, eds. Developing a Protocol for Observational Comparative Effectiveness Research: A User's Guide. Rockville, MD: Agency for Healthcare Research and Quality; January 2013. p. 7-20. AHRQ Publication No. 12-EHC099. Available at www.effectivehealthcare.ahrq.gov/Methods-OCER.cfm. 2. Parfrey P, Ravani P. On framing the research question and choosing the appropriate research design. Methods Mol Biol 2009;473:1-17. PMID: 19160729. http://www.ncbi.nlm.nih.gov/pubmed/19160729 3. Richardson WS, Wilson MC, Nishikawa J, et al. The well-built clinical question: a key to evidence-based decisions. ACP J Club. 1995 Nov-Dec;123(3):A12-3. 4. Thabane L, Thomas T, Ye C, et al. Posing the research question: not so simple. Can J Anaesth 2009 Jan;56(1):71-9. PMID: 19247780. http://www.ncbi.nlm.nih.gov/pubmed/19247780
Notes	

Record ID	2 AHRQ 2014
Document type	Handbook
Document main feature	Guide to encourage patients, researchers, clinicians, and others to become involved in its Effective Health Care (EHC) Program.
Agency	AHRQ
Authors	
Title	Stakeholder Guide 2014
Formulating Assessment Question	Developing the Key Questions Good research requires a good set of research questions. The key research questions for each systematic review are formulated and refined with the help of Key Informants to ensure that research addresses the questions important to decision makers, represents an accurate scope of issues, and produces the most valuable product (see Box 3). Key Informants often include the nominator as well as other decision makers who can contribute to defining the scope and Key Questions of a research report. Key Informants may include patients and caregivers, clinicians (including both generalists and experts in relevant specialties), representatives of relevant professional and consumer organizations, insurers and health plan representatives who make coverage and benefit decisions, public policymakers, and others with experience in making health care decisions relevant to the topic. During the topic refinement process, the focus of the original nomination may be narrowed, expanded, or shifted depending on the input received from the Key Informant. This input is gathered through Key Informant calls, which are scheduled and coordinated by the EPC assigned to do the research. One or several calls may be held Appendix C. Research Questions Systematic reviews are a type of research review that synthesizes the available scientific evidence on the comparative effectiveness, benefits, and harms for a variety of diagnostic, treatment, and health care delivery decisions. They provide syntheses of relevant evidence to inform real-world health care decisions for consumers, clinicians, and policymakers. Systematic reviews are designed to answer a set of questions. The questions may be about how different tests or treatments work, or how they compare with one another. These Key Questions direct the researchers on what to look for in the evidence. Key questions help to ensure that the research stays focused on the findings that consumers, clinicians, and health care policymakers need to make good decisions. For example, investigators studying the evidence about different treatments available for people with acid reflux disease will engage a team of patients, clinical experts, researchers, and others to think through the important issues for people with this condition. The team then develops a list of questions that are most relevant to consumers, clinicians, and policymakers. They will make sure the questions reflect as many of the available treatments for acid reflux disease as possible, the benefits of these treatments for different groups of people, and the possible side effects of each treatment for different groups of people. Typically these questions are generated during the topic refinement process. However, Key Questions can be suggested as part of a topic nomination. Key Questions generally use a patient, intervention, comparison, outcomes (treatment and setting) [PICO(TS)] format to maximize

the usefulness of the final report. Public comment on a set of draft Key Questions helps researchers continue to think about what is most important to ask so that the research report can be as useful as possible.

Figure C-1. Guidance for Key Questions

Use questions that ask about indications for multiple procedures

Weak	What are the appropriate indications for arthroscopic surgery?
Strong	Does arthroscopic surgery improve [certain outcomes] for [certain types of] patients?
Strong	For what types of patients is there strong evidence that arthroscopic surgery improves [certain outcomes]?

Ask questions that are specific about effectiveness and evidence

Weak	Can [test Y] be used as a screening for hypertension?
Strong	How effective is [test Y] as a screening for hypertension?

Be specific about the aspect of health care that is of interest

Weak	What are the effects on health care of defined-contribution models?
Strong	How does the utilization of previously covered health care services change when employers offer defined-contribution models to their employees?

	Ask questions that are specific to reviewing available evidence Weak Should patients with severe mental illness be placed in community-based care or treated in inpatient settings? Strong What is the evidence that placing patients with severe mental illness in community-based care yields the same or better access, effectiveness [on certain outcomes], and costs compared with placement in inpatient Ask questions that will provide a basis for determining relative performance Weak Do high-volume hospitals provide superior cardiac care? Strong Are physicians practicing at academic medical centers or hospitals designated as "centers of excellence" for cardiac care more likely than those at other acute care hospitals to provide beta blockers to patients who have had heart attacks
Identifying research gaps	
From Research Gaps to Research Needs	Identification of Evidence Needs Identification of evidence needs is a central recurring activity that drives research and dissemination throughout the EHC Program. In order to gain the widest perspective into what questions need to be answered, all stakeholders—including consumers, clinicians, policymakers, and other decision makers—are encouraged to identify and suggest topics for research. Research suggestions from all sources and all topic nominations are posted on the EHC Web site at www.effectivehealthcare.ahrq.gov. The EHC Program reviews these suggestions based on a series of questions: • How widespread and serious is the disease or problem proposed for study? • How much controversy exists about treatment? • What are the potential impacts for improving care and/or reducing costs? • Would research results be relevant to Federal health care programs such as Medicare, Medicaid, or the Children's Health Insurance Program (CHIP)? • Would research results be relevant or helpful for vulnerable and underserved populations: low-income groups; racial/ethnic minorities; women; children; the elderly; individuals with special health care needs, such as those with disabilities; those who need chronic care or end-of-life care; or those who live in inner-city or rural areas? In addition, evidence synthesis also identifies future research needs as part of the research process. In the case of systematic reviews, this includes a formal engagement with stakeholders to prioritize gaps identified during the review of research. Future Research Needs

A Future Research Needs paper is a document produced by an EPC, usually the one preparing the main research report. After completing a research review, including identification of evidence gaps, the EPC convenes a group of stakeholders, including investigators, funders, and others, to prioritize future research needs as they relate to the research topic (see Box 8). The results of these discussions and prioritization are summarized in a separate Future Research Needs paper.
Methods of involving stakeholders in the development of the Future Research Needs papers are being tested. Research institutions consult with decision makers regarding how and what type of research should be prioritized to meet the identified evidence gaps.
The role of a stakeholder at this point is to participate in discussions to describe and prioritize research needs.
Stakeholders involved in identifying research needs should expect to—
• Read and review portions of the research report.
• Review suggestions and draft language regarding the prioritization of research gaps and needs for additional evidence.
• Provide comments in individual conversations or in group settings, such as dedicated meetings or conference calls.
• Have the process take up to 2 months.

In a transparent and systematic formal process, all stakeholders, including clinicians, funding agencies, and researchers, consider the gaps between available medical knowledge and the needs of clinical practice that are identified in the systematic reviews. Participants in the discussion include the researchers who worked on the individual review where the gap was first identified, stakeholders with interest in the topic, clinicians with particular expertise in the topic area, and agencies with funds for potential future research. Also involved are researchers with expertise in the clinical area and in study design, who can help identify evidence needs and develop new research projects based on the findings of the systematic review. It is hoped that this process will help shape future research plans and set priorities for a national investment in new research.
Inputs to the evidence gap identification process include nominations and recommendations of stakeholders by groups such as the Federal Coordinating Council for Comparative Effectiveness Research and the Institute of Medicine's project on Priority Setting for Comparative Effectiveness Research, as well as AHRQ's systematic review process.

Standardized Selection Criteria for Topics
Appropriateness
• Represents a health care drug, intervention, device, or technology available (or soon to be available) in the United States.
• Relevant to Medicare, Medicaid, CHIP, and other Federal health care programs.

Importance
• Represents a significant disease burden; affects a large proportion of the population or a priority population (e.g., children, elderly adults, low-income, rural/inner city, minorities, or other individuals with special health care or access issues).
• Is of high public interest; affects health care decision making, outcomes, or costs for a large proportion of the U.S. population or for a priority population in particular.
• Was nominated/strongly supported by one or more stakeholder groups.

	• Represents important uncertainty for decision makers. • Incorporates issues surrounding both clinical benefits and potential clinical harms. • Represents important variation in clinical care or controversy in what constitutes appropriate clinical care. • Represents high costs due to common use, high unit costs, or high associated costs to consumers, patients, health care systems, or payers. Duplication • Avoids potential for redundancy (i.e., is not already covered by an available or soon-to-be available high-quality systematic review by AHRQ or others). Feasibility • Effectively utilizes existing research and knowledge by considering— o Adequacy (type and volume) of research for conducting a systematic review. Newly available evidence (particularly for updates or new **technologies).** Potential Value • Has potential for significant health impact: o To improve health outcomes. o To reduce significant variation in clinical practices known to be related to quality of care. o To reduce unnecessary burden on those with health care problems. • Has potential for significant economic impact: o To reduce unnecessary or excessive costs. • Has potential for change: o The proposed topic exists within a clinical, consumer, or policymaking context that is amenable to evidence-based change. o A product from the EHC Program could be an appropriate vehicle for change. • Has potential risk from inaction: o Unintended harms from lack of prioritization of a nominated topic. • Addresses inequities and vulnerable populations (including issues for patient subgroups). • Addresses a topic that has clear implications for resolving important dilemmas**.**
Main documents cited	
Notes	

Record ID	3 Aslam 2010
Document type	Article
Document feature	Journal article
Agency	
Authors	Aslam S and Emmanuel P
Title	Formulating a researchable question: A critical step for facilitating good clinical research Indian J Sex Transm Dis. 2010 Jan-Jun; 31(1): 47–50
Formulating Assessment Question	FINER CRITERIA (feasible, interesting, novel, ethical, and relevant) As proposed by Hulley et al. [Table 1], a research question should be formulated keeping in mind the FINER (feasible, interesting, novel, ethical, and relevant) criteria[5] and that the answer should fill gaps in the existing knowledge. The following points should be considered while assessing a research question. Determining the required resources The feasibility of conducting a research project is based on the research question and should be considered early in the process in order to avoid waste of resources and intellectual energy. This is sometimes difficult for a new investigator and they need guidance from their mentors.[4] Consider doing a pilot or proof of concept study to assess the feasibility; Consult a biostatistician early in the project in order to choose less costly design and common outcomes; Consider feasibility of enrolling the intended number of subjects from the population of your interest. Also, consider expanding your inclusion criteria and modifying exclusion criteria if it is difficult to enroll the intended number; and Consider cost of each element of the study design, research staff, and resources. Significance of making it interesting and relevant An important question may not seem interesting the way it is presented. It is a challenge to present a research question clearly and engage the interest and attention of the reviewers. Research is too much work to not have a passion for what you are investigating. You will have more support for your study, and it will be easier to publish if the topic is novel and also interests your collaborators, colleagues, and the community at large. It is important to pursue a research question with a passion of getting the truth out of the matter.[5] This is how we all perceive research; commitment to a high-quality

	systematic and unbiased completion of an innovative project. If your question can explain a given problem while pointing toward a specific aspect which is missing then your project can get a great deal of support. Refining research question A focused research question leads to a systematic planning of a research project. The difficulty in framing a research question is not due to the lack of ideas. The challenge is to transform a novel research question into a valid study design which is the next step in refining a research question.
Identifying research gaps	
From Research Gaps to Research Needs	
Main documents cited	
Notes	

Record ID	4 avalia-t
Document type	Articles_reports
Document feature	research report
Agency	avalia-t
Authors	
Title	Transcatheter aortic valve implantation: results of a post-introduction observation study undertaken in Galicia.
Formulating Assessment Question	
Identifying research gaps	
From Research Gaps to Research Needs	The law governing the procedure for incorporating health techniques, technologies and procedures into the Galician Health Service (Servizo Galego de Saúde/SERGAS) provides that, where scientific evidence on a potentially relevant technology (technique, device or procedure) does not suffice for the purpose of taking a final decision about its definitive inclusion in the service portfolio, that technology may then become subject to an assessment study, thus linking its authorisation to a commitment to gather further data . The assessment protocol was developed in accordance with the work system proposed in the "Methodological guide to post-introdu observation", published by the National Health System (NHS) as part of its National Quality Plan . Starting from the systematic review condu following the request for authorisation to include TAVI in the SERGAS portfolio (internal document), the protocol was drawn up by a multidiscipl team made up of technical staff from the Galician Agency for Health Technology Assessment (Axencia de Avaliación de Tecnoloxías Sanitaria Galicia/avalia-t) and interventional cardiologists and cardiac surgeons from the three health centres authorised to perform this technique. They j agreed on key questions and information that would be both relevant and feasible to collect and, taking available resources into account, proce to plan the design, data-collection and data-analysis. Insofar as the study design was concerned, it was agreed that a prospective observational study would be implemented covering all patients who underwent TAVI at any of the three authorised health centres. Proposals and recommendations for improving the use of TAVI in the context of SERGAS In order to rationalize the use of the procedure, namely in avoidance of either under or over utilization, and therefore lead to a more optimal delivery and justifiable health care expenditure, a recommendation was made regarding the need to establish more concrete indications and requirements for authorisation. This proposal has taken form with the implementation of a nation-wide project within the framework of the Spanish NHS Network of Health Technology and Service Assessment Agencies (Red Española de Agencias de Evaluación de Tecnologías y

	Prestaciones del SNS) targeted at establishing appropriate use criteria for supporting final decision making on reimbursement criteria. This work, about to be delivered, was carried out in collaboration with a group of national health care professionals from cardiology, heart surgery and haemodynamics/interventional cardiology, who were designated by the Spanish Society of Cardiology (Sociedad Española de Cardiología/SEC) and Spanish Society for Cardiovascular-Thoracic Surgery (Sociedad Española de Cirugía Torácica-Cardiovascular/SECTCV). A further recommendation was that key performance indicators (structure, process and outcome), based on reference standards, should be developed and implemented to provide a continuous measurement of service quality and identify areas for improvement. This project too was undertaken in the framework of national-network collaboration, and has resulted in 23 proposed indicators along with their reference standards (pending implementation). The indicators, based on evidence and the consensus of a panel of experts made up of 15 specialists, are about to be made publically available.
Main documents cited	
Notes	

Record ID	5 Ballini 2010a
Document type	Article
Document feature	Journal article
Agency	ASSR-RER - EMILIA-ROMAGNA, ITALY
Authors	Ballini L, Minozzi S, Negro A, Pirini G, Grilli R
Title	A method for addressing research gaps in HTA, developed whilst evaluating robotic-assisted surgery: a proposal Health Research Policy and Systems 2010, 8:27 http://www.health-policy-systems.com/content/8/1/27
Formulating Assessment Question	a)The theoretical rationale Immature technologies still in the process of having their clinical place and relevance defined, are often proposed f or a variety of clinical indications and the literature reports a large array of patients, diseases and outcomes [9]. It is therefore necessary to clarify the innovative elements of the technology and its potentials. Starting from the technical characteristics of the technology, a theoretical rationale for its clinical effectiveness is defined and an evidence profile is mapped to outline the research questions aimed at proving the theoretical rationale. All relevant outcomes related to technical performance, feasibility, safety, clinical effectiveness and cost-effectiveness are specified. The decision to define relevant outcomes before analysing the scientific literature is based on the reasoning presented by the GRADE group, an international collaboration that has researched and proposed a method for the development of recommendations for clinical practice [10]. This method, discussed, critiqued and adopted by several guideline agencies, aims at a transparent process for the appraisal of evidence and the weighing up of benefits and risks of health interventions. It is claimed that discussion and agreement upon relevant outcomes, prior to reviewing the scientific literature, ensures that evaluation of the published research and subsequent development of recommendations are made explicit and unbiased by the search results. As literature on immature technologies is often limited to feasibility and safety outcomes, the initial experts' input for the definition of outcomes related to clinical effectiveness proves indispensable.
Identifying research gaps	b) The uncertainty profile Immature technologies are commonly supported by a low quality body of evidence (i.e. case series and uncontrolled studies) unsuitable to draw any firm conclusions from. Despite this, it is still possible to explore this uncertainty. Following the traditional line of development and evaluation of a new technology - from technical performance to cost-effectiveness -the Regional Observatory for Innovations developed a system for grading levels of uncertainty. The principle used to differentiate between levels of uncertainty is an adaptation of the grading of the level of evidence developed by the GRADE group. The GRADE's method for the development of recommendations for clinical practice involves assessment of both the level of evidence and of the strength of each recommendation. Quality and level of evidence is classified and graded according to whether "further research is [more or less] likely to change the level of confidence in the estimate of effect" [12]. In order to evaluate and categorize evidence drawn from low quality studies, we analysed results according to the likelihood that further studies and of

better methodological quality would change size and direction of estimates. Using this adapted criterion, the results of the studies are classified into the following four categories:

Level of uncertainty	Description
Steady results : results that are highly unlikely to be changed by further studies.	Results derived from well conducted comparative trials, i.e. systematic reviews of randomised controlled trials, several randomized controlled trials or quasi randomised trials or controlled non randomised studies with adequate adjusting for confounding factors, large sample sizes and concordant statistically significant results. Example of Da Vinci robot: steady results limited to absolute costs
Plausible results: consistent results, coming from sufficiently numerous observational studies, which would probably not change significantly if evaluated through randomised clinical trials.	a) consistent results derived from high quality observational studies (i.e. prospective comparative cohort studies with adequate adjusting for confounding factors) showing remarkable results for real benefits unlikely to be changed for direction of estimate by further randomised trials; b)consistent results related to outcomes that do not demand evaluation through comparative studies, as judgements are based on performance against absolute values or thresholds and the new technology is not required to perform better than the current alternatives. Example of Da Vinci robot: plausibly stable results of a robotic-assisted surgical intervention related, for feasibility, to results showing duration of intervention consistently keeping below maximum-time duration threshold and, for safety, to results consistently showing keeping below a maximum quantity of blood-loss threshold
Uncertain results:	Results coming from uncontrolled studies related to outcomes that need rigorous comparative studies, as their evaluation relies on differences between estimates and

	results that would most probably change, in both size and direction of estimate, if evaluated through randomised clinical trials.	because the new technology is required to perform differently from the current alternatives. Example of the Da Vinci robot: uncertain results related to surgical outcomes (i.e. adequate margins) and secondary clinical outcomes (such as continence, sexual potency for prostatectomy, time to nutrition for gastrointestinal surgery)
	Unknown results	Unreported or non-existent results on all outcomes judged by the panel to be relevant for the evaluation of the technology. Example of the Da Vinci robot: unknown results related to outcomes such as disease-free time, recurrence, survival, mortality etc. not assessed by any of the published studies
From Research Gaps to Research Needs	d) Assessment of research capacity of the context Once a list of clinical indications and relating research questions is drawn up, priority for research proposals is decided using the following criteria: - existing high-profile professional expertise and institutes of excellence capable of employing and evaluating the technology through appropriate research programmes; - adequate estimated size of the target population for the intended clinical use, for which a plausible beneficial clinical impact is expected. The proposed method, based on the above assumptions, is applied in a five step process (Figure 1) carried out by a multidisciplinary panel of experts. Outputs of each phase of the process used to evaluate the Da Vinci robot are described below. Step 5: Recommendations for clinical research Coherently with the limited knowledge that accompanies immature technologies, assessment reports cannot come to firm conclusions on the opportunity to adopt a technology or not. They can nevertheless provide information supporting restrain of unjustified diffusion in clinical practice, while endorsing clinical use within an experimental setting. Output of step five was the list of clinical indications appropriate for Regional research programmes. At the end of the process, the proposed areas of research for the experimental use of the Da Vinci robot in our Region were decided to be radical prostatectomy, colo-rectal surgery and bariatric surgery.	
Main documents cited		
Notes		

Record ID	6 Ballini 2010b
Document type	HTA report
Document feature	HTA report
Agency	ASSR - RER, Emilia-Romagna italy
Authors	Ballini L, Minozzi S, Pirini G, Negro A, Guidi G
Title	Innovative Radiation Treatment in Cancer: IGRT/IMRT Dossier 199 - 2010 - Agenzia Sanitaria e Sociale Regionale - Regione Emilia-Romagna http://asr.regione.emilia-romagna.it/wcm/asr/collana_dossier/doss199.htm
Formulating Assessment Question	Definition of the problem and research questions A panel of regional experts from several disciplines (radiotherapy, medical physics, oncology, nuclear medicine, radiology, statistics, economics, epidemiology and health research methodology) was convened to establish the information necessary to determine the clinical role of IGRT/IMRT, assess results of scientific literature, identify research gaps that need to be filled to complete the technology's evidence profile. To achieve these tasks the panel agreed on the following definition of the clinical rationale for IGRT/IMRT: A better correction for set up errors and organs' motion and a consequent more accurate dose targeting can decrease toxicity and/or increase clinical effectiveness of radiation treatments with radical intent of tumours in proximity of vital organs. The comparator was chosen to be any conformal radiotherapy with bi-dimensional image acquisition. Based on the above defined clinical rationale, which considers only radiation treatments with radical intent of tumours in proximity of vital organs, the panel agreed to evaluate the role of IGRT/IMRT only for the following tumours: prostate, head and neck, lung, brain and pancreas. The specific research questions identified are listed below (Table 1).
Identifying research gaps	Using this criterion an uncertainty profile has been outlined that distinguishes results in four categories: - Steady results: results that are highly unlikely to be changed by further studies. - Plausible results: consistent results on estimate of size and direction of effect, which would probably not change significantly if evaluated through randomised clinical trials. - Uncertain results: results on estimates of size and direction of effect that would most probably change, if evaluated through randomised clinical trials. - Unknown results: absence of results. The purpose of this evidence mapping according to levels of uncertainty, was to define the state of knowledge of the technology and to understand how current research is far from, or close to, answering clinically relevant questions. Expected outcome of this appraisal was to chart a future research course of action and define the experimental use of the technology within the regional health system.

	Classification of uncertainty and identification of research gaps Results of the literature review were charted on the evidence profiles defined for each research question and results for each dimension and outcome were classified according to their level of uncertainty. Available literature was judged to give sufficient information on technical performance for all research questions, with the exception of those related to pancreatic cancer. However the information on safety and clinical efficacy was judged to be very scarce. Overall we found: - some information on safety for use in patients with prostate cancer; -. some information on safety and very little on efficacy for use in patients affected by lung, head and neck and metastatic brain cancer; no information on use in patients with pancreatic cancer and with primary brain tumours. Quantity and quality of existing research were among the criteria applied for the prioritisation of future clinical research questions
From Research Gaps to Research Needs	Prioritisation of clinical research questions One of the aim of the panel's work was to develop research recommendations for further evaluation of the role and clinical impact of IGRT/IMRT. The priority for clinical research topics was defined using a structured process. Participants were involved in modified Delphi and RAND processes and presented with a voting form for each clinical scenario, related to the 5 tumours. The voting forms provided the following information: □ estimated target population; □ estimated treatment costs; □ a list of relevant clinical outcomes (suggested by the panel); □ estimates of performance of standard therapy (3D conformal) and of IGRT/IMRT (when available) for each clinical outcome. Participants were asked to place a vote next to each clinical outcome, expressing relevance in both clinical and research terms. They were then asked to rate each research indication in terms of the following priority's determinants:
Main documents cited	
Notes	

Record ID	7 Bennett 2012
Document type	Article
Document feature	Journal article
Agency	
Authors	Bennett WL, Robinson KA
Title	High Priority Research Needs for Gestational Diabetes Mellitus JOURNAL OF WOMEN'S HEALTH Volume 21, Number 9, 2012
Formulating Assessment Question	Using a systematic review on GDM as a starting point, we developed an eight-step process: (1) identification of research gaps, (2) feedback from the review's authors, (3) translation of gaps into researchable questions using population, intervention, comparators, outcomes, setting (PICOS) framework, (4) local institutions' stakeholders' refinement of research questions, (5) national stakeholders' use of Delphi method to develop consensus on the importance of research questions, (6) prioritization of outcomes, (7) conceptual framework, and (8) evaluation. Steps 1, 2, and 3: Identification of research gaps from review and formulation of 17 research questions In step 1, two investigators independently abstracted statements about research gaps from the published AHRQ evidence report10 and five articles based on findings from the review.14–18 The two investigators compared and combined the lists using a consensus process. In step 2, we sought feedback from the eight authors of the 2008 systematic review via electronic communication. In step 2, we sought feedback from the eight authors of the 2008 systematic review via electronic communication. For step 3, our research team organized the list of gaps into the population, intervention, comparators, outcomes, setting (PICOS) framework. We then translated these gaps into 17 new research questions. Step 4: Refinement of the 17 research questions by institutionally based local stakeholders For step 4, we invited six stakeholders from our own institution (local stakeholders) with expertise in GDM research or patient care to provide feedback on the 17 research questions. A list of the local stakeholders is available in the final AHRQ report. Stakeholders first completed an online questionnaire in which we listed the 17 draft research questions and asked them to comment on (1) the clarity of the questions (or suggest alternate wording), (2) the clinical benefit and importance of addressing the questions, using a 9-point Likert scale, where 9 indicated highly clinically important/high clinical benefit and 1 indicated unlikely to have clinical importance or benefit, and (3) the feasibility for researchers to conduct a study that would address the research questions, using a 9-point scale, Finally, we asked the local stakeholders to consider study design needs and challenges for each of the research questions. Following step 4, we refined each question and added questions suggested by the stakeholders to yield 19 research questions.

	Step 5: Consensus development by national stakeholders about research questions' clinical benefit/importance, leading to 15 final questions We identified national leaders and experts in GDM and invited nine of them to be stakeholders for this project (national stakeholders). We used the Delphi method for consensus development using an online form. We refined all research questions based on comments. The research questions without consensus were retained and entered into the next round. In Delphi rounds 2 and 3, we also provided stakeholders with information about how the other stakeholders had scored the questions in the prior Delphi round (the mean and range of the clinical benefit/importance scores) as well as a brief synopsis of comments and changes we made to the questions. Following completion of step 5, we eliminated 4 of the 19 research questions, as 3 had failed to achieve consensus and 1 had achieved consensus but as having medium clinical benefit/importance. During Delphi round 1, national stakeholders additionally commented on the study needs, challenges, and feasibility issues that had been identified from the local stakeholders' meeting. Comments on study needs, challenges, and feasibility were collated with the feedback from the local stakeholder meeting and organized into the PICOS framework Step 6: Prioritization by national stakeholders of outcomes for the two questions on medication and delivery management During Delphi round 3, national stakeholders completed step 6 of the process by prioritizing the maternal and fetal outcomes related to the research questions on medication and delivery management (which corresponded to the original review's questions I and II). Steps 7 and 8: Refinement of 15 questions and evaluation of process by all participants Step 7 involved the final refinement of the questions after Delphi round 3 and the development of a conceptual framework to display the results of the process, which included high priority questions and outcomes. In step 8, we developed an online evaluation tool (using SurveyGizmo) and invited all systematic review authors (except the three who were involved with this project) and local and national stakeholders to evaluate the process.
Identifying research gaps	
From Research Gaps to Research Needs	
Main documents cited	
Notes	

Record ID	8 Berger 2009
Document type	Guideline/article
Document feature	ABSTRACT Objectives: […]Nonrandomized studies of treatment effects using secondary databases may supplement the evidence based from randomized clinical trials and prospective observational studies. Recognizing the challenges to conducting valid retrospective epidemiologic and health services research studies, a Task Force was formed to develop a guidance document on state of the art approaches to frame research questions and report findings for these studies. Thus, the objective of this report is to lay out good research practices for comparative therapeutic effectiveness studies using secondary databases. We present the report in three sections: Defining, Reporting and Interpreting Nonrandomized Studies; Design Issues; and Analytical Issues. By describing best practice, this report will serve to improve future research, assist in evaluating the validity of existing studies, and suggest how these studies should be interpreted for decision-making; […] [p.1045].
Agency	ISPOR
Authors	Berger ML, Mamdani M, Atkins D, Johnson ML
Title	Good Research Practices for Comparative Effectiveness Research: Defining, Reporting and Interpreting Nonrandomized Studies of Treatment Effects Using Secondary Data Sources: The ISPOR Good Research Practices for Retrospective Database Analysis Task Force Report—Part I VA L U E I N H E A LT H Volume 12 • Number 8 • 2009
Formulating Assessment Question	Defining the Question [p.1045]. […]the development of evidence is ideally an iterative process between decision-makers, those who generate evidence and those who evaluate and summarize the body of evidence relevant to particular health policy questions. Prospective Specification of Research and Protocol Development [pp.1046-47] Arguably, the most important and challenging part of research is to clearly and precisely articulate the objective of a study in the form of a focused research question […]. we recommend the practice of a priori specification of the research question and study design in a formal study protocol and data-analysis plan is strongly advised to assure end-users that the results were not the product of data-mining. […] As part of the protocol, the rationale for the observational study should be explicitly stated. […] When defining the research question, four primary characteristics are proposed: *Relevance and Rationale* The research questions and hypotheses should be highly topical and meaningful from a clinical, policy, or research methodology perspective not only at time of study conception but, perhaps more importantly, at the anticipated time of submission for publication or presentation to the relevant audience. *Specificity*

The research question should be concise yet unambiguous, should relate to the stated research objectives where relevant, should state the intervention and outcome of interest where relevant, should identify the patient population, and should focus on one primary end point. Existing data sources must be adequate to provide valid identification of the appropriate patients, interventions, and outcomes. The protocol methods section should discuss the strengths and weaknesses of a secondary database with respect to its suitability in answering the primary research questions.

Novelty

Proposals should clearly identify what a new study can add to existing knowledge. At one extreme, there may be an absence of literature that directly relates to the proposed study question thereby making the proposed research question novel. Alternatively, the proposed study design for the given research question may improve on previous studies. Previous findings may have been inconclusive, conflicting or questioned because of study limitations. Finally, even when some research exists (including clinical trials), there may be a need to validate findings. As the number of well-designed studies addressing a specific question whose findings are consistent with each other increases, the value of an additional study addressing this question diminishes.

Feasibility

Investigators should recognize that conducting a rigorous observational study can be as challenging as conducting trials and should ensure that studies are feasible with respect to power of the study to answer a question, time and resources required, and ability to link necessary data sources. There should also be adequate numbers of patients and events to yield sufficient power for the primary analysis. Timing can be important because some areas change so rapidly that the answers may no longer be relevant if it takes several years to collect and analyze data. Finally, even where data already exist, there can be substantial hurdles to linking data from different systems to conduct the intended analysis.

In formulating the research question with the abovementioned characteristics, two suggestions may be helpful: 1) “begin at the end” [11]; and 2) know the limitations of the available data. Envisioning the one key table or figure required to answer the research question is extremely helpful in focusing the research question and understanding what can feasibly be extracted from the available data. Also, a sound understanding of data limitations will also help to understand which research questions should or should not be studied with the available data sources.

Once the research question has been defined, a sound study protocol should be developed with this study question in mind [12]. Key components of a study protocol include study background and rationale, research question/objective, study design, study population, data sources and storage where relevant, study timeframe, specific study definitions, one prespecified primary end point, secondary end points, statistical analysis (including sample size and power where relevant), informed consent process where relevant, and mock output tables and/or figures [12]. A written detailed data analysis plan (DAP) should also accompany the protocol; a good DAP will include definitions of outcomes, measures of treatments, and identify all covariates. The DAP should provide general specification of any modelling that is contemplated. We recognize that analytic plans often require adjustment once researchers begin to analyze secondary datasets.

We recommend that researchers be transparent about their ex ante analytic plans, provide justification for subsequent changes in analytic models, and report out the results of their ex ante analytic plan as well as the results from its modifications. In addition, researchers may wish to establish explicit limits on the evolution of the analytic plan—beyond which any results should be considered hypothesis-generating—and not appropriate for making clinical practice or policy recommendations. For example, one might consider establishing the boundary when a hypothesis-testing study changes into a hypothesis-generating study. Following extraction of the analytic dataset and completion of prespecified primary analyses, researchers frequently discover “bugs” in their analyses—perhaps because of coding problems in the data or because of the

	algorithms applied to define exposure; appropriate correction of these “bugs” is well accepted. Nevertheless, if important flaws become evident in the analytic approach such that different analytic approaches must be applied, this should signal that the study should be considered hypothesis-generating and not hypothesis-testing. Recommendations • A priori specification of the research question and study design in a formal study protocol and data-analysis plan is strongly advised. • Be transparent about ex ante analytic plans, provide justification for subsequent changes in analytic models, and report out the results of their ex ante analytic plan as well as the results from its modifications.
Identifying research gaps	
From Research Gaps to Research Needs	See “Novelty” section reported earlier
Main documents cited	
Notes	

Record ID	9 Brown 2006
Document type	Article
Document feature	This paper suggests a format to make research recommendation.
Agency	
Authors	Brown P, Brunnhuber K, Chalkidou K, Chalmers I, Clarke M, Fenton M, Forbes C, Glanville J, Hicks N J, Moody J, Twaddle S, Timimi H, Young P
Title	How to formulate research recommendations BMJ VOLUME 333 14 OCTOBER 2006
Formulating Assessment Question	
Identifying research gaps	
From Research Gaps to Research Needs	The paper provides a format to present research recommendations (gaps). “Summary points: No common guidelines exist for the formulation of recommendations for research on the effects of treatments Major organisations involved in commissioning or summarising research compared their approaches and agreed on core questions The essential items can be summarised as EPICOT+ (evidence, population, intervention, comparison, outcome, and time) Further details, such as disease burden and appropriate study type, should be considered as required” [p.806] Suggested format for research recommendations on the effects of treatments Core elements E Evidence (What is the current state of the evidence?) P Population (What is the population of interest?) I Intervention (What are the interventions of interest?) C Comparison (What are the comparisons of interest?) O Outcome (What are the outcomes of interest?) T Time stamp (Date of recommendation) Optional elements d Disease burden or relevance t Time aspect of core elements of EPICOT

	s Appropriate study type according to local need
Main documents cited	
Notes	

<table>
<tr><th>Record ID</th><th>10
Carey 2012</th></tr>
<tr><td>Document type</td><td>Power point presentation</td></tr>
<tr><td>Document feature</td><td>Twenty slide presentation on Identifying and Prioritizing Research Gaps</td></tr>
<tr><td>Agency</td><td>UNC - The Cecil G. Sheps Center for Health Services Research</td></tr>
<tr><td>Authors</td><td>Carey T, Yon A, Beadles C,Wines R</td></tr>
<tr><td>Title</td><td>Identifying and Prioritizing Research Gaps - 2012</td></tr>
<tr><td>Formulating Assessment Question</td><td></td></tr>
<tr><td>Identifying research gaps</td><td><u>Identify Research Gap</u>:
For children less than 6 years of age with disruptive behavior disorder or ADHD, limited data are available about the efficacy and effectiveness of psychosocial treatment programs (e.g., parent training and summer behavior treatment programs), alone or in combination with pharmacological interventions, compared with other psychosocial treatment programs, alone or in combination with pharmacological interventions. (KQ 1)

<u>After One Round of Prioritization Apply PICOTS and Develop Research Question</u>:
<table><tr><th>P</th><th>I</th><th>C</th><th>O</th><th>T/S</th></tr><tr><td>Age < 6 years Diagnosed with ADHD or at risk for ADHD or diagnosed with disruptive behavior disorder (including ODD and CD by DSM)</td><td>Psychosocial interventions alone (including parent training and school-based interventions)</td><td>Pharmacological treatments, alone or in combination with psychosocial treatments</td><td>Outcomes for children and parents*</td><td>6 Months/ 1Year

Private clinic, community clinic</td></tr></table>
Research Question: For children less than 6 years of age with disruptive behavior disorder or ADHD, what is the comparative efficacy and effectiveness of specific psychosocial treatments alone compared with pharmacological treatments alone or in combination with psychosocial treatments for patient outcomes?</td></tr>
<tr><td>From Research Gaps to Research Needs</td><td>AHRQ piloted 8 Future Research Needs (FRNs) Projects in 2010 to extract research gaps from a systematic review, transforming them into prioritized research questions with aided by diverse stakeholder groups [slide 61].
1. Systematic review is published with EPC-determined research gaps
2. Orientation of stakeholders to CER question, FRN process, and prioritization criteria
3. Elaboration and consolidation of research gaps through iterative process with stakeholders
4. Priority ranking of the research gaps</td></tr>
</table>

	5. Transformation of research gaps into needs 6. Refinement and re-ranking of priorities by stakeholders 7. Addition of study design considerations Transformation of Research Gaps into Needs [slide 11]. • Gaps are generally in the form of a declarative sentence. • Needs are questions similar to research questions in a grant proposal. • Most organizations use PICOTS framework: Population, Intervention, Comparator, Outcome, Timeframe, Setting. • Methods questions may be important, but may not be a fit for PICOTS.
Main documents cited	AHRQ EPCs have published multiple FRN methods papers to date
Notes	

Record ID	11 Carlyle 2013
Document type	Report
Document feature	Report based on research conducted by the Minnesota Evidence-based Practice Center (EPC) under contract to the AHRQ
Agency	AHRQ
Authors	Carlyle M, Ouellette J, Khawaja I,. Wilt TJ
Title	Treatment for Restless Legs Syndrome: Future Research Needs *Future Research Needs Paper* Number 38 - AHRQ Publication February 2013
Formulating Assessment Question	
Identifying research gaps	
From Research Gaps to Research Needs	Methods We used a deliberative process to identify and prioritize research questions relevant to the evidence gaps identified in the CER. Figure B illustrates the eight steps used to accomplish the objectives of this project. First, research gaps identified in the CER were translated into research questions. Second, a diverse stakeholder panel with representation from various perspectives relevant to the topic was assembled. We held a conference call with stakeholders to refine the original research gaps identified during the CER process. Based upon these conversations, we refined and added to our initial list of research gap questions. These are separated into categories (methodological research questions that need to be addressed to enhance the usefulness of current research, and topical research questions that have not been sufficiently addressed in the current literature). Because the stakeholders believed that some research questions that were considered out of scope from our review were critical to future comparative effectiveness research we elected to leave them in for prioritization processing. We sent the list of research questions to the stakeholders for ranking. Stakeholders numerically ranked their top three methodological research questions from a total of six and their top five topical research questions from a total of fourteen. Rankings were weighted according to stakeholder numerical ordering of questions. Based on the natural breakpoints in these rankings, we determined high, moderate, and low priority research gap questions. High priority questions were deemed research needs. We then identified and discussed research design considerations for research needs. Discussions with stakeholders revealed their deep concern that the lack of basic understanding of RLS and how it works greatly impedes the potential for forward movement of research in the field. Therefore a number of questions were added to the prioritization process that are outside of the scope of the original CER, but that stakeholders felt were important earlier steps that would improve the ability to design and conduct research that will ultimately answer who would benefit from what RLS treatments. We analyzed weighted rankings for stakeholders

	participating in the Web-based prioritization process. From the seven stakeholders invited to rank research questions, six (86 percent) ranked both methodological and topical questions. We describe separately research needs that were within and outside the original CER scope. Methodological Research Needs Natural breakpoints in weighted rankings revealed two moderate-priority methodological research questions, one within the scope of the original CER and one outside of it. Because no methodological research question appeared to be of high priority, we considered the moderate priority methodological research questions to be research needs. Addressing methodological research needs will improve the quality and enhance the clinical utility and translation of current and future research on treatments for RLS. Topical Research Needs A natural breakpoint in weighted rankings of topical research questions revealed five research needs, two within the scope of the original CER and three outside of it. All topical research needs addressed the PICOTS (population, intervention, comparison, outcome, timing, setting) elements of populations and interventions. Addressing topical research needs will enhance understanding of efficacy and comparative effectiveness which was limited in the draft CER. This FRN project refined and prioritized research needs relevant to the KQs addressed in the draft CER, "Treatment for Restless Legs Syndrome. Additionally, questions were proposed that while outside the scope of the current CER, were identified as gaps in the body of literature that Stakeholders felt impedes the field greatly. Therefore, multiple gaps in evidence were identified that required future research to improve delivery of health care for patients identified with RLS. "We conducted a deliberative process to refine and expand research gaps identified in the CER through conversations with stakeholders with various perspectives of expertise on the topic. This process identified six methodological and fourteen topical research questions thought to address identified evidence gaps. We then had stakeholders rank research questions. The highly ranked questions were deemed research needs. Stakeholders prioritized three methodological and five topical research needs. Addressing methodological research needs will enhance the quality, clinical utility and comparability of future studies of RLS treatments. A common set of patient-centered and intermediate outcomes, with guidance on interpreting clinically important changes in outcomes scale scores will provide researchers with standardized and validated approaches to collecting outcomes data and determining effectiveness. Guidance on how RLS interventions should be defined in research studies and variables to report in studies as determined by a multidisciplinary panel will, when utilized, enhance the quality of research on the topic
Main documents cited	
Notes	

Record ID	12 Chalkidou 2007
Document type	Article
Document feature	Journal article
Agency	
Authors	Chalkidou K
Title	Making a decision to wait for more evidence: when the National Institute for Health and Clinical Excellence recommends a technology only in the context of research R Soc Med 2007;100:453–460
Formulating Assessment Question	...
Identifying research gaps	...
From Research Gaps to Research Needs	NICE has adopted a number of approaches to dealing with uncertainty. Throughout the topic selection process, NICE has always made a case against developing guidance in areas where the evidence is scarce;13 instead, these topics would be forwarded to NHS Research and Development Programmes. When important evidence gaps are identified during the guidance development process, NICE issues research recommendations, encouraging further research to help fill those gaps and inform future updates of its guidance. Nevertheless, there will always be cases where the available evidence is insufficient to support a positive—or negative—recommendation. In these cases, NICE advisory bodies can consider issuing a recommendation for the use of the intervention only in the context of research. (OIR) OIR recommendations have been statutory valid alternatives to yes and no decisions since NICE was set up by government in 1999. They represent the only rational way for addressing uncertainty, consistent with NICE's principles of transparency and methodological robustness. As demonstrated in a number of cases so far, OIR recommendations can be viable and workable decision options as long as there is some co-ordination between the research and decision-making communities. Our study brings together all occurrences of such NICE decisions and describes how they have evolved over the years in response to the generation or absence of new evidence. We have not discussed here those cases where an OIR decision should have been made by NICE but was not, neither have we sought to identify any OIR that were made inappropriately given the circumstances. To do either of the above we would need to establish clear decision criteria as to when OIR recommendations are justified.
Main documents cited	
Notes	

Record ID	13 Chalkidou 2009
Document type	Article
Document feature	The article describes a pilot prioritization process moving from CER to research question.
Agency	
Authors	Chalkidou K, Whicher D, Kary W, Tunis S
Title	Comparative effectiveness research priorities: Identifying critical gaps in evidence for clinical and health policy decision making International Journal of Technology Assessment in Health Care, 25:3 (2009), 241–248.
Formulating Assessment Question	See “Transforming Identified Research Gaps into Researchable Questions”
Identifying research gaps	Uncertainty is not a topic dealt with, nevertheless “(vi) Uncertainty surrounding the use of the intervention […]” is one of the criteria used to prioritize research gaps.
From Research Gaps to Research Needs	Selecting a Comparative Effectiveness Report. The 2007 EPC report Comparative Effectiveness Review of Percutaneous Coronary Interventions (PCI) and Coronary Artery Bypass Graft Surgery (CABG) (5) was selected as the starting point for this project. Several criteria informed our selection of this specific review, including the following: (i) Timing; this was a recently concluded report and thus considered to be a topical and up-to-date review; (ii) Amenability of topic to CER; (iii) Inclusion of one or more new technologies that have potential for fast diffusion and high cost impact across the healthcare system; (iv) Inclusion of one or more new technologies that have potential for bringing about important health gains to the population; (v) Existence of previous or ongoing initiatives harvesting patient and consumer input in this field; and (vi) Consistency with overall AHRQ priorities. Collating the Evidence Gaps and Convening a Multistakeholder Working Party. After selecting a comparative effectiveness review, a multistakeholder workgroup, comprising representatives from hospitals, payers, product manufacturers, clinicians, researchers, consumers, and government agencies, was convened to undertake the prioritization process […]. The workgroup was convened on three occasions throughout the project to help identify, review, refine, and prioritize the evidence gaps and, in parallel, to help develop, in an iterative manner, the actual prioritization criteria and process. Additional input was provided by workgroup members between meetings, as required. Initially, CMTP staff, workgroup members, and project consultants with expertise in this clinical area generated a list of gaps in current evidence surrounding the clinical use of PCI and CABG using the discussion section of the PCI versus CABG EPC report (5) as a starting point. Information from other current systematic reviews and evidence-based policy documents, peer-reviewed publications, and reviews of published studies were also incorporated into the list of evidentiary gaps, as were recommendations from expert consultants, including the authors of the review and workgroup members. Transforming Identified Research Gaps into Researchable Questions.

	Once identified, the evidence gaps were translated into researchable questions, again through several iterations between group members, with support from our expert consultants who had experience in trial design […]. The Prioritization Process. There are several different approaches to prioritization, including formal consensus methods such as Delphi and nominal group techniques and economic impact approaches such as the payback approach or expected value of information models. […], we opted for an informal nominal group prioritization process based on an explicit set of criteria pre-agreed upon by the group. […] A set of priority setting criteria were developed in collaboration with the workgroup and served as general guiding factors when prioritizing: (i) Impact on patient health/outcomes, and the intervention effectiveness compared to available alternatives; (ii) Current and projected use of the intervention: variation in practice and diffusion rates; (iii) Safety concerns; (iv) Quantity and quality of the research so far including systematic reviews and research currently planned or in progress; (v) Most appropriate research design and feasibility of research, including costs, randomization issues, and timing, particularly in relation to fast evolving or diffusing technologies; and (vi) Uncertainty surrounding the use of the intervention, particularly in population subgroups (e.g., by age, gender, ethnicity, comorbidities, and so on). Workgroup members were asked to score each research question using a scale of 3 to 1 (with 3 representing higher and 1 representing lower importance) by integrating the suggested criteria in a qualitative manner, where appropriate, rather than scoring each question against each criterion. The prioritization process consisted of two rounds of scoring. After seeing the results of the first round of scoring, participants discussed their scores and the resulting rankings. This discussion was followed by a second round of scoring, during which workgroup members were provided with additional information on relevant ongoing or recently reported research related to the evidence gaps under consideration […]. All voting took place anonymously. After each round of scoring, the mean and median score for each question were calculated and the research questions were ranked, with those receiving the highest mean priority score at the top of the list. Additionally, the mean deviation from the median score was calculated for each of the questions to assess the degree of agreement among the workgroup members. The mean and median were also calculated separately for each of the stakeholder groups to determine if and how stakeholder groups differed in their responses. A Wilcoxon rank sum test was performed to determine if the degree of change in the overall rankings between the first and second rounds of scoring was significant. Consultation with Professional Organizations. After the end of the process, the input of professional societies was sought on the final list of prioritized questions, including the American College of Cardiologists (ACC), the Society of Thoracic Surgeons (STS), and the Society for Cardiovascular Angiography and Interventions (SCAI). We draw on these additional comments in the discussion section of the study.
Main documents cited	
Notes	

Record ID	14 Choudhury 2010
Document type	Power point presentation
Document feature	Sixteen slide presentation held in 18 & 29 November 2010
Agency	NICE
Authors	Choudhury M
Title	NICE Research Recommendations: Process & Methods
Formulating Assessment Question	Due to circularity of the entire process, 'final research recommendations' are the first step of the following round (assessment question)… PICO format is considered the standard for high quality research recommendation/assessment question. November 2010
Identifying research gaps	Here uncertainty is an output of systematic review and is the basis for research recommendations.
From Research Gaps to Research Needs	Existing process [slide 3-5] - Guidance-developers […] and NICE […] produce guidance including recommendations for research (production); - NICE (R&D) extract all 'research recommendations' from published guidance and add to the NICE research recommendations database (available on the NICE website) (publication); - Guidance-developers prioritise research recommendations to be published (Up to 5high-priority research recommendations published but many others identified); NICE R&D work with NICE Centre Directors to prioritise and promote research recommendations for funding (prioritisation). Updated process [slide 6-7] - Developed to ensure research recommendations are […] considered in light of all available evidence; - Research recommendations should be part of the full guidance production cycle (evidence synthesis through to funding opportunities) - Complements […] centre-specific process and methods guides - Important gaps are identified early and translated into clear research recommendations; Prioritised research recommendations are supported through various funding streams; Standalone research recommendations get picked up by researchers to address unmet research priority. Synthesis of the process [slide 12-13] 1. Uncertainties are identified by systematic review and advisory body 2. Identification of key uncertainties 3. Key uncertainties translated into draft research recommendations with rationale [strong emphasis on PICO formats, ndr – cfr slide 16] 4. Consultation on draft research recommendations

	5. Research recommendations finalised and issued with guidance 6. Research recommendation entered onto web-based database 7. Liaison with researchers and research funders 8. Reviewing of research recommendations as part of guidance review cycle
Main documents cited	**NICE Research Recommendations Process and Methods Guide 2011**
Notes	

Record ID	15 Claxton 2011
Document type	Article
Document feature	Research paper
Agency	York University
Authors	Claxton K, Palmer S, Longworth L, Bojke L, Griffin S, McKenna C, Soares M, Spackman E, Youn J
Title	Uncertainty, Evidence and Irrecoverable Costs: Informing Approval, Pricing and Research Decisions for Health Technologies CHE Research paper - October 2011
Formulating Assessment Question	
Identifying research gaps	2.1 Key principles and assessments needed The key principles and assessments fall into four broad areas: i) Expected cost-effectiveness and population net health effects (including benefits, harms and NHS costs). ii) The need for evidence and whether the type of research required can be conducted once a technology is approved for widespread use. iii) Whether there are sources of uncertainty which cannot be resolved by research but only over time. iv) Whether there are significant (opportunity) costs which will be committed and cannot be recovered once the technology is approved. Guidance will depend on the combined effect of all these assessments because they influence whether the benefits of research are likely to exceed the costs and whether any benefits of early approval are greater than withholding approval until additional research is conducted or other sources of uncertainty are resolved. This can be complex since these different considerations interact. For example, the effect of irrecoverable costs will depend on the need for additional research and will also influence whether research is worthwhile. The sequence of assessments, decisions and resulting guidance can be represented by a flow chart or algorithm. Although such a representation is an inevitable simplification of the necessary trade-offs it helps to: i) identify how different guidance might be arrived at; ii) indicate the order in which assessments might be made; iii) identify how similar guidance might be arrived at through different combinations of considerations; and iv) identify how guidance might change (e.g., following a reduction in price), and when it might be reviewed and decisions reconsidered. The complete algorithm is complex (reported in Appendix A, Parts I to III), representing the sequences of assessments and associated decisions, each leading to a particular category and type of guidance. However, the key decision points in the algorithm, reflecting the main assessments and judgments required during appraisal, can be represented as a simple 7 point check list (see Section 3.1). Table 3.1a Checklist for OIR and AWR (technologies expected to be cost-effective) 1 Is it cost-effective? Yes 2 Are there significant irrecoverable costs?

3 Does more research seem worthwhile?
4 Is the research possible with approval?
5 Will other sources of uncertainty resolve over time?
6 Are the benefits of research greater than the costs?
7 Are the benefits of approval greater than the costs?

Four broad categories of guidance are represented within the algorithm and include 'Approve', 'AWR', 'OIR' and 'Reject'. Each of the categories is further subdivided and numbered to indicate the different types of apparently similar guidance that could arise from different considerations. 'Delay' is not considered a particularly useful category since NICE always has the opportunity to revise its guidance, i.e., a decision to 'Reject' can always be revised but it is only with hindsight that 'Reject' might appear to be delayed 'Approval'. The distinction made between assessment and decision reflects the NICE appraisal process; first critically evaluate the information, evidence and analysis (an assessment), which can then assist the judgements (decisions) which are required in appraisal when formulating guidance.

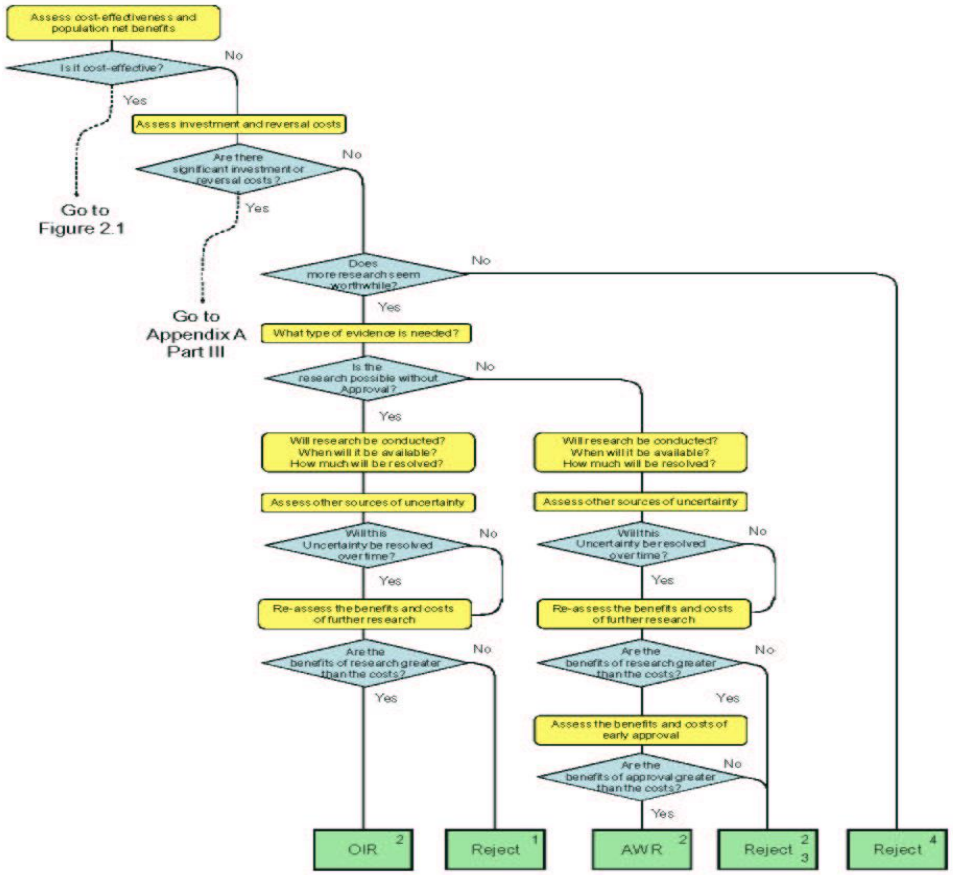


Figure 2.2 Technologies not expected to be cost-effective

However, irrecoverable costs may be much more common. Even in the absence of capital investment in equipment and facilities, most new technologies offer a 'risky investment profile' for each patient treated. Generally they impose initial per patient treatment costs which exceed the immediate health benefits (see Section 3.3.1). These irrecoverable treatment costs are only offset by cost savings and health benefits in the longer run, i.e. initially negative net health effects (losses) are only gradually compensated by later positive ones (gains). Therefore, a technology expected to be cost-effective may be expected to 'breakeven' (when accumulated 'gains' compensate earlier 'losses') after some considerable time. If guidance is likely to change it is possible that initial losses will not be compensated by later gains and the expected additional net health effects will not be realised[19]. This type of 'investment profile' becomes significant (has some influence on a decision to approval) if

From
Research Gaps
to Research
Needs

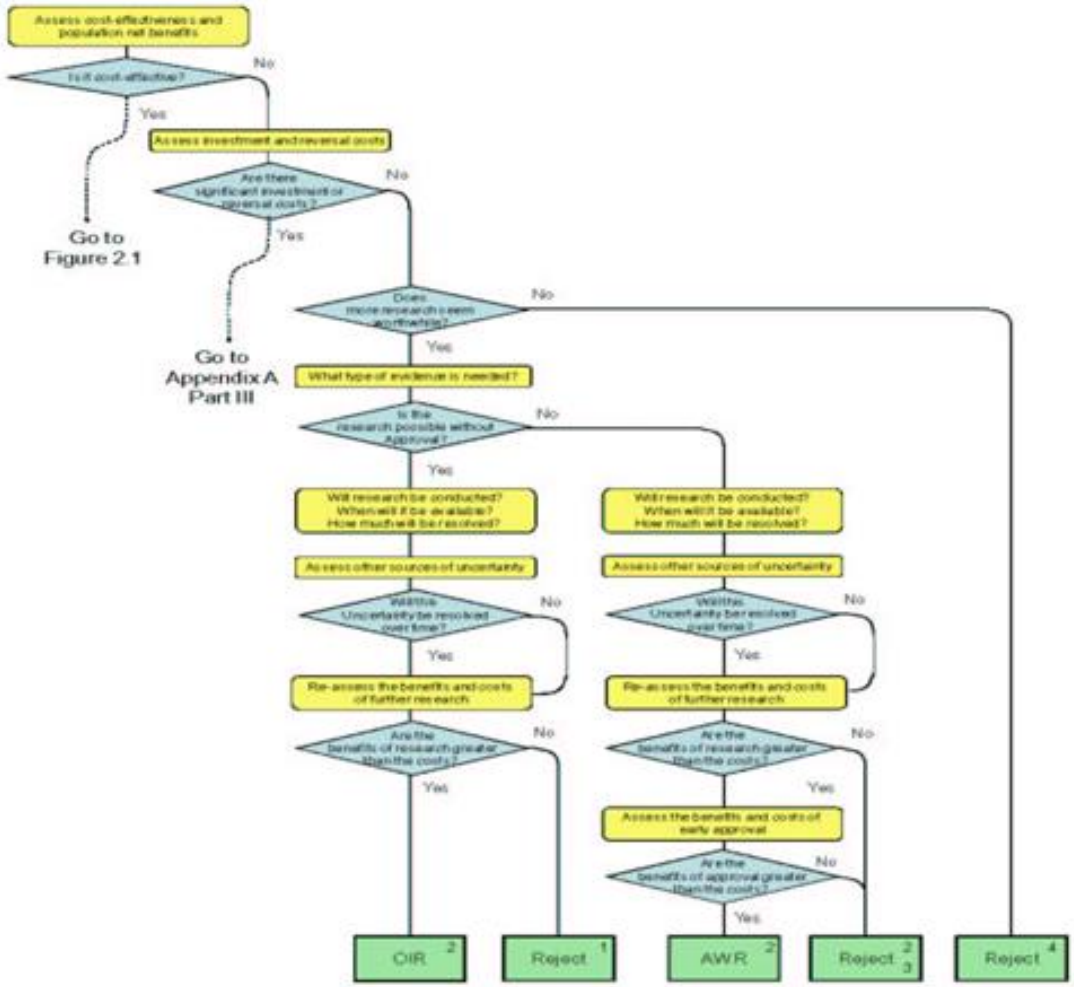


Figure 2.2 **Technologies not expected to be cost-effective**

	Assessing the prospects of research When considering OIR or AWR guidance there must be some assessment of: i) the type of research needed to address the key uncertainties; ii) whether this will be regarded as ethical and can be undertaken while the technology is approved for use; iii) whether it is likely to be a priority for public funding and be commissioned; and iv) when it is likely to report. Is further research required? This requires judgements about: i) how uncertain a decision to approve or reject a technology might be based on the estimates of expected cost-effectiveness; and ii) whether the scale of the likely consequences of this uncertainty might justify further research. Some assessment of the potential consequences of uncertainty is important because it indicates the scale of the population NHE that could be gained if the uncertainty surrounding this decision could be immediately resolved, i.e., it represents an expected upper bound on the benefits of more research.20 If the potential benefits of further research are unlikely to justify the costs, then a judgement that more research does not seem worthwhile will lead directly to guidance in the following circumstances Assessing the consequences of uncertainty Some assessment is required of: i) how uncertain a decision based on expected cost-effectiveness might be; and ii) what the consequences, in terms of population NHE, are likely to be if an incorrect decision is made. This judgment, of how uncertain a decision might be, can be informed by the probabilistic analysis (PSA) already used to estimate costs and QALY and is required as part of the NICE reference case[35-36]. The probability that EECP is cost-effective is 0.428 (see Table 3.5a),21 which would translate into approximately 800 QALYs (see Figure 3.3a) over the technology time horizon,22 based on the expected or average difference between NHE. However, the difference in NHE when EECP is not the correct decision is not necessarily the average. In fact, it is very unlikely to be the average and such estimates may substantially under or overestimate the expected consequences of uncertainty.
Main documents cited	
Formulating Assessment Question	
Notes	

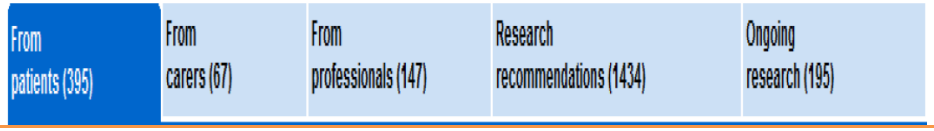
Record ID	16 Eisenberg 1999
Document type	Article
Document feature	Journal article
Agency	
Authors	Eisenberg JM
Title	. Ten lessons for evidence-based technology assessment. Jama. 1999;282(19):1865-9.
Formulating Assessment Question	
Identifying research gaps	
From Research Gaps to Research Needs	Evidence-based technology assessment is a critical public good. It can benefit all who are concerned about the appropriate use of health care services and products. Technology assessment has come a long way since Laennec's new diagnostic aid was described as "a dangerous instrument." Technology is rarely inherently good or bad, always or never useful. The challenge is to evaluate when in the course of an illness it is effective, for whom it will enhance outcomes, and how it should be implemented or interpreted. Health care technologies will not reach their potential unless they are translated, used, and continuously evaluated
Main documents cited	
Notes	

Record ID	17 ENCePP 2010
Document type	Handbook
Document feature	The document is a guideline suggesting best practice on study protocol writing.
Agency	EMA
Authors	ENCePP
Title	Guide on Methodological Standards in Pharmacoepidemiology (Revision 2) The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). Guide on Methodological Standards in Pharmacoepidemiology (Revision 2). EMA/95098/2010. Available at http://www.encepp.eu/standards_and_guidances
Formulating Assessment Question	"The protocol should cover at least the following aspects: - The research question the study is designed to answer, […]. […] should include a background description that expounds the origin […] and the state of present knowledge of the research question; - The main study objective and possible secondary objectives, which are operational definitions of the research question […]; - The source and study populations to be used to answer the research question […]; - Exposures of interest […]; - Outcomes of interest […] , - The covariates and potential confounders […]; - The statistical plan for the analysis […]; - The identification of possible biases. - Major assumptions, critical uncertainties and challenges" [General aspects of study protocol, p.4]. "The research question and the associated objectives address the knowledge or information to be gained from the study" [Research question, p.5]
Identifying research gaps	chapter "4.2.3. Methods to handle bias and confounding" [p.17] deal with such a problem in a study design.
From Research Gaps to Research Needs	
Main documents	**1.** Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies **2.** ISPE GPP

cited	**3.** FDA's Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Health Care Data Sets **4.** ENCePP Checklist for Study Protocols also **5.** Developing a Protocol for Observational Comparative Effectiveness Research: A User's Guide **6.** Writing narrative literature reviews
Notes	

Record ID	18 EUnetHTA 2013
Document type	Survey
Document feature	Excel summary of responses to the WP7 SG2 Survey on ADC, sent to twenty agencies*, asking for: 1. How are research recommendations/requests formulated in the HTA report? 2. Is there a standardized format for the research recommendation/question?
Agency	EUnetHTA
Authors	WP7 SG2
Title	
Formulating Assessment Question	The WP7 SG2 lead, HAS, performed in 2013 a Survey on the possibilities and conditions for performing harmonised Additional Data Collection (ADC) among EUnetHTA partners. The aim of the survey was to allow deeper understanding of HTA bodies' practices in the domain of additional data collection and to explore the possibilities and conditions for performing harmonized data collection in different countries. It has been conducted in two parts: • initial survey (4 questions) to identify EUnetHTA partners with a significant experience in ADC recommendations/requests • more detailed survey (25 questions) for partners identified as having significant experience in the field. 1. How are research recommendations/requests formulated in the HTA report? 1.1 as simple conclusion that more evidence is required, but without more indications for the ADC: 5 1.2 with some indications for the ADC: 8 1.3 with details on the additional study: 6 1.4 other: 1 2. Is there a standardized format for the research recommendation/question? 2.1 yes: 6 (4 quotes for PICO format) 2.2 more or less: 2 2.3 no: 9 2.4 NA: 3
Identifying research gaps	
From Research Gaps to Research Needs	The results of the survey showed that: • six agencies (30%) may express their research recommendations in a detailed manner in the HTA report, while eight (40%) provide rather limited indications for further research at the stage of production of the HTA report. Five (25%) don't provide any detail on the additional study, and just state that more evidence is required. • In eleven agencies (55%), HTA doers themselves are involved in the definition of the research question for ADC, in one it is the appraisal

	committee that is in charge of that task. • Six agencies (30%) stated using a standardized format for expressing their ADC research recommendations/questions, either PICO or EPICOT. These results confirmed the need to further work on structuring and harmonizing ADC recommendations.
Main documents cited	
Notes	*A.Gemelli, AGENAS, AhtaPol, AIFA, ASSR, avalia-t, CVZ, GBA, HIQA, IQWIG, ISC III, KCE, NETSCC, NICE, osteba, Romania, Regione Veneto, SBU, SNHTA, TLV.

Record ID	19 Fenton 2010
Document type	Power point presentation
Document feature	36 slide presentation held at “Practice NICE Research Recommendations Workshops” (2010). The presentation shows real examples rather than methodology issue.
Agency	UK DUETs and James Lind Alliance
Authors	Fenton M, Firkins L Practice NICE Research Recommendations Workshops” (2010)
Title	Collection of uncertainties and Prioritisation in Practice
Formulating Assessment Question	
Identifying research gaps	Only definition of uncertainty typology: Types of uncertainty about the effects of treatments [slide 29] ‘We’re uncertain whether anyone knows the effects’ → uncertain uncertainty ‘We’re uncertain what the effects will be on you’ → stochastic uncertainty ‘We’re uncertain because we don’t know your values’ → value uncertainty ‘We’re uncertain because no-one knows the effects’ → certain uncertainty Sources of uncertainties about the effects of treatments [slide 33]: 
From Research Gaps to Research Needs	First problem: Questions that are important to patients and clinicians have been ignored by researchers [slide 18] Second problem: Outcomes that are important to patients and clinicians have been ignored by researchers [slide 21] How often are treatment uncertainties considered important by patients and clinicians reflected in the research agenda? [slide 26] Prioritising uncertainties assembled in UK DUETs, for additional research [slide 36]
Main documents cited	Database of Uncertainties about the Effects of Treatments, DUETs: library.nhs.uk/duets/
Notes	

Record ID	20 Firkins 2010
Document type	Power point presentation
Document feature	Thirty slide presentation held at “Practice NICE Research Recommendations Workshops” (2010). Presentation shows JLA priority setting way
Agency	James Lind Alliance
Authors	Firkins L
Title	Prioritising uncertainties assembled in UK DUETs, for additional research/ Tackling treatment uncertainties together (Patients and Clinicians)
Formulating Assessment Question	…
Identifying research gaps	…
From Research Gaps to Research Needs	Support Priority Setting Partnerships → Support and raise the profile of patient / clinician involvement in priority setting → Gain evidence and share [slide 11] The five stages of a PSP [slide 12]: 1. Initiation: Who starts it off 2. Consultation: Who do we need to tell 3. Collation: Collecting uncertainties 4. Prioritisation: Sorting them into order 5. Reporting: The funding opportunities
Main documents cited	James Lind Alliance Guidebook
Notes	

Record ID	21 Frankel 2000
Document type	Article
Document feature	ABSTRACT: This is the second in a series of four papers on understanding and doing qualitative research […]. Here, we focus on problems of study design, including question development, literature review, identifying a target audience and resource needs assessment. […]
Agency	
Authors	Frankel RM, Devers KJ.
Title	Study Design in Qualitative Research—1: Developing Questions and Assessing Resource Needs *Education for Health, Vol. 13, No. 2, 2000, 251–261*
Formulating Assessment Question	Qualitative Research Study Design - Developing a Research Question. There is agreement that good qualitative studies answer clearly stated, important research questions (Frankel & Devers, 2000). In some cases, developing a good research question at a study's outset may be relatively straightforward. This occurs when there are well-developed theoretical and conceptual frameworks, and much is already known about the topic. The existing research literature itself may point to areas where further research is needed. In other cases, the task of developing the primary research question(s) is more difficult or may be the major focus of the research (sometimes the task is understanding what the right question is). Many qualitative researchers pursue research in certain areas because the existing theoretical and substantive literature does not adequately capture or reflect their personal experience or those with whom they are close. For example, one of us (K.J.D.) conducted ethnographic research about how triage decisions were made in adult intensive care units (ICUs) after observing marked differences in the conduct of this process while pursuing a larger, quantitative study. Finding scant literature describing differences and why they might occur, Devers designed a qualitative study to address this gap (1994). When relatively less is known about a topic, change is rapid, or discovering new theoretical or substantive knowledge is emphasized, the qualitative re searcher may begin with a more exploratory research question and refine it through a series of studies. For example, although the term "managed care" is frequently used, researchers often find it difficult to define. Qualitative approaches can be used to describe key dimensions of managed care or how it affects specific aspects of health care (e.g. doctor–patient relationship) (see e.g. Waitzkin & Fishman, 1997) so that a more complete understanding and definition can be developed.
Identifying research gaps	
From Research Gaps to Research Needs	
Main documents cited	

Notes

Record ID	22 Hannon 2008
Document type	Article
Document feature	Journal article
Agency	
Authors	Hannon EL.
Title	Randomized clinical trials and observational studies: guidelines for assessing respective strengths and limitations. JACC Cardiovasc Interv. 2008;1:211-7.
Formulating Assessment Question	
Identifying research gaps	
From Research Gaps to Research Needs	Criteria for Evaluating Quality of RCTs and OS In view of the possible threats to validity in both RCTs and OS, the following are some questions to ask when evaluating the quality of a study: Quality of the database. Does the database contain all of the characteristics/variables known to be necessary to obtain valid conclusions? Are the variables collected and measured in a well-defined clinically meaningful manner? If it is an observational database, does it contain the patient risk factors known to be significant predictors of the outcomes being tracked and studied? Is unmeasured confounding/selection bias a significant threat to the findings of the study? Patients. Are the patients in the study the right patients to test the study hypothesis? If the study is an observational database, is there enough information about patients to make appropriate exclusions? If the study is an RCT, are the exclusion and inclusion criteria broad enough to inform broad-based treatment decisions made on the basis of the study findings? Outcomes. Are the outcomes used in the study meaningful ones? Are there combined end points that mix important outcomes (e.g., mortality) with relatively unimportant or subjective outcomes. Are important outcomes included individually? Size and generality of the database. Is the database large enough to yield the statistical power needed to identify clinically meaningful differences in the important outcomes? “Clinically meaningful differences” should be defined in advance of the study. Is the sample of patients generalizable to other settings? Is there just a single site or very few sites that may not be representative of outcomes at other sites because of special circumstances such as physician quality, hospital quality or exceptional resources?

	Analysis strategy. If the study is based on an observational database, are differences in patient risk factors between treatments being controlled for adequately using a combination of multivariable adjustment and a method for testing selection bias such as propensity analysis? Follow-up. Is the follow-up period long enough to capture the outcomes being evaluated? Is the follow-up process complete and does it mirror real-world practice? Is the study compromised by loss to follow-up? Conclusions The aforementioned criteria (and perhaps others I have inadvertently omitted) are the most important determinants of whether a database and the methodology for analysing it are adequate for obtaining valid conclusions, or whether a given database/analysis plan is superior to another one, regardless of whether the database is an RCT or an observational database. The design and ultimate conduct of the study is the principal criterion to consider, not the type
Main documents cited	
Notes:	

Record ID	23 Huang 2006
Document type	Articles
Document feature	Symposium Proceedings
Agency	
Authors	Huang X
Title	Evaluation of PICO as a Knowledge Representation for Clinical Questions **AMIA 2006 Symposium Proceedings**
Formulating Assessment Question	Our study shows that the PICO framework is best suited for representing therapy questions, and considerably less-suited for diagnosis, etiology, and prognosis questions. In some cases, it is difficult to encode certain question classes without modifying the existing PICO structure or introducing counterintuitive elements. Given that the PICO framework is a well-established tool for formulating clinical queries, any limitations of the framework itself could potentially impact the quality of clinical evidence retrieved under its guidance. This study reveals a number of challenges associated with PICO analysis, which will serve as a basis for refining the principles of clinical query formulation
Identifying research gaps	
From Research Gaps to Research Needs	
Main documents cited	
Notes	The paper deal with the adequacy and flexibility of the PICO representation in terms of being able to capture salient characteristics of clinical questions. The author studied these issues by manually mapping real-world clinical questions into PICO frames and examining the results.

ID	24 Jacobson 2013
Document type	Poster
Document feature	The poster shows the Swedish process of filling knowledge gaps in health care
Agency	SBU
Authors	Jacobson St, Mowafi F, Tranaeus S, Heintz Emelie
Title	Collaboration – the way to fill knowledge gaps
Formulating Assessment Question	
Identifying research gaps	
From Research Gaps to Research Needs	What is a knowledge gap? According to SBU, a knowledge gap is present when: 1. systematic reviews reveal that a health technology has uncertain medical effects 2. there is no systematic literature review available. Knowledge gaps in SBU's database originate from several different sources, e.g. national or international systematic reviews, national guidelines, other agencies and through tips submitted to SBU. To confirm the lack of evidence in the latter, a literature search is conducted and the scientific evidence appraised. If SBU confirms a knowledge gap, it is published in the database. The process of filling knowledge gaps in health care requires collaboration on several levels: 1. Systematic reviews assess clinical research leading to 2. identification of treatments where knowledge is lacking. 3. Prioritizing and selecting the most urgent clinical questions, preferably by clinicians and patients, to be answered by 4. high quality research as well as funds in support. 5. Updating the evidence assessment to ensure that the knowledge gap is filled. 6. Priority setting and planning by decision makers leading to 7. benefits for patients.
Main documents cited	Official database on SBU's website, www.sbu.se.
Notes	

Record ID	25 James Lind Alliance 2010
Document type	Handbook
Document feature	guidebook
Agency	
Authors	James Lind Alliance
Title	James Lind Alliance Guidebook.
Formulating Assessment Question	
Identifying research gaps	Priority Setting Partnerships bring patients and clinicians together to work through the JLA process. The aim of a Priority Setting Partnership is to identify patients' and clinicians' shared priorities for research into the treatment of specific health problems. Gathering treatment uncertainties Uncertainties will come from four sources: • patients • carers • clinicians • existing literature Organisations and individuals participating in a Priority Setting Partnership should approach their members and the people they represent to ask them to submit their uncertainties. This is usually done using surveys, in electronic and paper formats. Alternatively, people can be consulted face-to-face. Patient-identified uncertainties It is important to ensure patients are as confident and empowered as clinicians to submit their questions about treatments Clinician-identified uncertainties Clinicians are requested to identify uncertainties which are immediately relevant to treating a patient with the particular health problem. They are asked to recall and share any issues which they have encountered during discussions or consultations between patients and those caring for them. Existing literature As well as uncertainties submitted by patients and clinicians, documented sources of information need to be searched for evidence of uncertainty, as these may then be included in the prioritization exercise. To enable open access to the full list and prioritized uncertainties identified by the Partnerships, the Partnerships are expected to ensure that, on completion of their priority setting exercise, uncertainties are prepared and formatted for inclusion in the UK Database of Uncertainties

about the Effects of Treatments (UK DUETs)
Uncertainties generally fall into four categories:
• uncertainties from patients, carers or clinicians
• indicative uncertainties, consisting of those submitted separately but which are similar to or duplicated by others formed by the PSP
• uncertainties from treatment guidelines, research recommendations and systematic reviews – these may be gathered at the same time as the literature is consulted to verify the uncertainties submitted via the survey
• uncertainties being addressed by ongoing research as confirmed by a relevant and reliable systematic reviews in study protocols or protocols for systematic reviews
It is therefore essential to adopt a systematic approach to managing and processing the survey submissions in order to create a list of uncertainties for prioritisation, and which will be entered into UK DUETs. Verify the uncertainties. Each uncertainty submitted, including indicative uncertainties of combined submissions as described above, needs to be verified as a true uncertainty. For example, some uncertainties may have already been addressed by research without all patients or clinicians being aware of this.
To check that an uncertainty is a true uncertainty, a search needs to be undertaken for relevant and reliable systematic reviews or guidelines, alongside any ongoing studies which might address the uncertainty. When checking an uncertainty against a systematic review, the review needs to be relevant and reliable. This can be measured by seeing if the authors follow a published methodology for undertaking the review, and if the methodology has made provision for managing bias. With guidelines, the author needs to have made efforts to identify all relevant and reliable trials or systematic reviews. Relevance and reliability can be further ascertained with the population confidence interval, enabling an informed reader to agree or disagree with the result. Narrative reviews, which do not give details or numerical results, may fail the requirements of relevance and reliability.
An uncertainty is deemed genuine when a reported confidence interval in a systematic review does not cross the line of no effect or line of unity. In addition to ascertaining statistical significance of an uncertainty, clinical significance needs to be checked by a clinician or person with relevant clinical knowledge who can confirm that the outcome of investigating the uncertainty would be clinically relevant.
When recording the date of the systematic review/guideline please use the most up-to-date review from Cochrane where available.
Identifying research recommendations
Treatment uncertainties identified in the research recommendations from the following sources indicates that they are confirmed uncertainties
- The Cochrane Database of Systematic Reviews
- the Database of Abstracts of Reviews of Effects (DARE)
- • NICE guidelines
- • SIGN clinical guidelines
- • Relevant Royal Colleges' guidance

The research recommendations may be reflected in the dataset generated by the survey, or they may be unique. There is a pragmatic decision to be made about how Priority Setting Partnerships identify uncertainties from these sources. For example, some guidelines are designed as guides for practice, not full explicit surveys of the literature to identify uncertainties and research recommendations. As such, these have sections including uncertainties and research recommendations. It is methodologically defensible to decide that these research recommendations should go forward into prioritisation. However, a more detailed read of a guideline will grade the evidence as being of high or

	low quality.. Finally, some apparent uncertainties can in fact be resolved with reference to existing research evidence – ie they are 'answerable questions' and not uncertainties. If a question about treatment effects can be answered with existing information but this is not known, it suggests that information is not being communicated effectively to those who need it. These findings may usefully inform future awareness-raising exercises and education programmes. Accordingly, the JLA recommends strongly that Partnerships keep a record of these 'answerable questions' and deals with them separately from the 'true uncertainties' considered during the research priority setting process. We suggest incorporating this commitment in the Partnership's Protocol. Ongoing trials and studies In addition to searching for relevant and reliable systematic reviews and guidelines, it is recommended that a search needs to be undertaken for ongoing studies which might address the uncertainty. The citation to the study also needs to 34 Version 5 © James Lind Alliance (2013) be recorded for each submission for entry into UK DUETs. This helps avoid waste in research by demonstrating where research is already commissioned that might address an issue and therefore does not need more How to prioritise uncertainties Interim priority setting An exercise to gather treatment uncertainties for prioritisation can yield a large amount of information. The most practical approach is to initially shortlist the uncertainties, in an interim priority setting exercise, and then proceed to a final priority setting workshop. Some Priority Setting Partnerships have gathered up to 2000 raw individual submissions (including duplicates and non-uncertainties). After checking, these have been refined to around 500 unique treatment uncertainties. The interim priority setting stage may be carried out by the whole Partnership, or in the initial stages by the representative Steering Group. Where the whole partnership is involved interim priority setting can be conducted by email and/or post or online, depending on the communication preferences of the partner organisations. Partners ask their members, colleagues or peers to: • examine the long list of treatment uncertainties • choose those which they would most want to see prioritised for research – usually this is 10, although Partnerships may opt for a lower number is this is deemed more manageable • rank them
From Research Gaps to Research Needs	
Main documents cited	
Notes	

Record ID	26 Lau J 2008
Document type	Power point presentation
Document main feature	Twelve slide presentation at: AHRQ Annual Meeting - September 10, 2008
Agency	Tufts Medical Center EPC
Authors	Lau J
Title	Methodological Issues in Systematic Review - Formulating Questions AHRQ Annual Meeting September 10, 2008
Formulating Assessment Question	Presentation of an Analytic framework for omega-3 FA intake and CVD Substantially rooted on PICO method to formulate research question on interventions
Identifying research gaps	
From Research Gaps to Research Needs	
Main documents cited	
Notes	

ID	27 Medicare 2006
Document type	Guide
Document feature	Guidance document
Agency	Centers of Medicare and Medicaid Services
Authors	
Title	National Coverage Determinations with Data Collection as a Condition of Coverage: Coverage with Evidence Development , 2006
Formulating Assessment Question	
Identifying research gaps	
From Research Gaps to Research Needs	**IV. Strength of evidence for national coverage determinations** When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether the evidence is of sufficient quality to support a finding that an item or service that falls within a benefit category is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. This critical appraisal of the evidence enables us to determine whether: 1) assessment questions specific to the process of the evidence evaluation can be answered conclusively; and 2) the investigational item or service will improve health outcomes for patients. An improved health outcome is one of several considerations in determining whether an item or service is reasonable and necessary. **A. Coverage with Appropriateness Determination (CAD)** If the evidence for an item or service being evaluated is adequate to determine that the item or service is reasonable and necessary under section 1862(a)(1)(A), CMS may determine that the item is covered under Medicare. Given the importance of the patient's factual circumstances in determining the appropriate treatment, coverage without conditions is rare. Most NCDs have restrictions that ensure that appropriate patients are receiving care by competent providers. CMS may have concerns that beneficiaries receiving the item or service meet the conditions specified in the NCD. In these cases CMS could require CAD, which allows CMS to ensure that new technology is provided appropriately to patients meeting specific characteristics as described in the NCD. CAD will only be invoked when there is adequate evidence to determine that the item or service is to be covered. However, when an NCD requires CAD, only items or services for patients who are included in the data collection are covered. CAD will be required when CMS is concerned that the data collected on a claims form is insufficient to determine that the item or service was appropriately provided as outlined

	in the NCD. The following are some concerns that may lead to a coverage decision that requires CAD as a condition of coverage **B. Coverage with Study Participation (CSP)** CSP will allow coverage of certain items or services for which the evidence is not adequate to support coverage under section 1862(a)(1)(A) and where additional data gathered in the context of clinical care would further clarify the impact of these items and services on the health of Medicare beneficiaries. In the past, this level of evidence would have prompted non-coverage decisions **VI. Data sources** **A. Registries** CMS may issue an NCD that requires data to be sent to a centralized database. Formal registries with qualified oversight ensure that data will be uniform, valid, and consistent with accepted standards and definitions. Medicare data from the database will be provided to CMS for the purposes outlined in the coverage determination. Data collected in this manner may be linked with Medicare claims data to confirm that data are submitted for patients receiving the item or service. Collection and use of this data will meet all relevant patient protections including the Privacy Act HIPAA, and 45 CFR Part 46. **B. Research studies** If CMS determines that the evidence for coverage of certain items or services is inadequate to establish Medicare coverage under 1862(a)(1)(A), Medicare may still reimburse for that item or service for Medicare beneficiaries enrolled in a research study that provides data and information to be used to evaluate that item or service, as well as reimburse for the routine costs incurred by Medicare beneficiaries in the study. To qualify for reimbursement, such a study must be designed to produce evidence that could be used in a future national coverage decision that would focus on whether the item or service should be covered by Medicare under 1862(a)(1)(A). Payment for the items and services provided in the study will be restricted to the Medicare qualified patients involved as human subjects in the study.
Main documents cited	
Notes	

Record ID	28 Moher 2008
Document type	Article
Document feature	"The aim of this report is to highlight issues in SR conduct with a focus on the field of nutrition and to make recommendations on improving SR conduct in this area" [Abstract].
Agency	
Authors	Moher D and Tricco AC
Title	Issues related to the conduct of systematic reviews: a focus on the nutrition field *Am J Clin Nutr* 2008;88:1191–9.
Formulating Assessment Question	"[…] developing a clear and concise question is probably the most important step in conducting an SR. The 4 components of an answerable question include 1) the patient, population, or problem (P); 2) the intervention, independent variable, or exposure (I); 3) the comparators (C); and 4) the dependent variables or outcomes of interest (O) (27). Sometimes an additional component is added, namely, study design (S), which is used to limit the SR to certain types of studies, such as cohort studies. These components are known collectively as PICOS (1). [Variations of PICOS also exist, such as one that adds a "D" for study design (PICO-D) and one that incorporates a "T" for timing and an "S" for setting (PICOTS).]" [p.1192]
Identifying research gaps	
From Research Gaps to Research Needs	Topic is not addressed. In table 5 [p.1197], recommendation 2 states: "Conduct a comprehensive search to develop a list of priority topics on which sufficient evidence exists to warrant an SR, and identify gaps in primary research. Develop a repository of SRs in nutrition to identify gaps and generate new SR questions".
Main documents cited	
Notes	

Record ID	29 NICE 2011
Document type	Handbook
Document	Methodological guidance

feature	
Agency	NICE
Authors	NICE
Title	Research Recommendations . Process and methods guidance NICE August 2011
Formulating Assessment Question	
Identifying research gaps	Box 1: Examples of different reasons for uncertainties There is no evidence available because: a. the relevant research has not been done b. the relevant research has been done, but not published c. the relevant research has been done and published, but the searches have failed to identify it Existing evidence is available but: a. the publication contains insufficient information due to inadequate reporting b. the research has been undertaken, but is not methodologically robust c. the research has been undertaken, but the results were inconclusive (e.g. conflicting) d. the research has been undertaken, but the study enrolled too few patients to be sure statistically that the results were not due to chance e. research into the question has been undertaken, but the results cannot be applied to the population in question (for example, the setting or social and cultural context is not comparable, the patient population differs, a different dosage of drug has been used) f. research has been undertaken into a related but different question (for example the comparator differs) g. the research is out of date – for example, a systematic review needs updating with recent trials, or clinical practice has changed h. the research cannot be understood due to language difficulties i. studies have been done, but their findings are inconsistent Step 2 – identification of key uncertainties The summarised list of uncertainties is reviewed and key uncertainties are identified. The most important are those that the advisory committees consider need to be resolved to inform future updates of guidance recommendations, but also that there will be clear benefits and added value to the NHS. For example, the uncertainties may relate to key aspects of patient care or public health that must be addressed as a priority. There are no limits to the number of key uncertainties that are identified, and it may be that none are identified at all. This process of identification/prioritising key uncertainties should be led by the advisory committees, with input from clinicians, researchers, patients and carers, service users or the target population, reviewers, health economists and Institute technical staff. The selection of key uncertainties can also be informed by any economic modelling that is undertaken. For example, the results of an economic modelling exercise may be sensitive to specific parameter or structural assumptions that could be further informed by research.

Additional probabilistic sensitivity analysis with the models used in the decision-making could be a possible method for establishing the value for money of additional research to reduce evidential gaps and help prioritise future research efforts. These techniques are known as „value-of-information" methods. While there is no requirement to routinely undertake such evaluations, they may be considered helpful in the process of identifying key uncertainties. The MRC-funded study will explore the utility of such methodology particularly in the context of technology appraisals (please refer to paragraph 1.6, above). It is anticipated that the results of this study will inform whether and when it may be appropriate to use this methodology

From Research Gaps to Research Needs

The NICE Research Recommendations process:

Translation of uncertainties into research recommendations
Each key uncertainty (if any have been identified) should be translated into a research recommendation with two components:
a structured stand-alone statement that sets out the question(s) that needs to be answered (Table 1); an explanation of the rationale for why the uncertainty has been identified as being key (Table 2).

The research recommendations need to be stand-alone statements because they will be abstracted into a database and may not be read in the context of the guidance. Therefore, the information contained in the recommendation must be sufficient to characterise the research that needs to be undertaken and convey why it must be done. This should ensure that the recommendation will be picked up for further exploration.

Table 1 Proposed format of research recommendations

Criterion	Explanation
Population	Define the population that the research needs to be undertaken in. Where appropriate, specify any of the following: diagnosis disease stage co-morbidities risk factors gender age ethnic group specific inclusion criteria specific exclusion criteria determinants of health health status or setting (for example, community or secondary care)
Intervention	Specify the intervention that needs to be evaluated. This can be: a drug a device a treatment a management strategy a psychological intervention a behavioural intervention a community intervention an organisational or population intervention a clinical prediction rule or prognostic factors. For public health this may also make reference to risk factors that the patient/population is exposed to. Where appropriate also consider providing information on: the type, frequency, dose, and duration (for intervention or exposure); any prognostic factor(s) or any diagnostic or screening test(s) that might be required.

		In the case of public health interventions the context and setting and method of delivery of the intervention may also need to be specified
	Criterion	Explanation
	Comparator(s)	If appropriate, state what the intervention needs to be compared to. For example, placebo, routine NHS care, alternative treatment or management strategy. Where appropriate also consider providing information on: the type, frequency, dose, and duration (for intervention or exposure); any prognostic factor(s) or any diagnostic or screening test(s) that might be required.
	Outcome	What will the researcher need to measure, improve, influence or accomplish to assess whether the intervention is effective? What are the clinical or patient-related outcomes of the intervention that should be measured to demonstrate this? If appropriate, consider providing information on: outcomes to be measured (for example, mortality, morbidity, quality of life, patient perception). Any surrogate outcomes must be validated. method and process of measurement (type, frequency or timing of measure) length of follow-up required. In the case of public health interventions the causal pathway should be specified as leading either to individual or population level outcomes.
	Study Design	If appropriate consider suggesting what might be the most appropriate study design to address the proposed question.
	Timeframe	Is there a timeframe in which the study needs to be completed? For example to inform a guidance review, or whether it is anticipated that the technology could be superseded before the results of any study are anticipated.
Main documents cited		
Notes		

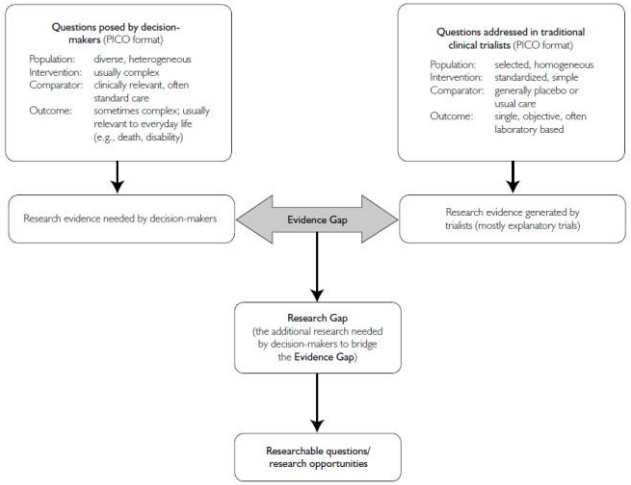
Record ID	30 NICE 2013
Document type	Handbook
Document feature	HtA manual
Agency	Nice
Authors	
Title	Guide to the methods of technology appraisal Process and methods guides http://publications.nice.org.uk/pmg9 Published: 04 April 2013
Formulating Assessment Question	The 'scoping' process examines the appropriateness of the proposed remit and defines what the appraisal will and will not examine. Scoping determines the nature and content of the evidence to be included in the assessment phase of the appraisal. However, the Appraisal Committee may consider issues that are not defined in the scope if necessary in the light of the evidence provided. The scope provides a framework for the appraisal. It defines the issues of interest (for example, population, comparators, and health outcome measures) and sets the boundaries for the work undertaken by the independent academic groups and the manufacturer(s) or sponsor(s) of the technology who produce reports for the Appraisal Committee. The issues for consideration in the appraisal that are described in the scope include: - the disease or health condition and the population(s) for whom treatment with the technology is being appraised - the technology (and the setting for its use; for example, hospital [inpatient and outpatient] or community if relevant) - the relevant potential comparator technologies (and the setting for their use if relevant) - the principal health outcome measures appropriate for the analysis - the costs, including when the Department of Health asks NICE to consider costs (savings) to the public sector outside the NHS and personal social services - the time horizon over which health effects and costs will be assessed - consideration of patient subgroups for whom the technology might be particularly clinically and cost effective - issues relating to advancing equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and society as a whole - other special considerations and issues that are likely to affect the appraisal, for example, existing relevant NICE guidance and the innovative nature of the technology.
Identifying research gaps	uncertainty in cost-effectiveness It is important for the model to quantify the decision uncertainty associated with a technology (that is, the probability that a different decision

	would be reached if the true cost effectiveness of each technology could be ascertained before making the decision). Models are subject to uncertainty around the structural assumptions used in the analysis. Examples of structural uncertainty may include how different states of health are categorised and how different pathways of care are represented second type of uncertainty arises from the choice of data sources to provide values for the key parameters, such as different costs and utilities, estimates of relative effectiveness and their duration. The implications of different estimates of key parameters must be reflected in sensitivity analyses (for example, through the inclusion of alternative data sets). Inputs must be fully justified and uncertainty explored by sensitivity analysis using alternative input values. third source of uncertainty arises from parameter precision, once the most appropriate sources of information have been identified (that is, the uncertainty around the mean health and cost inputs in the model).
From Research Gaps to Research Needs	Research recommendations When the evidence of clinical effectiveness or impact of a technology on other health outcomes is either absent, weak or uncertain, the Appraisal Committee may recommend that the technology is used only in the context of research or while the technology is recommended as an option, research is also conducted. Before issuing such recommendations the Committee will consider the following factors: - the need for and potential value to the NHS of additional evidence that can inform the development of NICE guidance and clinical practice on the use of the technology - the uncertainty in the analysis and what could be gained by reconsidering the decision in the light of research findings - whether the research is feasible in circumstances when the Appraisal Committee recommends the intervention for NHS use outside the context of research - irrecoverable costs incurred from introducing the technology - the likely net benefits for all NHS patients of use only in a research setting during the time that the recommended research is being conducted. In considering these factors the Committee will balance the potential net benefits to current NHS patients of a recommendation not restricted to research with the potential net benefits to both current and future NHS patients of being able to produce guidance and base clinical practice on a more secure evidence base. Recommendations on the use of technologies only in the context of research will not include consideration of which organisation (public or private) will fund the research. The Appraisal Committee will consider: The Appraisal Committee will consider: - the likelihood that the research needed will be commissioned and successfully report

	- the time it is likely to take for research findings to be available to inform subsequent NICE guidance and clinical practice - other factors which may impact on the value of Evidence Generation, such as other research that is underway or likely to be commissioned and completed
Main documents cited	Guidance for multiple technology appraisal process Guidance for single technology appraisal process.
Notes	

Record ID	31 Scott 2008
Document type	Article
Document feature	Abstract Health technology assessments (HTAs) are an as yet unexploited source of comprehensive, systematically generated information that could be used by research funding agencies to formulate researchable questions that are relevant to decision-makers. We describe a process that was developed for distilling evidence gaps identified in HTAs into researchable questions that a provincial research funding agency can use to inform its research agenda.
Agency	
Authors	Scott NA, Moga C, Harstall C, Magnan J
Title	Using Health Technology Assessment to Identify Research Gaps: An Unexploited Resource for Increasing the Value of Clinical Research HEALTHCARE POLICY Vol.3 No.3, 2008
Formulating Assessment Question	
Identifying research gaps	
From Research Gaps to Research Needs	Identifying Evidence Gaps, Research Gaps and Researchable Questions [p. e112-e114] […] When comparing health technologies, the questions posed by healthcare decision-makers are often structured differently from those addressed in clinical trials (Figure 1). […]

FIGURE 1. The relationship between evidence gaps and research gaps



The resulting evidence gap can be defined as all the evidence missing from a body of research on a particular topic that would otherwise potentially answer the questions of decision-makers (clinicians, other practitioner groups, administrators, policy makers) (Figure 1). By systematically summarizing the available evidence in response to policy-driven questions, HTAs routinely identify evidence gaps that are relevant to policy makers and the attendant "research gaps," that is, the additional research needed, from a policy maker's perspective, to address the evidence gap in the available primary research. There are almost always fewer research gaps than evidence gaps because, while it would be nice to know everything (the evidence gap), most of the time decision-makers must be content with picking a few aspects of the evidence gap that would be the most useful for informing decisions and the most practicable to answer within the time and resource constraints of the research environment (the research gap).

Thus, HTAs are an as yet unexploited source of systematically generated, comprehensive information that could be used by research funding agencies to bridge the evidence gap and formulate researchable questions that are relevant to decision-makers. However, relying solely on the producers of HTA reports to identify research gaps will result in an extensive list, but not necessarily one that is relevant to clinicians or policy makers (de Vet et al. 2001), since HTAs are circumscribed by the inherent limitations of the evidence base they summarize. Any endeavour to derive researchable questions from the research gaps identified by HTAs must include researchers, policy makers, clinicians, consumers and the public, since each group will often have different opinions on the need for future research and how it should be designed, financed and developed (Black 2001; Lomas et al. 2003).

Using HTA to Inform the Research Funding Agenda

World experience

From the results of a recent survey of members of [INAHTA] […] it appears that only two countries, Belgium and the United Kingdom, have a

formal process for linking the identification of research gaps from HTA reports to the research funding process […]. Among many other HTA agencies, the use of HTA reports to help funding agencies address evidence gaps usually occurs in an ad hoc, serendipitous fashion, if at all. […] The system in the United Kingdom, which seems to be the most comprehensive and systematic, is facilitated by two agencies, the National Coordinating Centre for Health Technology Assessment (NCCHTA) and the National Institute for Health and Clinical Excellence (NICE). NICE issues guidance for the National Health Service on public health, clinical practice and the use of health technologies. Evidence gaps identified by NICE guidance reports are fed into the NICE Research and Development Programme, where they are prioritized by a Research and Development Advisory Committee according to their importance, relevance and feasibility. As NICE is unable to commission research directly, the research recommendations and their priority ranking are published on the NICE website. High-priority topics are actively promoted to public and private research funding bodies […].

[…] the NCCHTA […] contracts review groups to undertake the HTA reports used to inform NICE guidance, […]. The HTA reports identify areas where further research is required, and this information is used by the NCCHTA, together with research recommendations from other sources, to establish a list of research topics. Informal descriptions of the research questions (vignettes) are then submitted to the relevant advisory panel and an HTA Prioritisation Strategy Group, which prioritize the topics according to their importance, urgency and potential cost […]. Although this system appears to work well, the separation of research prioritization and commissioning from reimbursement decisions is not ideal […].

Canadian experience: A pilot project in Alberta, Canada

In Alberta, a unique situation exists in which an independent, government-sponsored HTA program is housed within a provincial research funding organization, the Alberta Heritage Foundation for Medical Research (AHFMR). […] Funding applications are assessed for their feasibility, importance and originality by external reviewers with expertise in the relevant field. The applications are then ranked by an AHFMR committee of reviewers […]. While the AHFMR designates broad research priority areas for different categories of funding, there is no mechanism for systematically and objectively identifying evidence gaps. Therefore, a pilot project was undertaken to

1. assess how well HTA reports published by the AHFMR HTA program could identify evidence gaps and delineate the concomitant research gaps and
2. develop a process for distilling researchable questions from the research gaps identified by an AHFMR HTA report to inform the research funding programs of the AHFMR.

OBJECTIVE 1: TO ASSESS HOW WELL AHFMR HTA REPORTS DELINEATE RESEARCH GAPS

An internal assessment was conducted of a consecutive series of HTA reports […] published by the HTA program between 2002 and 2003 […]. All bat one of the reports were produced in response to questions posed by health ministry policy makers, who are the main clients of the HTA program.

The problem of limited evidence was reported severally in the reviewed HTA reports, but evidence and research gaps were not consistently or clearly highlighted and were often embedded within lengthy discussion sections. More useful information on evidence gaps was gleaned from personal interviews with the HTA researchers than from reading their reports […].

OBJECTIVE 2: TO DEVELOP A PROCESS FOR DISTILLING RELEVANT RESEARCHABLE QUESTIONS FROM THE RESEARCH GAPS IDENTIFIED IN AHFMR HTA REPORTS

Two questionnaires were developed, one for researchers and one for clinicians/policy makers, to simultaneously formulate researchable

questions from the research gaps uncovered in HTA reports and to capture the different perspectives and priorities of a representative cross-section of stakeholders […]. […] The questionnaires focused on two HTA reports […] published by the HTA program on chronic pain and were piloted with an Information Sharing Group on Chronic Pain […].

The results were compiled into a list of research questions on chronic pain, reflecting the three stakeholder perspectives (health services research, clinical and policy), along with the names of potential researchers identified in the questionnaire as being willing to undertake the research. […] The consensus was that the process held promise and could work on a case-by-case basis. In addition, the following comments were made:

• A dedicated group needs to be identified that will have the commitment to shepherd the process from start to finish. It is important for the HTA program to link the stakeholders.

• Research in Alberta is largely investigator driven, so a paradigm shift is required. The research gaps project may be an important step in achieving this.

• The level of complexity of the process should reflect the research dollars available for funding.

• Using HTAs to identify research gaps could provide the AHFMR and its stakeholders with a mechanism for pinpointing research needs.

Moving from Theory to Practice

Implementation issues

PRIORITIZING THE RESEARCH QUESTIONS

Priority should be given to medical and health services research that is most likely to improve health and the performance of the healthcare system […]. Since it is unrealistic to expect that all HTA reports will automatically undergo the process outlined to identify research gaps, formalized, objective criteria for prioritizing which HTA reports are chosen must be developed. Also, in cases where a number of researchable questions are identified from an HTA with no clear front runner, there must be an established process and criteria for prioritizing these questions.

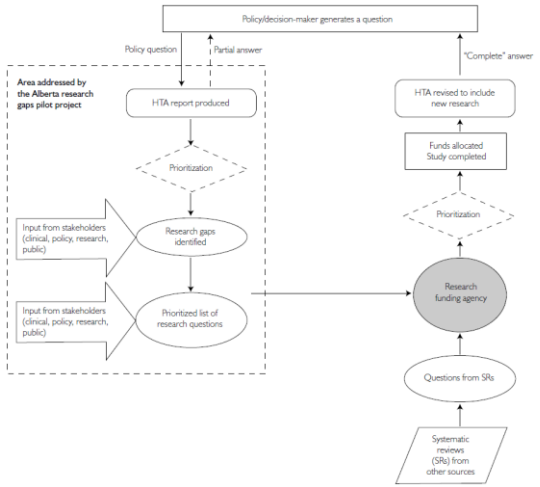
Assembling a representative group that can provide a balanced review of the funding proposals may be challenging. In addition, the entire process must be shepherded to ensure that it is timely, that the proposals focusing on the research gaps do not get side lined by other funding priorities and that the needs of all stakeholders are taken into account in the research design. Questions identified in HTA reports, which are often based on international research, must also be contextualized against local needs, the extant research capacity and the mandate of the funding agency. […] consideration should be given to the question of pursuing an out-of-province collaboration and possible sources of additional research dollars. The role of other Canadian HTA agencies in coordinating and establishing research policy also needs to be ascertained to ensure a unified strategy […].

To ensure acceptance by stakeholders in the research community, additional targeted funds may need to be found for identified research gaps rather than shifting money within the pool of currently available dollars. Care must also be taken to ensure that explanatory trials and basic curiosity-driven research are not underfunded as a result of an increased focus on policy-related research […].

[…] ESTABLISHING A FEEDBACK LOOP

For the process of identifying research gaps to be effective, the funded research needs to be fed back into another HTA, or some other mechanism, to provide the answer to the decision-maker who originally asked the question and close the loop (Figure 3).

FIGURE 3. Flow diagram of the conceptual framework for the feedback loop involving research gaps identified by HTAs



Main documents cited

Notes

ID	32 Stamenkovic 2011
Document type	handbook
Document feature	Methodological guide on post-registration studies
Agency	HAS
Authors	Stamenkovic S, Vray M et al
Title	Les études post-inscription sur les technologies de santé (médicaments, dispositifs médicaux et actes) November 2011
Formulating Assessment Question	
Identifying research gaps	
From Research Gaps to Research Needs	A. Premier objectif : Décrire les conditions d'utilisation d'un produit de santé 1. Les différents types d'études réalisables Pour décrire les conditions d'utilisation d'un produit de santé (médicament ou dispositif) en conditions réelles d'utilisation et en vérifier le bon usage, il est logique de recourir aux études observationnelles descriptives. _ Les études transversales sans suivi des patients Lorsque l'objectif est de décrire les caractéristiques des patients et des conditions initiales de prescription, le plus souvent une étude transversale avec recueil de données à un instant donné peut être menée sans suivi ultérieur des patients. Il faudra s'assurer toutefois que les conditions de prise en charge des patients s'inscrivent dans un contexte relativement stable, afin que les résultats obtenus soient représentatifs de la prise en charge effective des patients. Dans le cas contraire, l'étude transversale pourra être répétée dans le temps afin de pouvoir décrire les changements intervenus ou un schéma d'étude avec suivi des patients (étude prospective) pourra être choisi. _ Les études prospectives avec suivi des patients Lorsque des données de suivi sont nécessaires (par exemple si l'on veut connaître la durée de traitement, l'observance des patients, les complications reliées à l'acte associé au dispositif médical, les arrêts de traitement et leurs motifs, etc.), un recueil prospectif avec suivi des patients doit être réalisé. Les aspects

méthodologiques importants à prendre en compte dans ce type d'étude sont développés dans le chapitre consacré aux études épidémiologiques observationnelles.

2. Etudes sur bases de données versus études spécifiques

Quand les données nécessaires sont directement disponibles à partir de bases de recueil déjà existantes, comme, dans le cas du médicament, la base de l'Assurance maladie (Système national d'informations interrégimes de l'Assurance maladie : SNIIRAM), notamment son Echantillon général des bénéficiaires (EGB) ou les panels « commerciaux » appartenant à des sociétés privées ou, dans le cas du dispositif, les données du Programme de médicalisation des systèmes d'information (PMSI), il est intéressant d'y avoir recours.

Les bases de données SNIIRAM, véhiculent, par l'intermédiaire du PMSI, l'ensemble des informations médicales signifiantes, saisies par les médecins au cours des hospitalisations (codes diagnostiques en CIM10 – Classification internationale des maladies 10e version - du motif d'hospitalisation et des principaux antécédents des patients, les actes techniques réalisés…). Elles comportent également l'ensemble des informations se rapportant à la prise en charge des patients en médecine de ville : identification, en Code CIP – Code identifiant de présentation - , des médicaments avec leurs dates de prescription et de délivrance, identification des examens biologiques réalisés et des actes techniques des médecins. Ces bases de données comportent également l'identification des maladies chroniques, en code CIM10, sous réserve qu'elles soient prises en charge à 100 % par l'Assurance maladie dans le cadre d'une Affection de longue durée (ALD). A contrario, il ne faut pas surestimer la possibilité de recourir en routine à ces données pour réaliser des études post-inscription. D'une part, les informations cliniques ne sont pas, aujourd'hui, enregistrées dans ces bases ; d'autre part, leur exploitation statistique s'avère encore particulièrement complexe. Cette complexité est liée à la nature même du SNIIRAM puisque les informations qui le constituent n'ont pas été recueillies dans un objectif d'étude mais dans le but de suivre les prestations versées aux assurés et aux professionnels de santé. Leur architecture, leur contenu et les référentiels informatiques intègrent donc des contraintes de production et évoluent avec la législation. C'est la raison pour laquelle, la capacité à réaliser des traitements statistiques fiables suppose d'être en mesure de connaître les modalités de gestion des dossiers de remboursement ainsi que les pratiques de saisie des informations par les techniciens des caisses et les professionnels de santé.

Enfin, il peut être tout à fait envisageable de répondre à la demande des institutionnels en combinant les sources de données, les bases de données et le recueil ad-hoc.

Dans le cas d'études prospectives, le recours à des cohortes et à des registres déjà existants est également encouragé (18). A ce sujet, le portail Epidémiologie - France6 a pour objectif de recenser et de décrire le contenu des bases.

B. Deuxième objectif : Mesurer l'impact d'un produit de santé sur la morbi-mortalité des patients en conditions réelles d'utilisation

1. Les différents types d'études réalisables

Pour répondre à la question de l'impact sur la morbi-mortalité des patients d'un produit de santé en conditions réelles d'utilisation, différents types d'études peuvent être proposés à la CT et à la CNEDiMTS : essai pragmatique, étude épidémiologique observationnelle comparative (étude de cohorte, étude castémoins, etc.), modélisation (32-36). Il n'existe aucune méthode parfaite, chacune présentant des avantages et des inconvénients. Aussi, le choix de la méthode doit être discuté et argumenté en fonction du contexte dans lequel s'inscrit l'étude (pathologie et produit de santé étudiés, contraintes administratives et réglementaires, etc.).

_ Les essais pragmatiques

Les essais pragmatiques, qui prévoient une allocation aléatoire des stratégies thérapeutiques, ont pour objectif d'évaluer leur intérêt dans les conditions effectives dans lesquelles ils sont utilisés en pratique (37-49). Les sujets qui sont inclus dans l'essai pragmatique ne font pas l'objet de critères de sélection aussi stricts que dans l'essai explicatif « classique », leurs conditions de suivi sont plus proches de la pratique courante et, en général, les critères de jugement reposent sur la mortalité ou la morbidité (50-52).

_ Les études épidémiologiques observationnelles

Dans les études épidémiologiques observationnelles, on ne fait, en théorie, qu'observer une population ou un phénomène sans intervenir, ou en intervenant le moins possible, sur leur évolution naturelle.

Les études à visée étiologique permettent de comparer des groupes de sujets traités aux sujets non traités (ou traités par une alternative), afin de mettre en évidence l'association entre le traitement considéré (médicament ou dispositif) et l'évolution de la pathologie. Elles semblent donc naturellement adaptées à la mesure de l'impact de morbi-mortalité ou de qualité de vie d'un médicament ou d'un dispositif en conditions réelles d'utilisation (53-55).

V. Focus sur les études épidémiologiques observationnelles : points méthodologiques

A. Représentativité/exhaustivité, données manquantes et sujets perdus de vue

A côté du contrôle des biais - qui sera abordé en seconde partie - les points méthodologiques qu'il est crucial de prendre en compte, pour que les résultats des études soient exploitables, concernent la représentativité de l'échantillon de l'étude par rapport à l'ensemble de la population, la limitation des sujets perdus de vue ainsi que des données manquantes (69-79).

1. Obtenir un échantillon représentatif ou assurer l'exhaustivité

Lorsqu'elles reposent sur la sélection d'un échantillon de sujets, la représentativité de cet échantillon est un élément primordial dans les études épidémiologiques. Elle doit permettre de s'assurer que les patients recrutés dans l'étude sont représentatifs de l'ensemble des patients pris en charge en France. Cette représentativité peut être obtenue soit par tirage au sort des unités incluses dans l'étude (centres, médecins et/ou patients), soit par méthodes statistiques (quotas). Cette représentativité doit s'appliquer quel que soit le

	type d'études choisi, qu'il s'agisse d'études spécifiques ou d'études effectuées à partir de panels existants. Les résultats des études ayant utilisé des panels commerciaux, avec recours à des écrans complémentaires, ont montré qu'en pratique un tel système fonctionnait mal du fait d'un taux trop faible de participation des médecins. Dans le cas où l'étude porte sur un échantillon de sujets, il est recommandé de mettre en place, parallèlement à l'étude, des registres de médecins et de patients afin de comparer les caractéristiques : les médecins ayant accepté à ceux ayant refusé de participer à l'étude, les médecins actifs à ceux n'ayant pas inclus de patients, les patients inclus dans l'étude à ceux vus en consultation. A chaque niveau, les motifs de non participation doivent être recueillis et décrits. 3. Limiter les données manquantes Un problème également crucial dans ce type d'étude est lié aux données manquantes (80). Il est toujours impératif de les limiter au maximum. En effet, dans ces études épidémiologiques, il est impossible d'écarter le fait que la donnée manquante ne soit pas informative. Aussi, le protocole doit prévoir un contrôle-qualité adéquat des données, par exemple un programme de gestion des données avec envoi de requêtes informatiques automatiques vers les médecins en cas de données manquantes ou d'incohérence. Des vérifications sur site doivent être prévues afin de vérifier les informations recueillies, sur l'ensemble des dossiers ou, plus généralement, sur un échantillon tiré au sort. Dans tous les cas, il faut décrire les caractéristiques des patients avec des données manquantes, en essayant si possible d'en préciser les raisons (perdus de vue, refus de répondre, censure, etc.) et de les comparer aux autres patients de l'étude.
Main documents cited	
Notes	

Record ID	33 Stone 2002
Document type	Article
Document feature	Journal article
Agency	
Authors	Stone P
Title	Deciding upon and refining a research question *Palliative Medicine* 2002; 16: 265± 267
Formulating Assessment Question	The process of deciding upon and refining a research question is one of the most basic elements in study design. If the research question is not well considered then the subsequent labour invested in choosing the research methodology, collecting and analysing the data, and writing-up the results will be wasted Why is it important to have a clearly defined research question? To promote clarity of thought To produce the study protocol To guide data-analysis To help ensure publication How is the research question formulated? (The problem, The intervention, A comparison (if appropriate or relevant), The outcome of interest) . What other considerations need to be taken into account when deciding upon the research question? Is the research proposal important? - Is it possible to answer the research question using ethical methods? Is answering the research question practical?(A research question may be well structured, important, and ethical but nonetheless be impractical to answer because there are insufficient resources to undertake the study), Are subjects likely to consent to participation in the study?
Identifying research gaps	
From Research Gaps to Research Needs	
Main documents cited	
Notes	

Record ID	34 Thabane 2009
Document type	Article
Document feature	Abstract Purpose The success of any research process relies, in part, on how well investigators are able to translate a clinical problem into a research question—a task that is not so simple for novice investigators. […] This paper describes the use of the PICOT structure in framing research questions and examines PICOT criteria as applied to the anaesthesia literature. […]
Agency	
Authors	Thabane L, Thomas T, Ye C, Paul J
Title	Posing the research question: not so simple Can J Anesth/J Can Anesth (2009) 56:71–79
Formulating Assessment Question	How to frame the research question [pp.73-74] *The PICOT approach* What is the research question? Anyone reading the report should be able to answer this first question. The general principle is that the title should reflect the research question; if it does not, the abstract should, followed by the text. The question should be framed in such a way that it is easily understood and can be rephrased in the reader's own words. First introduced in 1995, the PICO format, later expanded to PICOT, is now a widely recommended strategy for framing research questions. Since its inception, several authors have advocated its use in framing research questions in different areas […] The PICOT approach requires that the framing of the research question specify the target Population, the Intervention of interest, the Comparator intervention, key Outcomes, and the Time frame over which the outcomes are assessed. The population can be described by certain eligibility criteria, qualifying disease condition of interest, or geographic location. The intervention is a controlled maneuver or exposure that can be manipulated and is often a new, experimental, or innovative approach. The primary goal may be to compare the intervention with an alternative standard (control), placebo (no intervention), or approach. The effect is evaluated by comparing outcomes in the underlying intervention groups. Note; the allocation of patients into intervention groups need not be random, although random allocation is generally considered the best approach in generating evidence. It is also important to state the key outcomes, which may be either clinical or process outcomes. […] The assessment of outcomes is completed over a specified time frame that is chosen (based on clinical considerations) to create the optimal difference between the intervention and the control groups (i.e., intervention effect). It is worth noting that the PICOT format is generally applicable to comparative studies or studies of association between exposure and outcome(s). Other useful approaches exist in the literature. […] Application of the PICOT approach: examples referring to the literature [p.77]

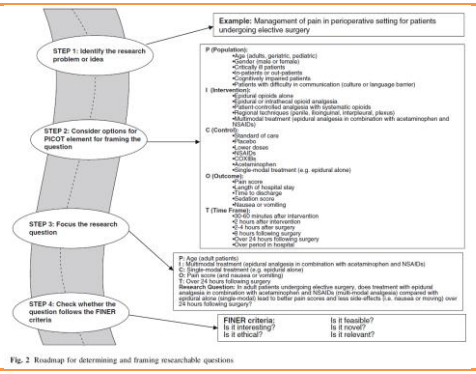


Fig. 2 Roadmap for determining and framing researchable questions

Identifying research gaps	
From Research Gaps to Research Needs	How to identify a research question [, p.72] In general, a good research question should be appropriate, meaningful, and purposeful. […] The FINER criteria state that a research question must be feasible, interesting, novel, ethical, and relevant. Knowing the desirable attributes of a good question and understanding how to achieve them can facilitate identifying the clinical problems that are worth the expenditure of intellectual energy and resources. This may be easy for experienced researchers, but novice or new researchers would need guidance. Here we mention some of the common strategies used to identify clinical research problems. (1) Relying on one's own clinical experience or practice; (2) discussing issues with other researchers at professional meetings; (3) following developments in the literature and identifying gaps in the literature; (4) discussing issues with a mentor; (5) being alert to new ideas and technological advances; (6) brainstorming with friends and colleagues; (7) keeping the imagination roaming; (8) searching information about the national and global burden of disease; and (9) using focus groups.

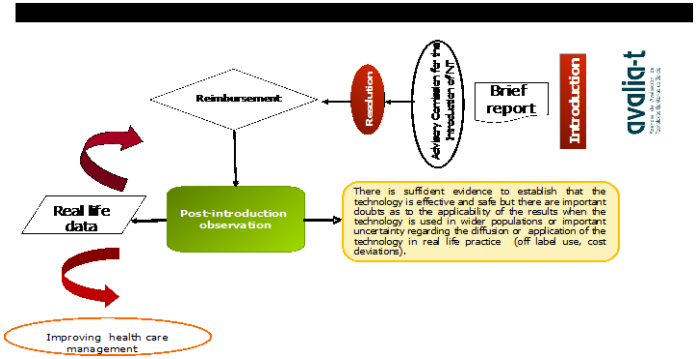
Main documents cited	**Table 5** Resources **Session topic** — **Key references** How to identify research problems or ideas • Articles a. Buelow JM. Identifying a Researchable Problem. Clin Nurs Specialist 2006;20(4):175 b. Chulay M. Good Research Ideas for Clinicians. AACN Adv Crit Care 2006;17(3):253–265 • Text books a. Haynes BR, Sackett DL, Guyatt GH, Tugwell P. *Clinical Epidemiology: How to do Clinical Practice Research*. Third Edition. Lippincott Williams & Wilkins, Philadelphia, PA 2006 b. Hulley SB, Cummungs SR, Browner WS, Grady D, Newman TB. *Designing Clinical Research, 3rd Edition*. Lippincott Williams & Wilkins, Philadelphia, PA 2007 c. DePoy E, Gitlin LN. Introduction to Research: Understanding and Applying Multiple Strategies. 3rd Edition. Elsevier Mosby: Philadelphia, PA 2005 How to frame questions using PICOT (see Table 2) • Articles a. Heddle NM. The research question. Transfusion 2007 Jan;47:15 b. Johnston L, Fineout-Overhold E. Teaching EBP: "Getting from Zero to One." Moving from Recognizing and Admitting Uncertainties to Asking Searchable, Answerable Questions. *Worldviews on Evidence-Based Nursing* 2005;2(2):98 c. Stone PW. Popping the (PICO) question in research and evidence-based practice. Appl Nurs Res 2002 Aug;15(3):197–198 d. McKibbon KA, Marks S. Posing Clinical Questions: Framing the Question for Scientific Inquiry. AACN Clinical Issues 2001 Nov;12(4):477–481 e. Geddes J. Asking structured and focused clinical questions: essential first step of evidence-based practice. Evidence-Based Mental Health 1999;2:35–36 f. Counsell C. Formulating Questions and Locating Primary Studies for Inclusion in Systematic Reviews. Ann Inter Med. 1997 Sep;127(5):380–387 g. Durbin Jr CG. How to Come Up With a Good Research Question: Framing the Hypothesis. Respiratory Care 2004 Oct;49(10):1195 • Text books a. Haynes BR, Sackett DL, Guyatt GH, Tugwell P. *Clinical Epidemiology: How to do Clinical Practice Research*, 3rd Edition. Lippincott Williams & Wilkins, Philadelphia, PA 2006 b. Hulley SB, Cummungs SR, Browner WS, Grady D, Newman TB. *Designing Clinical Research*, 3rd Edition. Lippincott Williams & Wilkins, Philadelphia, PA 2007 c. Systematic Reviews: Synthesis of Best Evidence for Health Care Decisions (eds. Cynthia Mulrow, Deborah Cook). American College of Physicians: Philadelphia, PA 1998 • Internet a. http://library.wcsu.edu/web/assistance/research/nursing/tutorial/c_picot/: Western Connecticut University Library resources b. http://consortiumlibrary.org/hsis/researchaids/handouts/ebp.php: Health Sciences Information Services Consortium library resources Framing research questions using other frameworks • *PICOS*: (stands for *P*atient population or *P*roblem, (22)*I*ntervention (treatment/test), *C*omparison (group or treatment), *O*utcomes, and *S*etting or study type) a. http://consortiumlibrary.org/hsis/researchaids/handouts/ebp.php: Health Sciences Information Services Consortium library resources • *PESICO* (stands for *P*erson (or problem), *E*nvironments, *S*takeholders, *I*ntervention, *C*omparison and *O*utcome) a. Schlosser RW, Koul R, Costello J. Asking well-built questions for evidence-based practice in augmentative and alternative communication. J Commu Dis 2007 Jun;40(3):225–238 Identifying research questions in Anesthesia • Articles a. Pronovost PJ, Berenholtz SM, Dorman T, Merritt WT, Martinez EA, Guyatt GH. Evidence-based medicine in anesthesiology. Anesth Analg 2001 Mar;92(3):787–94
Notes	

Record ID	35 Varela Lema 2007
Document type	Handbook
Document feature	"The guideline's principal aim is to establish a structured methodological framework for observation of new technologies after their introduction into general clinical practice. The specific objectives of this guideline are: 1. to establish a methodological tool for identifying and prioritising new health technologies eligible for post-introduction observation; 2. to identify possible data-collection instruments and assess their usefulness and feasibility in post-introduction observation of new technologies; and, 3. to establish the principal outcome indicators for assessing different aspects considered in post-introduction observation." [p.33]
Agency	avalia-t - SPAIN
Authors	Varela Lema L, Ruano Raviña A, Cerdá Mota T, Blasco Amaro JA, Gutiérrez Ibarluzea I, Ibargoyen Roteta N, et al.
Title	Post-introduction Observation of Health Technologies. Methodological guideline. Abridged version. Quality Plan for the National Health System. Galician Health Technology Assessment Agency; 2007. HTA Reports: avalia-t No. 2007/02
Formulating Assessment Question	
Identifying research gaps	
From Research Gaps to Research Needs	Prioritisation of new health technologies for post-introduction observation The prioritisation tool (PriTecTools) consists of a web application which can be accessed via the web page of avalia-t (http://avalia-t.sergas.es/). This tool lists the prioritisation criteria grouped by domains and allows for up to 50 different technologies to be scored and compared. By scoring the prioritisation criteria from 1 to 9, the tool automatically calculates the score for each domain and the total score for each technology, furnishing the absolute and weighted scores (absolute; base 100, i.e., transformation of weighted score on a scale of 0 to 100; % total score). Furthermore, it furnishes the results in a comparative manner for the different technologies selected. PriTec.observation enables reports to be generated and any data and results obtained in situ to be stored in the form of tables and figures, so that these may be used in subsequent work sessions. No data entered into the application are stored on the web, which guarantees the total confidentiality of any data introduced. The tool is available in both S Spanish and English. A full explanation on the tool's operation and score calculation can be found on the web application Data-collection instruments At present, post-introduction observation could be undertaken by means of clinical registries, using questionnaires completed by clinicians for collecting data of an administrative and clinical nature at the time of short-term intervention/treatment and telephone surveys of patients for medium/long-term follow-up. In the near future, electronic medical records could be the tool of choice for post-introduction

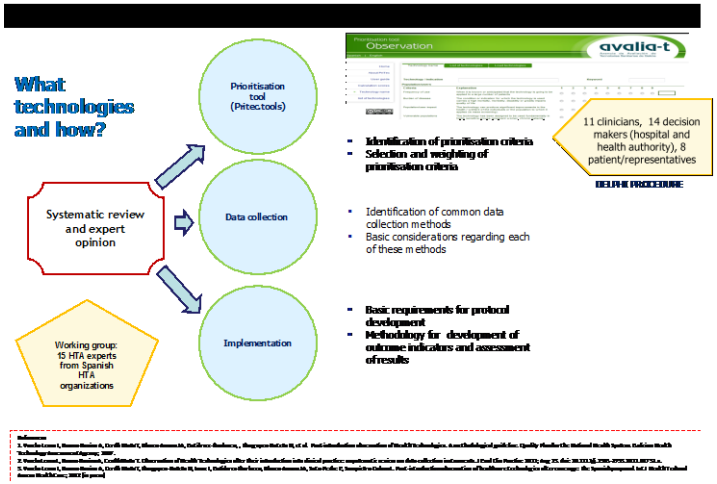
	observation. Implementation and outcome indicators The outcome indicators proposed are valid to identify and measure important deviations in the utilization of new technologies once they are diffused within the health care system and identify effectiveness and safety problems.
Main documents cited	
Notes	

Record ID	**36** **Varela Lema 2012**
Document type	Power point presentation
Document feature	Sixteen slide presentation held at the "9th HTAi - Bilbao. 26th June 2012"
Agency	avalia-t
Authors	Varela Lema L, Queiro Verdes T, López García M, Puñal Riobóo J
Title	Post-introduction observation of health care technologies after coverage - The Galician experience with percutaneous aortic valve replacement (TAVIs) 9th HTAi - Bilbao. 26th June 2012"
Formulating Assessment Question	
Identifying research gaps	
From Research Gaps to Research Needs	

Post-introduction observation conditional coverage scheme



Methodological guideline developed within the National Health Quality Plan



Main documents cited
Notes

Record ID	37 Velentgas 2013
Document type	**Handbook**
Document feature	**User's guide**
Agency	**AHRQ**
Authors	**Velentgas P, Dreyer NA, Nourjah P, Smith SR, Torchia MM, eds.**
Title	**Developing an Observational CER Protocol: A User's Guide** **AHRQ Publication No. 12(13)-EHC099. Rockville, MD: Agency for Healthcare Research and Quality; January 2013.** **www.effectivehealthcare.ahrq.gov/Methods-OCER.cfm.**
Formulating Assessment Question	Table 1.1. Framework for developing and conceptualizing a CER protocol

Domain	Relevant Questions
Identify Decisions, Decision makers, Actions, and Context	What health care decision or set of decisions are being considered about the comparative effectiveness, risks, or benefits of medical treatment, management, diagnosis, or prevention of illness and injury? Who are the decision makers and in what context is the decision being made?
Synthesize the Current Knowledge Base	What is known from the available scientific evidence and what is unknown because the evidence is insufficient or absent?
Conceptualize the Research Problem	What research questions or series of questions are critical to reduce decisional uncertainty and gaps in the current knowledge base?
Determine the Stage of Knowledge Development	What stage of knowledge is the study designed to address?
Apply PICOTS Framework	For a particular question, what study populations, interventions, comparisons, outcomes, time frame, and settings are most important to the decision maker(s) in weighing the balance of harms and benefits of action? Are some research questions easier to operationalize than others? Are intervention effects expected to be

	homogeneous or heterogeneous between different population subgroups?
Discuss Evidentiary Need and Uncertainty	What level of new scientific evidence does the decision maker need to make a decision or to take action?
Specify the Magnitude of Effect	What is a clinically meaningful difference in the study endpoints from the perspective of the decision maker? What is a meaningful difference from the patient's perspective (e.g., symptoms interfering with work or social life)?

Conceptualizing the Research Problem

In order to conceptualize the problem, stakeholders and other experts should be asked to describe the potential relationships between the intervention and important health outcomes. This description will help researchers develop preliminary hypotheses about the stated relationships. Likewise, stakeholders, researchers, and other experts should be asked to enumerate all major assumptions that affect the conceptualization of the research problem, but will not be directly examined in the study. These assumptions should be described in the study protocol and in reporting final study results. By clearly stating the assumptions, protocol reviewers will be better able to assess how the assumptions may influence the study results. Based on the conceptualization of the research problem, investigators and stakeholders should make use of applicable scientific theory in designing the study protocol and developing the analytic plan. Research that is designed using a validated theory has a higher potential to reach valid conclusions and improve the overall understanding of a phenomenon. In addition, theory will aid in the interpretation of the study findings, since these results can be put in context with the theory and with past research. Depending on the nature of the inquiry, theory from specific disciplines such as health behaviour, sociology, or biology could be the basis for designing the study. In addition, the research team should work with stakeholders to develop a conceptual model or framework to guide the implementation of the study. The following list of questions may be useful for defining and describing a study's conceptual framework in a CER protocol:

- What are the main objectives of the study, as related to specific decisions to be made?
- What are the major assumptions of decision makers, investigators, and other experts about the problem or phenomenon being studied?
- What relationships, if any, do experts hypothesize exist between interventions and outcomes?
- What conceptual model will guide the study design and interpretation?

    What is known about each element of the model?

Can relationships be expressed by causal diagrams?	
Identifying research gaps	While the primary aim of research is to produce new knowledge, the Normand and McNeil concept of evidence emphasizes that research helps create knowledge by reducing uncertainty about outcomes. However, rarely, if at all, does research eliminate all uncertainty around most decisions. In some cases, successful research will answer an important question and reduce uncertainty related to that question, but it may also increase uncertainty by leading to more, better informed questions regarding unknowns. As a result, nearly all decisions face some level of uncertainty even in a field where a body of research has been completed. This distinction is also critical because it helps to separate the research and subsequent actions that decision makers may take based on their assessment of the research results. Those subsequent actions may be informed by the research findings but will also be based on stakeholders' values and resources. Hence, as the definition by Normand and McNeil implies, research generates evidence but stakeholders decide whether to act on the evidence. Scientific evidence informs decisions to the extent it can adequately reduce the uncertainty about the problem for the stakeholder. The following questions are suggested for discussion with stakeholders to help elicit the amount of uncertainty that is acceptable so that the study design can reach an appropriate level of evidence for the decision at hand: • What level of new scientific evidence does the decision maker need to make a decision or take action? • What quality of evidence is needed for the decision maker to act? • What level of certainty of the outcome is needed by the decision maker(s)? • How specific does the evidence need to be? • Will decisions require consensus of multiple parties?
From Research Gaps to Research Needs	In designing a new study, investigators should conduct a comprehensive review of the literature, critically appraise published studies, and synthesize what is known related to the research objectives. Specifically, investigators should summarize in the protocol what is known about the efficacy, effectiveness, and safety of the interventions and about the outcomes being studied. Furthermore, investigators should discuss measures used in prior research and whether these measures have changed over time. These descriptions will provide background on the knowledge base for the current protocol. It is equally important to identify which elements of the research problem are unknown because evidence is absent, insufficient, or conflicting. When reviewing the literature, investigators and stakeholders should identify the most relevant studies and guidelines about the interventions that will be studied. This will allow readers to understand how new research will add to the existing knowledge base. Furthermore, clinical experts should be consulted to help identify gaps in current knowledge based on their expertise and interactions with patients
Main documents cited	
Notes	

Record ID	38 Vlassov
Document type	Articles_reports
Document feature	letter
Agency	
Authors	Vlassov V
Title	How to formulate research recommendations BMJ VOLUME 333 28 OCTOBER 2006
Formulating Assessment Question	
Identifying research gaps	
From Research Gaps to Research Needs	The recommendation “no further research is needed” is necessary to protect patients from harmful or useless research and to save limited resources for clinical research. I searched Cochrane reviews for their recommendations, and found that only 17% of reviews do not recommend further research. The most serious reason for not recommending “no further research” does not seem to be the absence of the appropriate format of recommendations, but rather the desire to avoid harm to the authors of the original research and damage to the field of their own research
Main documents cited	
Notes	

Annex D
Examples of practical application of the process

Section A:

Example - Innovative Radiation Treatment in Cancer (Image guided Radiation Treatment (IGRT/ Intensity modulated Radiation treatment-IMRT) - ASSR-RER

An HTA report on new systems of Image Guided Radiation Therapy (Tomotherapy and Accelerators with Cone-Beam CT) associated with Intensity Modulated Radiation Therapy (IGRT/IMRT) was commissioned by the Regional Health Authority to the Agency for Health and Social Care of the Emilia-Romagna Region (ASSR-RER) in 2010 (Ballini 2010b).

Main declared objectives were to assess potential clinical benefits and establish criteria of appropriate use, to critically appraise results of published research, to evaluate economic and organizational impact of the technology and to identify recommendations for clinical research.

A panel of regional experts from several disciplines (radiotherapy, medical physics, oncology, nuclear medicine, radiology, statistics, economics, epidemiology and health research methodology) was convened to establish the information necessary to determine the clinical role of IGRT/IMRT, assess results of scientific literature, identify research gaps that need to be filled, in order to complete the technology's evidence profile and formulate recommendations for further research. To achieve these tasks the panel agreed on the following definition of the clinical rationale for IGRT/IMRT: a better correction for set up errors and organs' motion and a consequent more accurate dose targeting can decrease toxicity and/or increase clinical effectiveness of radiation treatments with radical intent of tumors in proximity of vital organs. The comparator was chosen to be any conformal radiotherapy with bi-dimensional image acquisition. Based on the above defined clinical rationale, which considers only radiation treatments with radical intent of tumors in proximity of vital organs, the panel agreed to evaluate the role of IGRT/IMRT only for the following tumors: prostate, head and neck, lung, brain and pancreas.

We report the assessment questions developed for intended clinical indication in prostate, lung and head & neck cancer :

Prostate Does IGRT/IMRT radical radiation treatment for patients with low or intermediate risk prostate cancer decrease toxicity compared to conformal radiotherapy with bi-dimensional image acquisition?

Does IGRT/IMRT radical radiation treatment, with a higher dose per fraction or hypofractionation, for patients with low or intermediate risk prostate cancer decrease toxicity and increase clinical efficacy compared to conformal radiotherapy with bi-dimensional image acquisition?

Lung Does IGRT/IMRT radical radiation treatment with hypofractionation for patients with T1 T2 N0 MO inoperable lung cancer, or patients with stage IIA,IIIA+B lung cancer, or patients with metastatic lung cancer (max 5cm) increase clinical efficacy without increasing toxicity compared to conformal radiotherapy with bi-dimensional image acquisition?

Head&Neck Does IGRT/IMRT radiation treatment with radical intent with hypofractionation - exclusive or associated with chemotherapy - in patients with any type of head and neck cancer, excluding those of the larynx, increase clinical efficacy and decrease toxicity compared to conformal radiotherapy with bi-dimensional image acquisition?

Evidence Profile tables were drawn for each question and Table 1 reports one example related to radical radiation treatment, with a higher dose per fraction, for patients with low or intermediate risk prostate cancer.

Table Annex D.1: STEP 1 - Evidence Profile for IGRT/IMRT in low-/intermediate-risk prostate cancer

Rationale				
A better correction for set-up errors and organs' motion and a consequent more accurate dose targeting can decrease toxicity and/or increase clinical effectiveness of radiation treatments with radical intent of tumors in proximity of vital organs				
Indication : Radical radiation treatment in patients with low (T1-T2 con Gleason score 2-6 e PSA < 10ng/ml) or intermediate (T2b-T2c con Gleason score 7 o PSA 10-20ng/ml)- risk prostate cancer				
Population	**Intervention**	**Comparator**		
Patients with low or intermediate risk prostate cancer with indication to non-surgical radical treatment	IGRT/IMRT radical radiation treatment, with hypofractionation with >dose per fraction	Radical radiation treatment with conformal radiotherapy with bi-dimensional image acquisition		
Domain: Safety				
Study Designs : **Randomized Controlled Trials, Prospective Non-Randomized Controlled/Uncontrolled Trials**				
Outcome- level of importance 1	**Outcome - level of importance2**	**Outcome -level of importance 3**	**Outcome- level of importance 4**	**Outcome - level of importance 5**
Acute gastrointestinal toxicity Expected < 15%	Acute genitourinary toxicity Expected < 38%-51%	Late gastrointestinal toxicity Expected ≤ 5%	Late genitourinary toxicity Expected ≤ 3%	Sexual dysfunctions Expected < 40-50%
Domain: Effectiveness				
Study Designs : **Randomized Controlled Trials**				
Outcome- level of importance 1	**Outcome - level of importance2**	**Outcome -level of importance 3**	**Outcome- level of importance 4**	**Outcome - level of importance 5**
Disease specific survival Expected > 80% (low risk); >65% (intermediate risk)	Local recurrence Expected < 10-15% (low risk); <25% (intermediate risk)	Loco-regional control Expected < 80-85% (low risk); <70% (intermediate risk)	Distant metastases Expected < 10% (low risk); <30% (intermediate risk)	Biochemical failure Expected < 15-20% (low risk); <50% (intermediate risk)

Once the multidisciplinary panel had defined all assessment questions of interest a systematic search was carried out, with no limits for starting date and up to June 2010, on main international websites for Health Technology Assessment (HTA) reports and on Medline and the Cochrane Library for primary studies and systematic reviews.

Results of the literature review were charted on the evidence profiles defined for each assessment question and results for each dimension and outcome were classified according to their level of uncertainty.

Available literature was judged to give sufficient information on technical performance for all assessment questions, with the exception of those related to pancreatic cancer. However the information on safety and clinical efficacy was judged to be very scarce and of very low quality.

Table 2 reports the results of the systematic review of literature mapped against the evidence profile related to low/intermediate -risk prostate cancer.

A graphical representation summarizing the results from all systematic reviews carried out within the HTA report on each assessment question is provided in Fig 1.

Fig. Annex D.1: Number of studies, by study design, for main HTA domain for all tumors

(reproduced from Ballini 2010b)

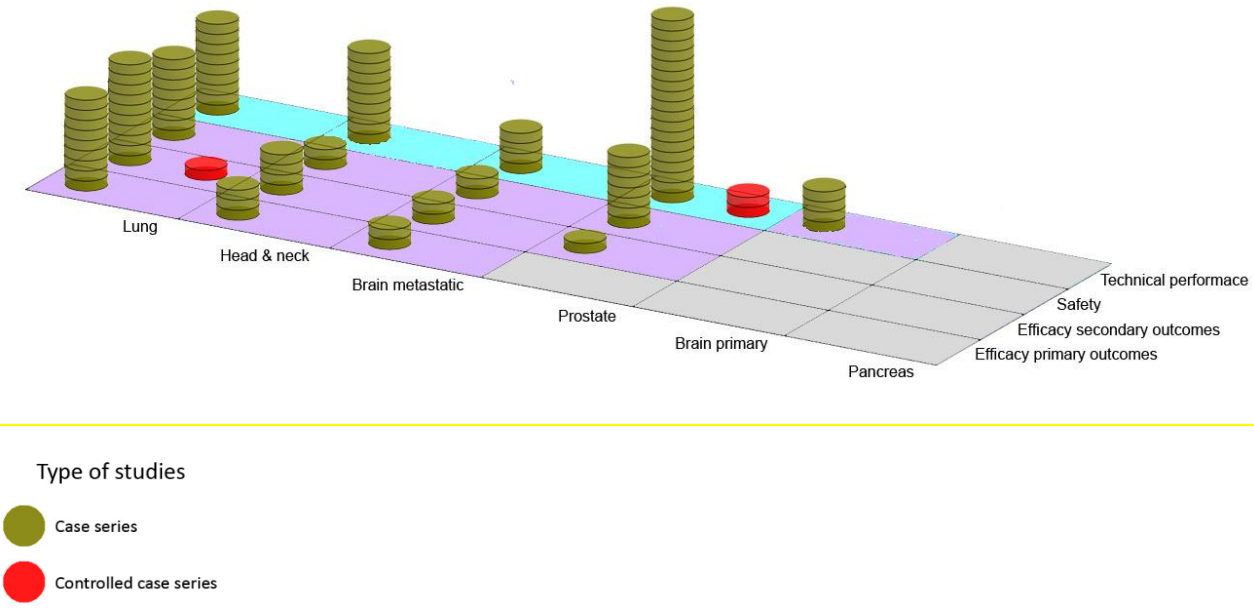


Table Annex D.2: Evidence profile and available evidence for IGRT/IMRT in low-/intermediate-risk prostate cancer

Rationale				
A better correction for set-up errors and organs' motion and a consequent more accurate dose targeting can decrease toxicity and/or increase clinical effectiveness of radiation treatments with radical intent of tumors in proximity of vital organs				
Indication : Radical radiation treatment in patients with low (T1-T2 con Gleason score 2-6 e PSA < 10ng/ml) or intermediate (T2b-T2c con Gleason score 7 o PSA 10-20ng/ml)- risk prostate cancer				
Population	**Intervention**	**Comparator**		
Patients with low or intermediate risk prostate cancer with indication to non surgical radical treatment	IGRT/IMRT radical radiation treatment, with hypofractionation with >dose per fraction	Radical radiation treatment with conformal radiotherapy with bi-dimensional image acquisition		
Domain: Safety				
Study Designs : Randomized Controlled Trials, Prospective Non-Randomized Controlled/Uncontrolled Trials				
Outcome 1	**Outcome 2**	**Outcome 3**	**Outcome 4**	**Outcome 5**
Acute gastrointestinal toxicity Expected < 15%	Acute genitourinary toxicity Expected < 38%-51%	Late gastrointestinal toxicity Expected ≤ 5%	Late genitourinary toxicity Expected ≤ 3%	Sexual dysfunctions Expected < 40-50%
Systematic Review Results*				
4 case series >Grade 2: range 0-25% (Low level of confidence)	4 case series >Grade 2: range 38%-51% (Low level of confidence)	1 case series Grade 3-4: 0 (Low level of confidence)	1 case series Grade 3-4: 0.6% (Low level of confidence)	1 case series 56% (Low level of confidence))
Domain: Effectiveness				
Study Designs : Randomized Controlled Trials				
Outcome 1	**Outcome 2**	**Outcome 3**	**Outcome 4**	**Outcome 5**
Disease specific survival Expected > 80% (low risk); >65% (intermediate risk)	Local recurrence Expected < 10-15% (low risk); <25% (intermediate risk)	Loco-regional control Expected < 80-85% (low risk); <70% (intermediate risk)	Distant metastases Expected < 10% (low risk); <30% (intermediate risk)	Biochemical failure Expected < 15-20% (low risk); <50% (intermediate risk)
Systematic Review Results*				
No studies	No studies	No studies	No studies	1 case series 7% (Low level of confidence)

* Date of search: June 2010

After discussing the results of the systematic review of literature, the panel identified the recommendations on further research taking into consideration: the prevalence and burden of the disease in terms of mortality and morbidity, the available evidence and the potential benefit of the technology in terms of impact on mortality and morbidity. The panel agreed on recommending comparative effectiveness trials capable of producing robust/conclusive results on clinical effectiveness on relevant clinical outcomes for appropriate target patients with no inclusion bias. Examples of recommendations for research formulated at the end of the process are reported below:

- Does radical radiation treatment with IGRT/IMRT with a higher biological dose in hypofraction regimen in patients with low (T1-T2 con Gleason score 2-6 e PSA < 10ng/ml) or intermediate (T2b-T2c con Gleason score 7 o PSA 10-20ng/ml_) risk prostate cancer improve biochemical recurrence without increasing toxicity, compared to treatment with 3D-CRT/IMRT?
- Does radical radiation treatment with IGRT/IMRT with a higher biological dose in hypofraction regiment in inoperable patients with primary lung cancer (T1-T3 e IIIA e B) increase local and loco-regional control without increasing toxicity, compared to treatment with 3D-CRT/IMRT?
- Does radical radiation treatment with IGRT/IMRT with higher dose (not in hypofraction regimen) in patients with head & neck cancer increase local control without increasing toxicity, compared to treatment with 3D-CRT/IMRT?

Section B:

Example -Transcatheter aortic valve implantation (TAVI)

Percutaneous transcatheter aortic valve implantation (TAVI) is an example of a technology that was incorporated into the Galician Health Care Service (Varela Lema 2014), linked to the collection of observational real world data. Bellow we illustrate the uncertainties that presented a high score and were considered by the stakeholders to be crucial and feasible for ascertaining the appropriateness and quality of care and determine the real impact in the health system.

Key uncertainty	Supporting information
Adequacy of diffusion	TAVI patients should be derived to 3 authorized centers
Adequacy of adoption	TAVI should only be adopted in centers that have a cardiac surgery department. TAVI should only be carried out by highly experienced interventional cardiologists and cardiothoracic surgeons. Interventional cardiologists must receive previous training Given the learning curve > 50 procedures/year are recommended.
Adequacy of implementation	The adoption of TAVI requires for the creation of a Multidisciplinary Committee
Off-label use	TAVI is only approved for patients with severe symptomatic aortic valve stenosis who are at very high surgical risk (EuroSCORE > 20) or inoperable patients that have a survival ≥ 1 year.
Adequacy of use	In the absence of evidence guidelines or recommendations on patient selection criteria, the key criteria for deciding which patients are candidates to TAVI are considered by a Multidisciplinary Committee The operability of patients is decided upon in many cases by the frailty and comorbidities that are judged by the surgeon to condition the surgical risk and survival of patients
Acceptability	-

Issue	Considerations regarding real world effectiveness and safety outcomes
Different applications	Appropriateness of patient selection criteria should be determined in all cases by the MD Committee taking into account the detailed clinical history, the anatomic and haemodynamic information (echocardiography), the size of the aortic annulus and degree of calcifications (MDCT measurements), fragility measurements and cognitive function
Different experience	The success of TAVI can greatly depend on the appropriate patient selection, individualizing the bioprosthesis type and size and the vascular access site for each case Operator experience is an important factor in determining TAVI outcomes (procedural success, strokes/transient ischemic attacks, coronary occlusion, pacemaker implantation, vascular complications, cardiac rupture and tamponade, aortic regurgitation, bleeding, aortic dissection, and death) .

Subgroup effectiveness	Outcomes can differ between delivery approaches and different types of devices in use.
Patient susceptibility groups	Especially sensitive groups (elderly patients, very high frailty, chronic lung disease, previous cardiac surgery) are liable of presenting higher complication or adverse event rates.
Patient reported outcomes	The improvement in health-related quality of life in real world settings is highly variable
Unexpected adverse events	High potential for serious periprocedural complications if patients are not adequately selected Unknown long term durability of valves
Risks to health professionals or environment	-

Issue	**Considerations regarding impact**
Organizational or structural impact	The adoption of TAVI requires for the creation of multidisciplinary groups and coordination among groups, and there is uncertainty regarding the real impact on the health care service (length of stay, waiting list, etc.)
Financial impact	The overuse of TAVI could lead to important overcosts the health care system
Ethical, social or legal impact	-

The following areas of investigations were recommended to monitor the performance of TAVI:

1. Do all adopting centers comply with preliminary requirements?
2. Have centers put in place adequate quality assurance standards and indicators?
3. What is the degree of use outside approved indications ?
4. How do utilization rates compare with what was anticipated from the hospital referral population?
5. Do utilization rates differ across centers?
6. How do baseline characteristics of patients differ from published literature?
7. Do baseline characteristics of patients differ among authorized healthcare centers?
8. How does success rate compare to published literature?
9. Does success rate differ among subgroups (centers, prosthesis, vascular access site)?
10. Do baseline characteristics of patients differ for the different prosthesis and vascular access site?
11. How do rate of complications and outcomes compare to published literature?
12. How do outcomes and adverse events differ among subpopulations?
13. What is the frequency of severe periprocedural adverse events (strokes/transient ischemic attacks, coronary occlusion, pacemaker implantation, vascular complications, cardiac rupture and tamponade, aortic regurgitation, bleeding, aortic dissection, and death)?

14. How does health related quality of life compare to published literature?
15. How do length of stay and waiting list compare to what was expected ?
16. What are the long term outcomes and adverse events?
17. What is the long term durability of the valve?
18. How do the financial costs differ from what was anticipated?