eunethta

EUnetHTA JA2
WP7 DELIVERABLE

Evidence submission templates to support production of core HTA information and rapid assessments: report

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Joint Action on HTA 2012-2015

Evidence submission templates to support production of core HTA information and rapid assessments: report

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WP 7 Lead Partner: Haute Autorité de Santé (HAS)
WP Subgroup Coordinator: National Institute for Health and Care Excellence (NICE)

Abbreviations

AGENAS: Agenzia Nazionale per i Servizi Sanitari Regionali
AIFA: Italian Medicines Agency
ASSR: agenzia sanitaria regionale Emilia-Romagna, Italy
CE: Conformité Européene (European Conformity)
COCIR: European Coordination Committee of the Radiological, Electromedical and Healthcare IT Industry
CONSORT: consolidated standards of reporting trials
CRD: Centre for Reviews and Dissemination
EDMA: European Diagnostic Manufacturers Association
EFPIA: European Federation of Pharmaceutical Industries and Associations
EPAR: European Public Assessment Report
EU: European Union
G-BA: Federal Joint Committee, Germany.
GYEMSZI: Gyógyszerészeti és Egészségügyi Minőség- és Szervezetfejlesztési Intézet
HIS: Healthcare Improvement Scotland
HTA: health technology assessment
LBI: Ludwig Boltzmann Institute for Health Technology Assessment, Austria
MD: medical device
MoH Czech Republic: Ministry of Health Czech Republic
MTEP: medical technologies evaluation programme
NCPE: National Centre for Pharmacoeconomics Ireland
NICE: National Institute for Health and Care Excellence
OGYEI: Országos Gyógyszerészeti és Élelmezés-egészségügyi Intézet [National Institute of Pharmacy and Nutrition – formerly GYEMSZI], Hungary
P: pharmaceutical
PIL: patient information leaflet
PRISMA: preferred reporting items for systematic reviews and meta-analyses
REA: relative effectiveness assessment
SG4: subgroup 4
SPC: summary of product characteristics
TA: technology appraisals
UK: United Kingdom
US: United States
WP7: work package 7
ZIN: Zorginstituut Nederland

Contents

Introduction

Aim

This report accompanies the evidence submission template, which has been completed as part of European Network of Health Technology Assessment (EUnetHTA) joint action 2. The aim of this work was to develop an evidence submission template for relative effectiveness assessment that covers evidence requirements requested from industry (that is, manufacturers, companies, marketing authorisation holders or their representatives) across Europe. The evidence submission template includes the evidence requirements from national European organisations responsible for reimbursement. It can be used to support health technology assessment (HTA) processes within a country (either regionally or nationally) and also joint assessments.

The evidence submission template is a tool that is designed to be flexible, so it can be used within agencies' existing processes and practices. A set of adaptation notes has been produced to accompany the template to support individual or multiple agencies wanting to adapt the tool for their processes. The notes clearly explain the links between the evidence submission template and the HTA CORE model and existing EUnetHTA methodological guidelines, as well as highlighting key areas for agencies to consider as part of the adaptation process. The evidence submission template is available in 2 forms, a long form with all evidence requirements, and a short form with only the most frequently requested evidence requirements.

The work was coordinated by the National Institute for Health and Care Excellence (NICE) in the UK, supported by other EUnetHTA partners. In addition to reviewing the drafts of the evidence submission template and the accompanying reports, partners took part in data extraction of the evidence requirements, quality assurance of the data extractions, analysis of the data extractions, template development and piloting of the draft evidence submission template.

Table 1: Agencies taking part in the process of template development

Data extraction and quality assurance	Data analysis	Submission template development	Piloting
AGENAS (MD) AIFA (P) OGYEI (P/MD) HIS (MD) LBI (MD) MoH Czech Rep (P/MD) NICE (P/MD) NCPE (P/MD) ZIN (P)	G-BA (MD) HIS (MD) AGENAS (MD) NICE (P/MD)	AGENAS (MD) AIFA (P) G-BA (MD) OGYEI (P) HIS (MD) MoH Czech Rep (P) ZIN (P) NICE (P/MD)	ZIN (P) LBI (MD) AIFA (P) HIS (MD) ASSR (MD)

Agencies took part in development of the submission templates for P, pharmaceuticals and/or MD, medical devices.

Methods used for establishing and analysing the evidence required by European national agencies

Collection of evidence requirements from national agencies

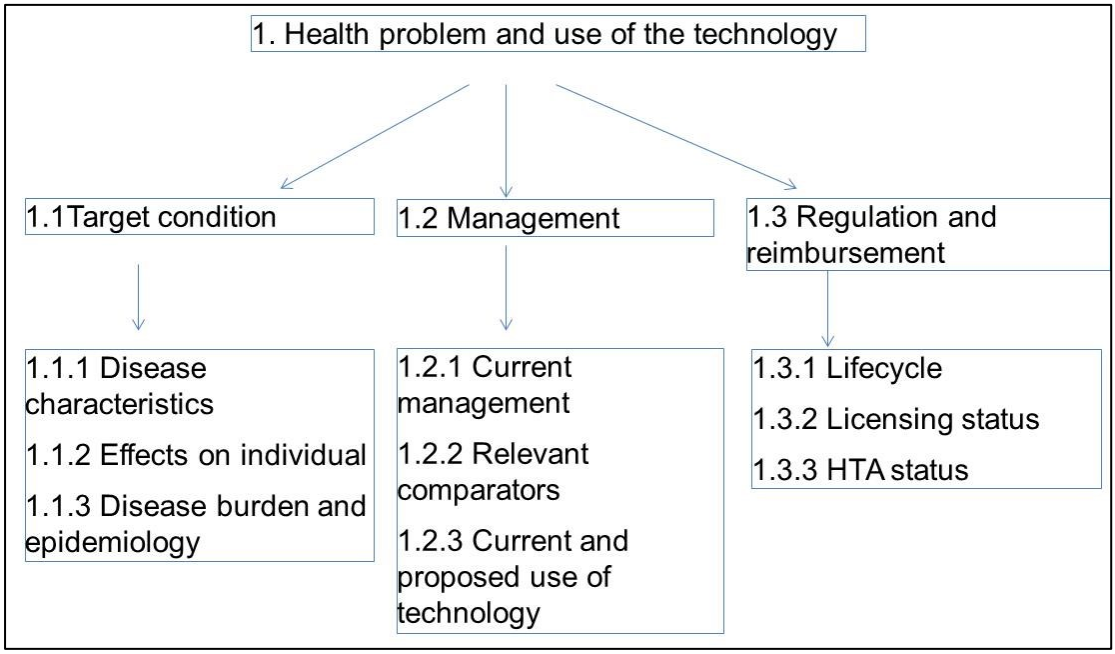
Evidence requirements were requested from national agencies involved in reimbursement of health technologies (pharmaceuticals and medical devices). Where such agencies were EUnetHTA partners they were directly contacted by email. Otherwise, the respective national EUnetHTA partner was asked to provide contacts (appendix 1).

When full English translations were not available or it was impossible to generate these within the timeframe of the project, translations of headings only were requested and used. The English translations provided by the national agencies were screened followed by an iterative process of clarification between NICE and the respective national contact until the best possible understanding of the information requested was available.

Analysis of evidence requirements

The remit of the work was to develop an evidence submission template reflecting the HTA CORE model domains used in the relative effectiveness assessment (REA) application of the HTA CORE model: health problem and use of the technology, description and technical characteristics of the technology, clinical effectiveness and safety. A framework was developed to categorise the information contained in the evidence requirements (an example used for describing the health condition and use of the technology is shown in figure 1). The first version of the framework for analysis was based around the domains, topics and issues included in the REA application of the HTA CORE model. The framework was tested by piloting it on a sample of national evidence requirements for pharmaceuticals and medical devices. It was then amended to ensure that all information from the evidence requirements could be categorised.

Figure 1: Framework for the health problem and use of the technology



Partners were asked to extract the relevant information from the evidence requirements into the framework using a data extraction form (appendix 2 and 3). Information was included in the data extraction form verbatim and the requested tables and figures were described. Each evidence requirement was data extracted by one partner and quality assured by a second partner. The quality assured data extractions were reconciled by a third partner to create a final version.

The finalised data extractions were analysed in Excel. Each of the pieces of information within a category of the framework was recorded, to create a list of the evidence requirements requested by agencies. The similarities and differences between the evidence requirements were then analysed by counting the number and range of items requested.

Development of the evidence submission template

The pieces of information compiled in the Excel sheet were grouped into common themes, and questions were designed to elicit the piece of information requested in the evidence requirement. Where possible, the questions and their groups used in the evidence submission template were related to HTA CORE model domains, topics, assessment elements and domain methodology.

Piloting

The draft evidence submission templates were piloted by partners at The Italian Medicines Agency (AIFA), Zorginstituut Nederland (ZIN) and the Ludwig Boltzmann Institute for Health Technology Assessment (LBI) as part of the pilot EUnetHTA joint assessments. Partners from Healthcare Improvement Scotland (HIS) piloted the evidence submission template as part of their work developing a national process for

evaluating medical devices in Scotland. Partners from the Agenzia sanitaria regionale Emilia-Romagna (ASSR) also piloted the evidence submission template as part of an update of their tools to support their regional processes for assessing medical devices.

Stakeholder engagement

WP7 SG4 collaborated with industry stakeholders in establishing the evidence requirements across Europe and for developing a draft evidence submission template.

For pharmaceuticals, the European Federation of Pharmaceutical Industries and Associations (EFPIA) completed their own analysis of the relationship between the assessment elements of the HTA CORE model and a sample of national evidence requirements. EFPIA developed their own proposal for an evidence submission template to use in joint assessments. An expert meeting was held in August 2013 and included presentations on the work completed and sharing the evidence submission template proposals.

For medical devices, the European Coordination Committee of the Radiological, Electromedical and Healthcare IT Industry (COCIR), European Diagnostic Manufacturers Association (EDMA) and EUCOMED were involved in an expert meeting held in May 2014 during which the draft evidence submission template for medical devices was presented and discussed.

Consultation

After piloting, an interim report and the draft evidence submission template were consulted on with:

- EUnetHTA partners
- Representatives of the EUnetHTA stakeholder advisory group, and
- European agencies involved in reimbursement who are not EUnetHTA members.

A total of 35 responses were received, 29 from EUnetHTA partners, 2 from stakeholder representatives and 4 from other agencies.

As part of the consultation, agencies were asked specific questions about the grouping of the questions, whether the draft evidence submission template reflected the agency’s evidence requirements, whether they would suggest amendments to the tables, include other types of information, extend the template to other applications, and whether they would like an online tool to allow agencies to create their own version of the evidence submission template for use in joint assessment or national processes.

In general the draft evidence submission template was considered to reflect the evidence requirements of the agencies. Some respondents noted that the evidence submission template reflecting all evidence requirements was wider than existing individual evidence requirements. Some agencies commented that a shorter version of the template would be useful for agencies with less HTA capacity than for more established agencies. The responses to the questions about the evidence submission template were positive, with support for the grouping of the questions and suggested tables. A number of suggestions were made to split up some sections, particularly about the target population and alternatives to the technology, and clarify the division between the methods of evidence synthesis, the results of evidence synthesis and the conclusions.

In terms of further work on the evidence submission template, 18 agencies out of 19 responding to the question supported the development of an online tool, and 13 agencies out of 19 responding supported extending the evidence submission template to other areas. The most commonly cited areas were costing and pricing (n=5) and economic evaluations (n=9). Other suggested areas for future work were budget impact (n=3), resource use (n=1), equalities issues (n=1) and other domains of the HTA CORE model for example, social, organisational, legal, ethical (n=3). In terms of extending to other applications 12 out of 17 agencies indicated that this would be useful, with 9 of these agencies specifically mentioning diagnostic technologies (n=9). Other applications mentioned were screening (n=2), digital health (n=1) and non-drug, non-device interventions (n=1).

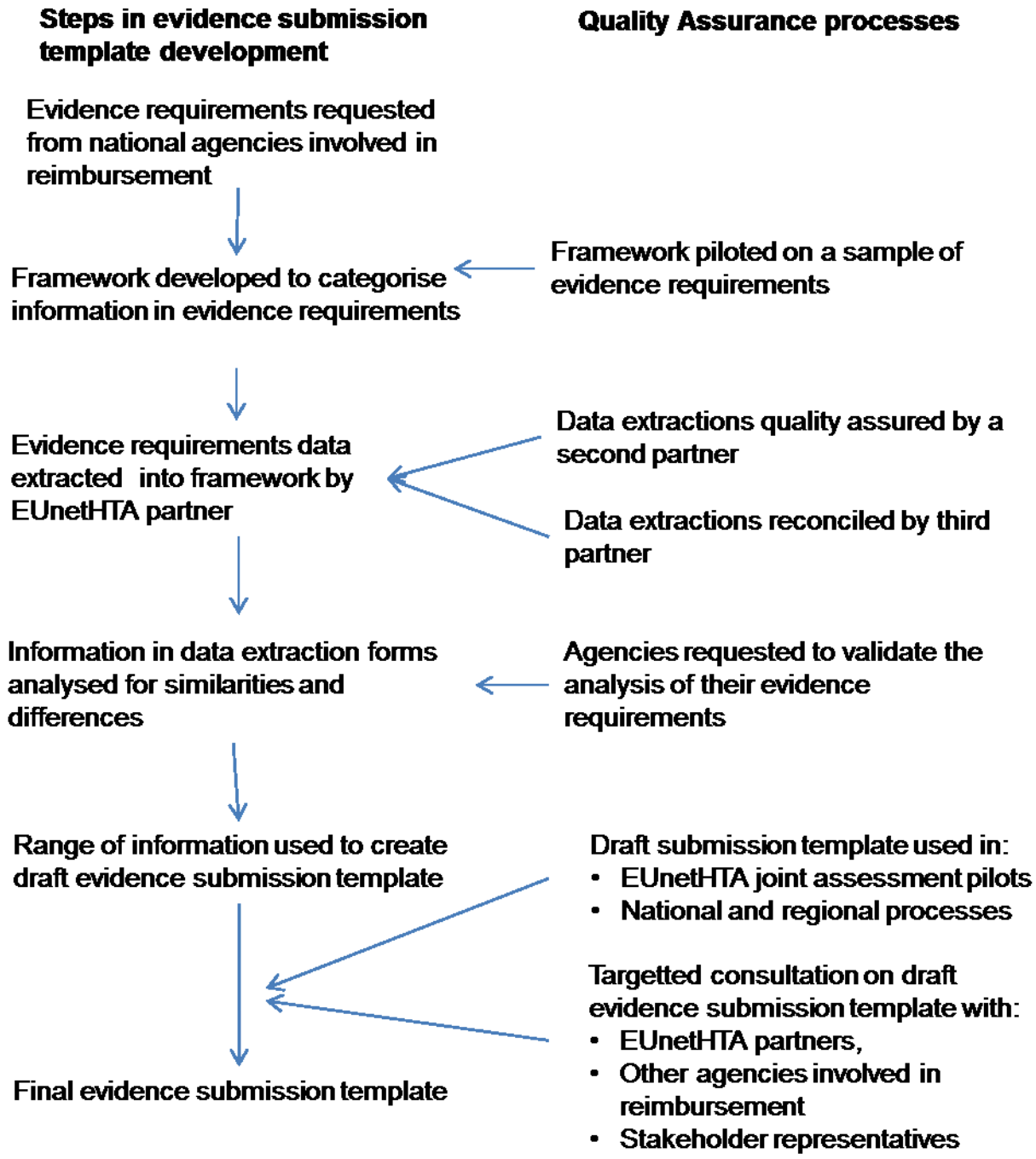
Other issues arising from consultation included questions about how to complete the evidence submission template, for example, requests for methodological guidance or the amount and type of information to provide. Further, comments were received about which questions should be included specifically for joint assessment, focussing on whether or not the information being requested was transferable across countries or relevant to decision-making for reimbursement.

In response to consultation 2 versions of the evidence submission template were developed; one including all the evidence requirements and one using a subset of the evidence requirements focusing on the most frequently requested information. Adaptation notes for agencies were developed, showing which of the questions were included in the short version of the evidence submission template. The adaptation notes also clearly explain how the questions relate to the HTA CORE model assessment elements.

It is beyond the remit of the evidence submission template to define the methodology to be used to answer the questions in the template, but the adaptation notes include links to the existing EUnetHTA methodological guidance. Because the adaptations needed for the template will depend on agencies' existing methods and processes, the notes also highlight specific areas raised in consultation where agencies (either as part of regional, national or joint assessment) may need to further adapt the

template to reflect their agencies' methods and processes. Figure 2 shows an overview of the development of the evidence submission template.

Figure 2: Process of developing the evidence submission template



Results

Evidence requirements received

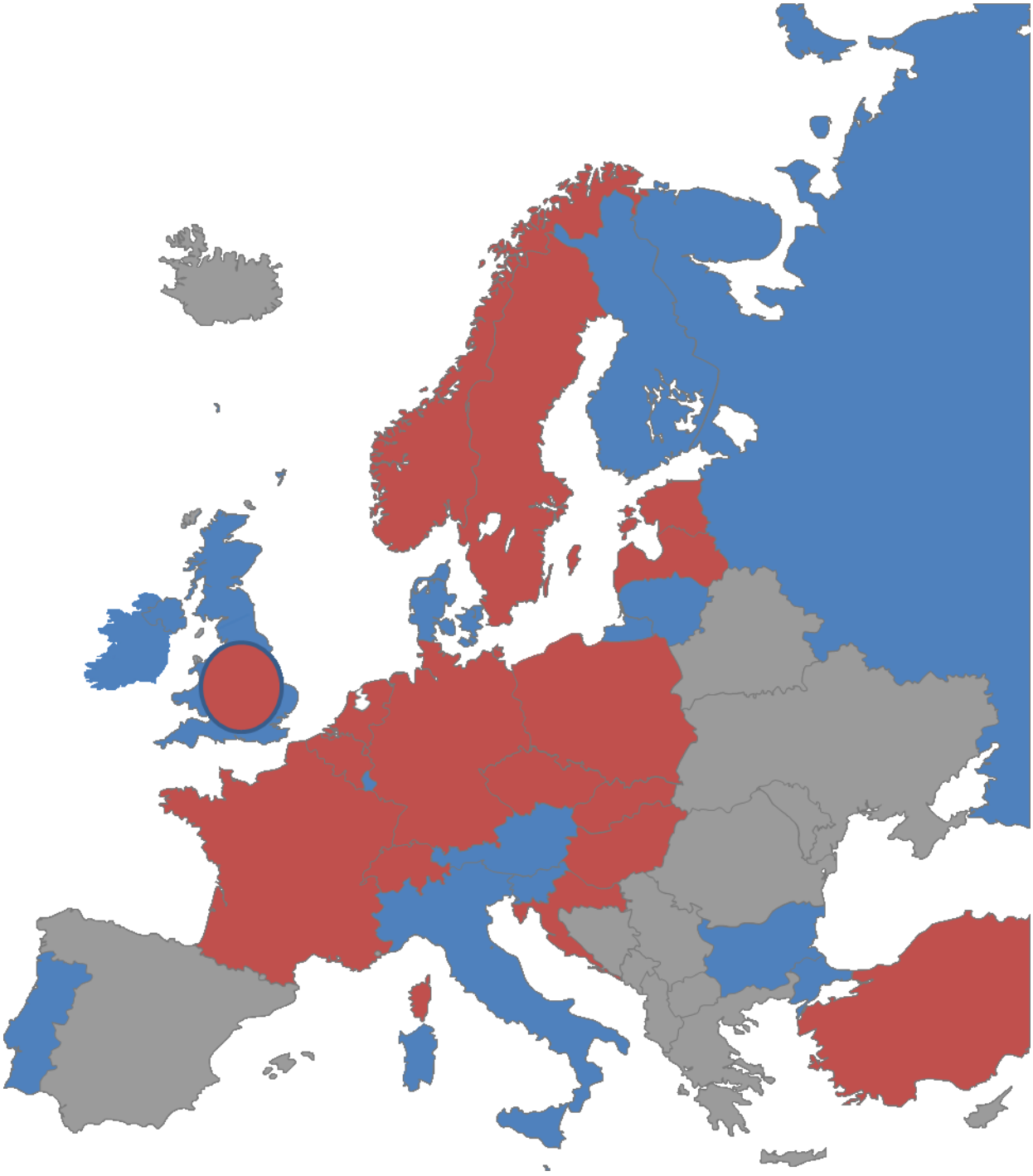
Evidence requirements were requested from 33 countries. Two countries (Greece and Cyprus) did not respond to requests for evidence requirements. Four further countries (Portugal, Finland, Denmark, Bulgaria) provided the evidence requirements for pharmaceuticals but could not confirm the evidence requirements for medical devices.

Thirty-one countries responded to the request for evidence requirements for pharmaceuticals, 2 countries indicated that they had no standardised national evidence requirements (Spain and Romania). Twenty-nine countries provided a national evidence requirement. The documents provided included checklists, templates, application forms and/or guidance documents. Norway indicated that there was one evidence requirement for pharmaceuticals appraised by the Norwegian Medicines Agency and one for pharmaceuticals appraised by the Norwegian Knowledge Centre.

Twenty-five countries confirmed their evidence requirements for medical devices. Of these, 9 countries indicated that they had no standardised evidence requirements. In some cases this was because the processes for reimbursement of medical devices were less centralised or not centralised (for example, Austria), or because there was a process but no templates were being used (for example, Luxembourg, Ireland). Twelve countries provided a different evidence requirement for medical devices. Of these, England provided a submission template for its medical technology evaluation (MTEP) programme and indicated that the evidence requirements differed depending on which programme (technology appraisals [TA] or MTEP) was used to assess the medical device. Hungary provided 2 checklists of information; one for medical devices used by patients and one for other medical devices. Switzerland provided 2 templates; one for the registration of medical devices and one for the reimbursement of medical technologies. Five countries (Estonia, Latvia, Poland, Norway, England [TA programme]) indicated that the same evidence requirements could be used for medical devices and pharmaceuticals. England indicated that the TA submission template could be used for pharmaceuticals or medical devices. The Norwegian Knowledge Centre indicated that the evidence requirement for medical devices were similar to the one they used for pharmaceuticals.

In summary, the total number of countries providing one or more evidence requirements was 29. The analysis is based on the evidence requirements used for pharmaceuticals in 29 countries, and evidence requirements used for medical devices for 16 countries (figure 3 and appendix 1).

Figure 3: Countries providing evidence requirements for pharmaceuticals (N=29) and medical devices (N=16)



Key: countries marked in red provided evidence requirements for both pharmaceuticals and medical devices and countries marked in blue provided evidence requirements for pharmaceuticals only.

Analysis of data

The questions and headings in the evidence requirements form the basis of the data analysis. Guidance documents (where these were provided) were used to help interpret the questions or headings. Evidence requirements differ in the extent to which they are prescriptive, with some including more general headings (for

example, Scotland) and some including a larger number of requests for specific information (for example, England, Germany, France). Furthermore, some evidence requirements include a relatively short standardised application form that accompanies a less prescriptive submission (for example, Denmark, Sweden, Finland). For the evidence requirements with a less prescriptive format, the analysis reflects only the specific items explicitly requested in the evidence requirements and may not fully capture the full range of information expected from companies by the agency.

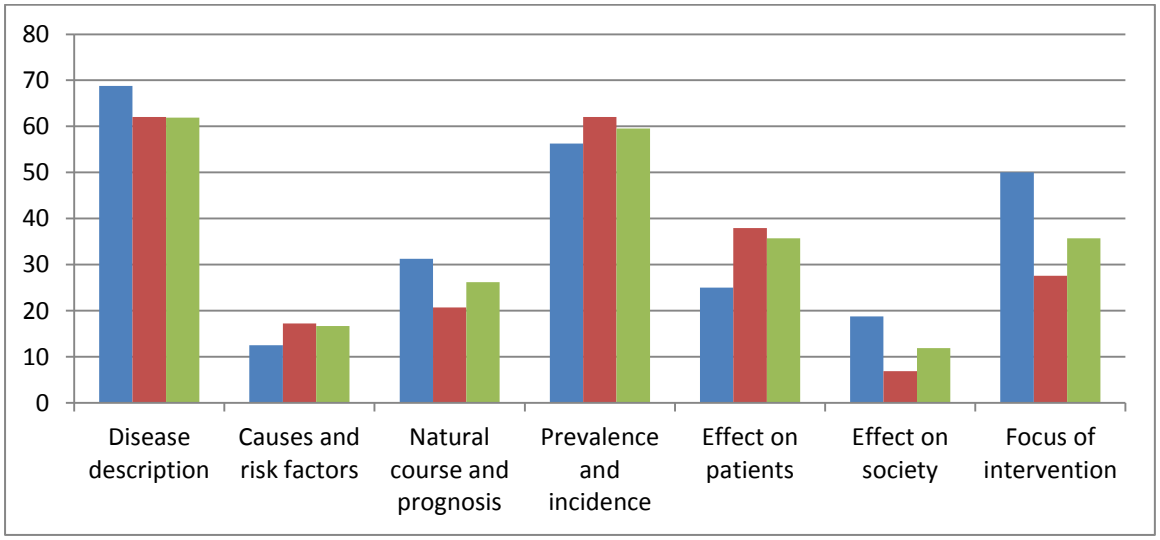
Furthermore, the analysis does not indicate which pieces of information are used by an agency in their decision-making. An agency recorded as not requesting a piece of information may indeed use this information in their assessment and appraisal of the evidence, but they may not request it from companies and instead perform the analysis themselves or complete it via a third party.

Health problem and use of the technology

Overview of the disease or health condition

In most (n=26; 62%) of the evidence requirements companies were asked to include a description of the disease or health condition. Considering aspects of the disease more specifically, in 17% (n=7) of the evidence requirements companies were asked to describe the causes or risk factors for the disease and in 26% (n=11) the natural course and progression of the disease. Prevalence and incidence of the condition was requested in over half of the evidence requirements (n=25; 60%). Some countries requested information on incidence and prevalence as part of budget impact analysis, rather than as background information. The emphasis placed on information about the disease differed between evidence requirements; for example Scotland had a one-page summary including an overview of the disease, positioning in the treatment pathway, comparators, rationale for development and target population. In other evidence requirements, such as the one provided by Slovenia, more specific descriptions of the clinical picture and course of the disease, and epidemiology including incidence, prevalence of disease, age, gender and risk factors were requested. In some cases background information was primarily used as part of the health economic submission (Denmark and Sweden).

Figure 4: Evidence requirements including a request for an overview of the disease or health condition (% of evidence requirements with information)



Evidence requirements: blue used for medical devices (N=16), red used for pharmaceuticals (N=29), green total unique sets of evidence requirements (N=42).

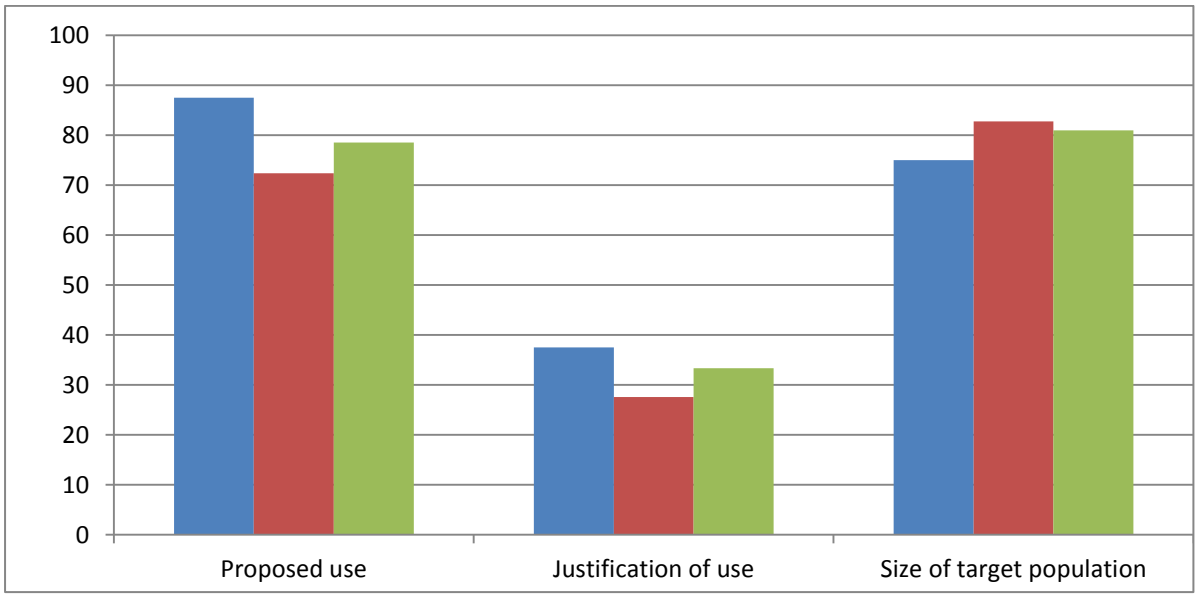
Compared to describing the disease, companies were less likely to be requested to describe the burden of disease on patients (n=15; 36%) and the consequences of the disease on society (n=5; 12%). The aspect of burden targeted by the technology was again requested in just over a third of the evidence requirements (n=15; 36%) (figure 4). The context of the information varied between submissions, for example England specifically requested information about life expectancy as part of the background information without referring to other aspects of disease burden. France

used information about the burden of disease on patients and society as part of the case for public health benefit.

Target population

Commonly requested information about the target population included a description of the proposed use or characteristics of the target population (n=33; 79%) and the size of the target population (n=34; 81%) (figure 5). In a smaller number of evidence requirements companies were explicitly asked to justify the proposed use of the technology (n=14; 33%). Some variations in the information requested are likely to stem from different agency processes, for example some agencies always appraise the full indication(s) in the marketing authorisation while others allow companies to propose a subgroup of the indication for reimbursement (for example Scotland and England). In evidence requirements for medical devices information on proposed use was more commonly requested than in evidence requirements for pharmaceuticals (88% compared with 72%).

Figure 5: Evidence requirements including a request for information on the target population (% of evidence requirements with information)



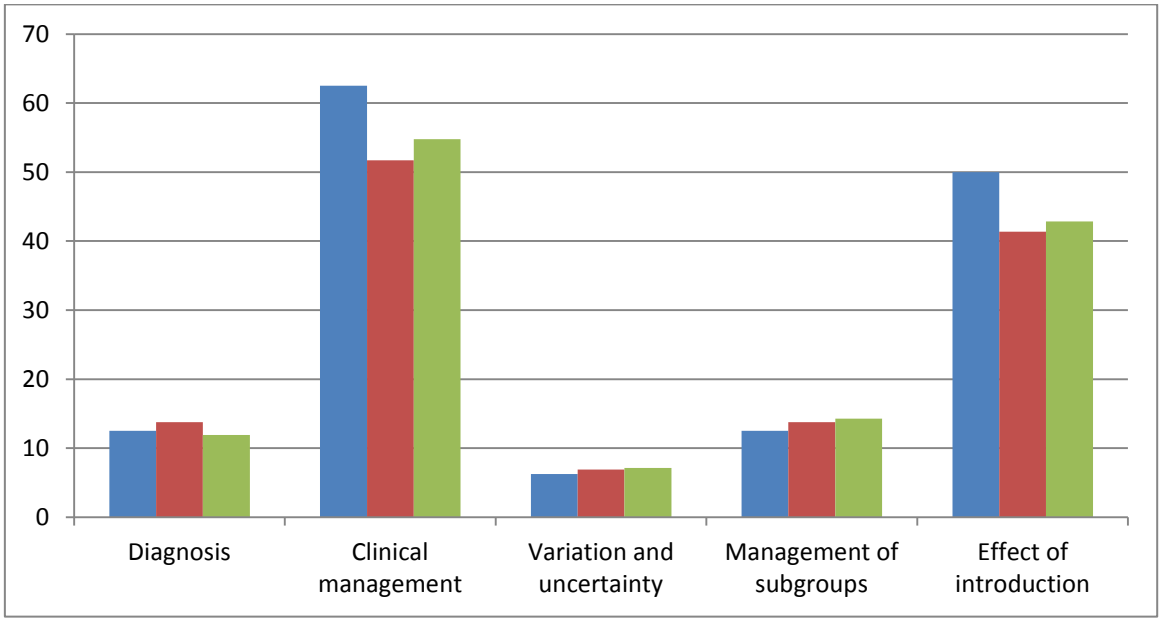
Evidence requirements: blue used for medical devices (N=16), red used for pharmaceuticals (N=29), green total unique sets of evidence requirements (N=42).

Clinical management

In 55% (n=23) of evidence requirements companies were asked to describe the current clinical management of the condition. Relatively few evidence requirements (n=5; 12%) included a specific request for information on diagnosis. For some agencies there may have been an expectation that diagnosis is included under clinical management, particularly where national or European clinical guidelines were requested. Relatively few evidence requirements included a specific request that companies describe uncertainty and variation in management (n=3; 7%) or how management may change for specific subgroups of patients (n=6; 14%). Again there

may have been an expectation among agencies that variations in management would be included under the general consideration of clinical management (figure 6). Information about the effect of the introduction of the health technology on the current clinical management of the target population was requested in 18 evidence requirements (43%). Evidence requirements for medical devices more commonly included a request for information on clinical management (63% compared with 52%) and the effect of introducing the technology on clinical management of the target population (50% compared with 41%).

Figure 6: Evidence requirements including a request for information on clinical management (% of evidence requirements with information)

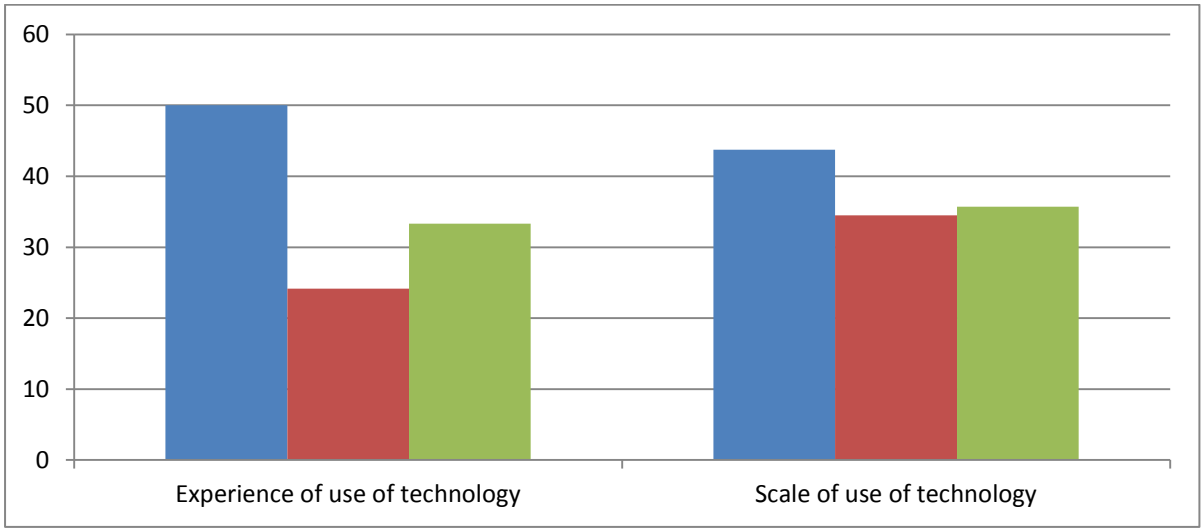


Evidence requirements: blue used for medical devices (N=16), red used for pharmaceuticals (N=29), green total unique sets of evidence requirements (N=42).

Current use of the technology

In under half (n=19; 45%) of the evidence requirements companies were asked about the current use of the health technology (either the type of current use and/or the frequency of use). The experience of use (for example, whether and how the technology is currently used) was requested in 33% (n=14) of evidence requirements and scale of use (that is, how much it is used) in 36% (n=15) of evidence requirements (figure 7). The experience of use of the technology was more frequently requested in the evidence requirements for medical devices than for pharmaceuticals (50% compared with 24%).

Figure 7: Evidence requirements including a request for information about current of use of the technology (% of evidence requirements with information)

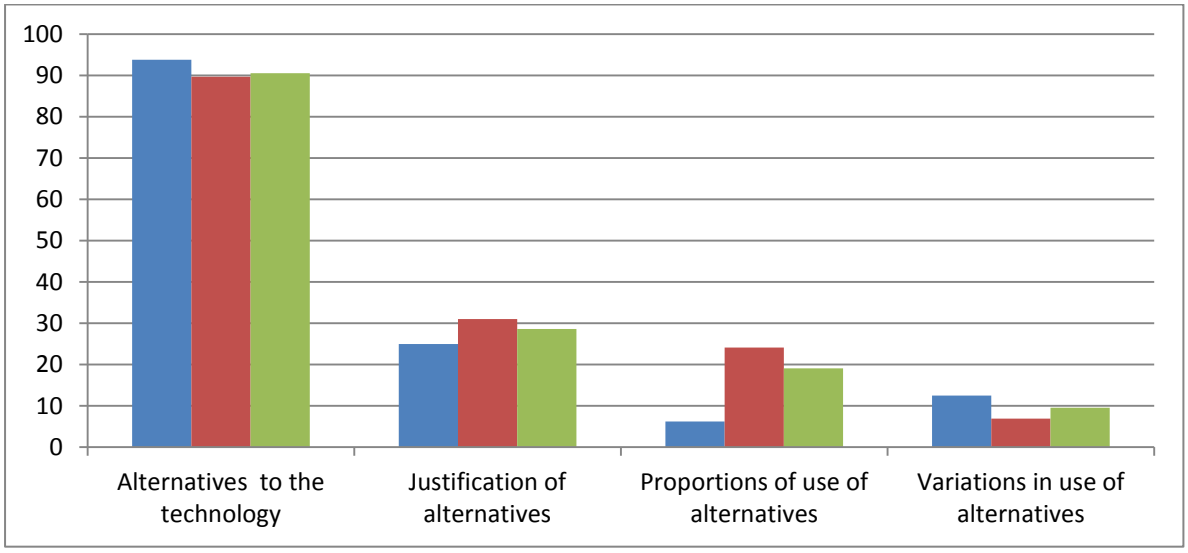


Evidence requirements: blue used for medical devices (N=16), red used for pharmaceuticals (N=29), green total unique sets of evidence requirements (N=42).

Alternatives to the technology

Companies were frequently asked to name the alternatives to the technology or the treatments to which the technology was added (n=38; 90%). In a smaller number of evidence requirements companies were specifically asked to justify the choice of alternatives (n=12; 29%). Companies were less frequently asked to provide information about the current use of alternative technologies for example, the proportion of use of each of the alternative technologies identified or variations in use of the different alternative technologies (figure 8). Detailed information about the use of alternative technologies was more frequently considered as part of budget impact or health economic analysis than as background information.

Figure 8: Evidence requirements including a request for information on the alternatives to the technology (% of evidence requirements with information)



Evidence requirements: blue used for medical devices (N=16), red used for pharmaceuticals (N=29), green total unique sets of evidence requirements (N=42).

Summary of the health problem and current use of technology

- All countries requested at least one piece of information relating to the health problem and current use of the technology.
- The most commonly requested items (all requested in more than 50% of evidence requirements) were a description of the disease, prevalence and incidence of the disease, proposed use, current clinical management, alternatives to the technology and size of the target population.
- Information relating to alternatives to the technology for example, the nature of their current use and amount of use were not frequently requested as background information.
- The information requested by national agencies for pharmaceutical assessments was generally similar to that requested for medical device assessment.
- In the evidence requirements for medical devices there were a higher number of requests for information about the aspects of disease burden targeted by the technology, experience of use of the technology and proposed use of the technology than for pharmaceuticals.

Description and technical characteristics of the technology

Features of the technology

The exact information requested differed depending on whether the technology was a pharmaceutical or a medical device. However, the evidence requirements used for each of these 2 types of health technologies were similar. For the countries with pharmaceuticals evidence requirements (n=29) the information requested was the generic name (n=28; 97%) and proprietary name (n=28; 97%), code (n=24; usually the ATC code; 83%) and class (n=11; 38%), as well as the active substance (n=19; 66%). For the countries with medical devices evidence requirements (n=16) the information requested was the name (n=15; 94%), class (n=8; 50%) and the nomenclature (n=9; 56%) or product code (n=8; 50%). The mechanism of action was requested equally among the evidence requirements used for pharmaceuticals and medical devices (38% and 38% respectively). Claimed benefits (for example, increased safety, health benefit, compliance) were also requested equally among the evidence requirements for pharmaceuticals and medical devices (59% and 50% for pharmaceuticals and medical devices respectively; figures 9 and 10).

Figure 9: Countries requesting features of the technology (pharmaceutical, % of countries requesting information)

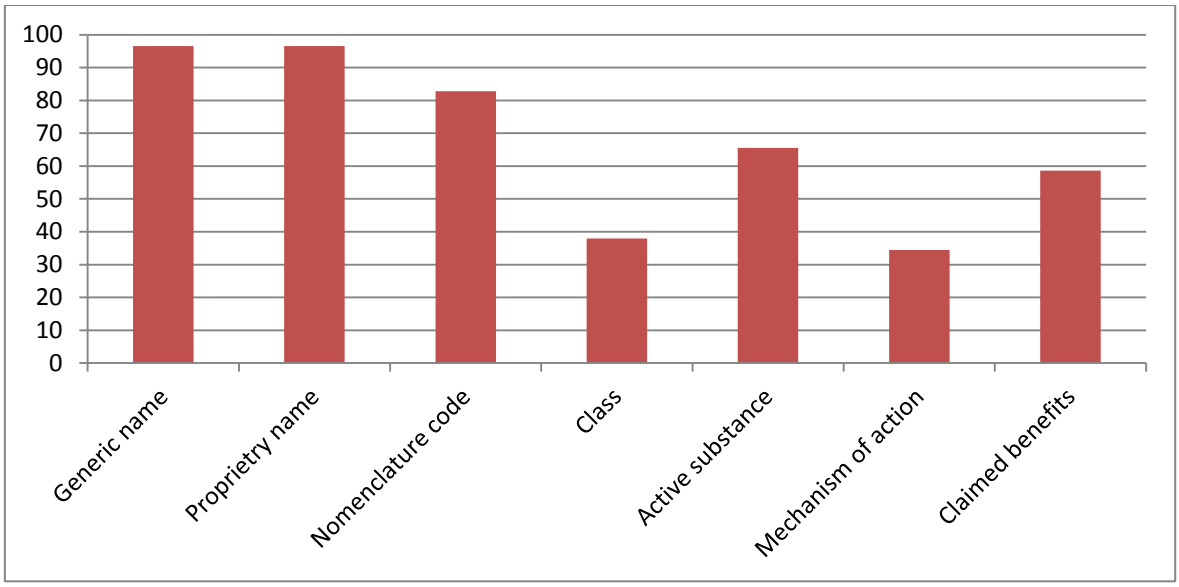
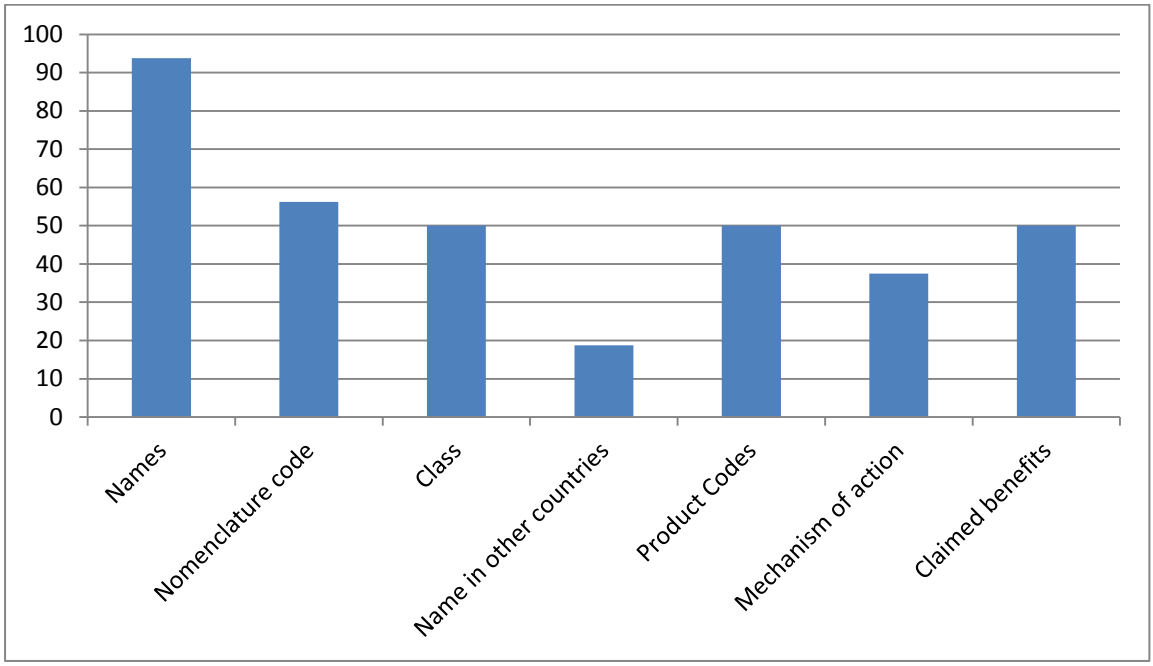
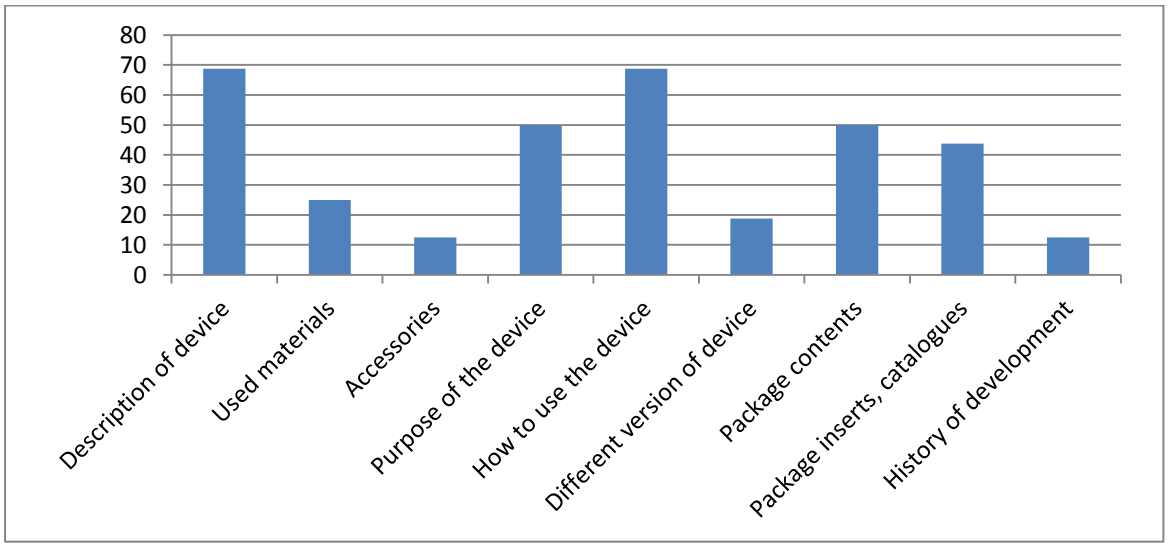


Figure 10: Countries requesting features of the technology (medical devices, % of countries requesting information)



The countries with evidence requirements for medical devices also requested detailed information on characteristics of the medical device (figure 11). Most commonly this was a detailed description of the device (n=11; 69%), its purpose (n=8; 50%) and how it is used (n=11; 69%) and less frequently the materials used (n=4; 25%) and accessories required (n=2; 13%). Only a small number of countries specifically asked for information about the history of development of the device (n=2; 13%) and different versions of the device (n=3; 19%).

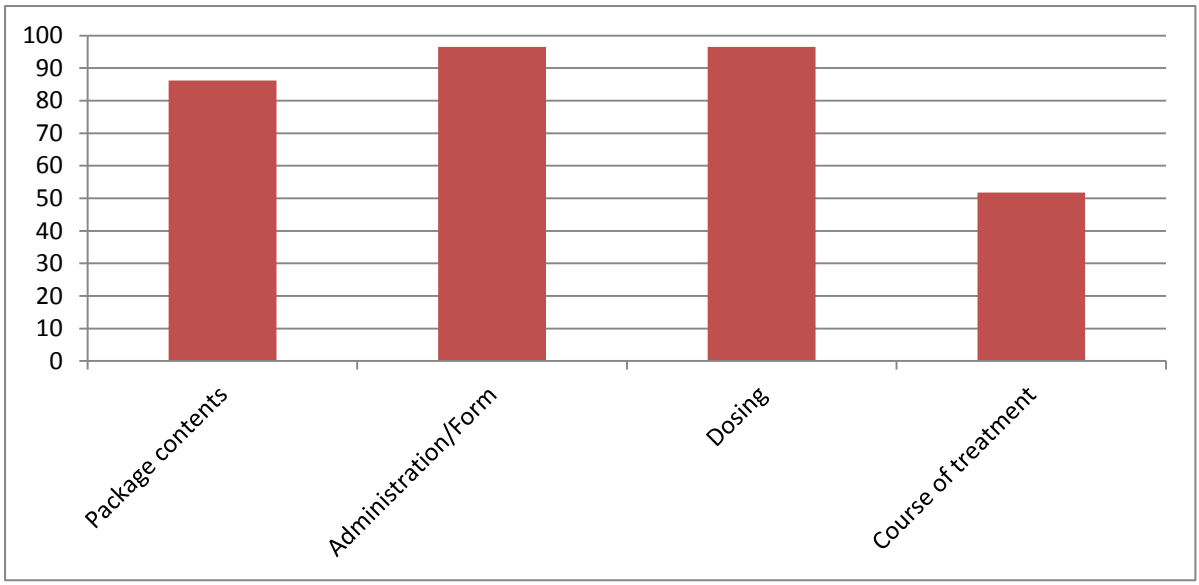
Figure 11: Countries requesting detailed characteristics of the medical device (% of evidence requirements with information)



Information about the package contents and package leaflets was frequently requested, but more so for pharmaceuticals than for medical devices. Information

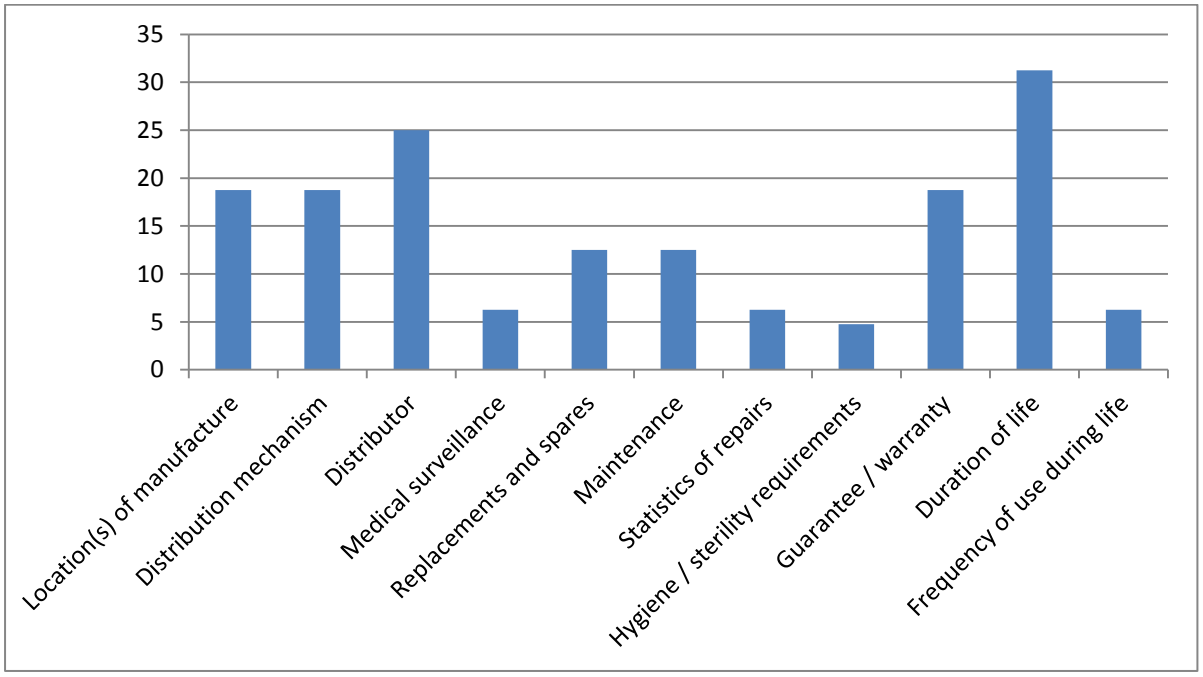
about package contents was requested in 86% (n=25) of the pharmaceuticals evidence requirements and 50% (n=8) of the medical devices evidence requirements. Information about dosing (n=28; 97%), administration (n=28; 97%) and the duration of a course of treatment (n=15; 52%) were asked for in evidence requirements for pharmaceuticals (figure 12). Some agencies reported taking this information directly from documents such as the summary of product characteristics rather than requesting it from companies in a submission. Pharmacokinetics and pharmacodynamic information was infrequently requested among the evidence requirements (n=4; 14% of evidence requirements used for pharmaceuticals), with only the Austrian evidence requirement including a detailed request.

Figure 12: Countries requesting information about administration and dosing of pharmaceuticals (% of countries requesting information)



In some evidence requirements for medical devices information about manufacture, quality assurance and follow-up was requested. However, this information was not requested frequently (figure 13), for example the most frequently asked questions were about distribution (n=4; 25%) and duration of life of the device (n=5; 31%). Most of this information was requested in only 1 or 2 evidence requirements. The differing nature of the information requested may reflect the differing roles that agencies have, for example some agencies may have a greater role in ensuring quality and availability of access of medical devices.

Figure 13: Countries requesting information about manufacture, distribution and follow-up (% of countries requesting information)



For most agencies the company submission was only one part of the package of information submitted for reimbursement. Rather than requesting companies include information about features of the technology in their submission, information about the characteristics of the technology may also be taken by the agencies from other documentation such as SPCs, EPARs and PILs in the case of pharmaceuticals and CE documentation, brochures, user manuals, package inserts and catalogues in the case of medical devices.

Regulatory approval status of the technology

Regulatory documentation is often requested together with company submissions, but countries also requested details of authorisation status as part of the company submission (figure 14). The information requested was in almost all cases the wording of the indication (n=38; 90%) and/or approval number (n=11; 26%), the date of receipt of approval (n=22; 52%), other indications available (n=23; 55%) and the restrictions and contraindications (n=12; 29%) placed on the authorisation. Less frequently requested information included the conditions applied to the authorisation (n=4; 10%), a summary of the discussions of the regulatory body (n=1; 2%) and ongoing procedures (n=1; 2%). Availability of the product in the country in which the assessment was being completed, for example launch date, was requested by 16 countries (38%). The information requested varied slightly between evidence requirements for medical devices and pharmaceuticals, reflecting the differing regulatory frameworks. For medical devices' evidence requirements there was more focus on authorisation status, while for pharmaceutical evidence requirements the focus was more on the indication under assessment, and the other indications approved.

Regulatory status in other countries was requested by a third of countries (n=17; 40%). The countries for which the regulatory status was requested differed, with 7 sets of evidence requirements specifying all other countries, 2 specifying only EU or European countries, and 5 specifying a combination of European and other countries such as the US, Canada and Australia. In 3 other evidence requirements information about availability in other countries was requested without specifically linking it to authorisation status.

As with features of the technology, some regulatory information is obtained by agencies themselves from documents such as SPCs, EPARs and PILs in the case of pharmaceuticals and CE documentation and package inserts in the case of medical devices. Therefore, some agencies do not specifically request this information from companies as part of a submission of evidence.

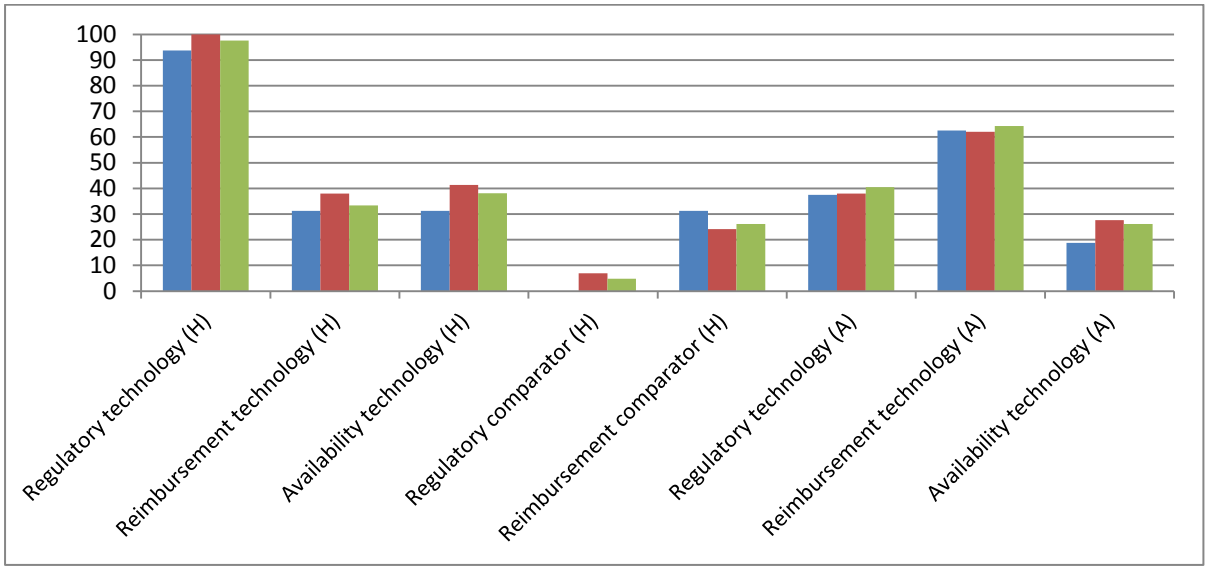
Reimbursement status of the technology

The reimbursement status of the technology was also frequently requested. In 27 (64%) of evidence requirements a summary of the reimbursement status of the technology in other countries was requested. This was most commonly other EU or European countries, or a defined selection of European countries. The information requested varied in detail and in most cases an indication of whether the product was reimbursed was requested. However, in other cases further details were requested including one or more of the specific indications reimbursed (n=10; 24%), level of reimbursement (n=15; 36%), reasons for restrictions or rejection of reimbursement (n=6; 14%) and date of decision (n=3; 7%). Information about reimbursement status was often accompanied by requests for information about pricing in other countries (see the section on cost information requested).

Regulatory and reimbursement status of the comparators

The approval status of comparators was only requested in a small number of evidence requirements (n=11; 26%). These asked that companies give the reimbursement status of the comparator(s) and in 2 of these evidence requirements the regulatory status of comparators was also requested (n=2; 5%). For some countries this would be because the processes within the organisation stipulate that comparators are authorised and/or reimbursed.

Figure 14: Evidence requirements including a request for approval status and availability (% of evidence requirements with information)



Evidence requirements: blue used for medical devices (N=16), red used for pharmaceuticals (N=29), green total evidence requirements (N=42). H = in country of application A = in other countries.

Requirements for use

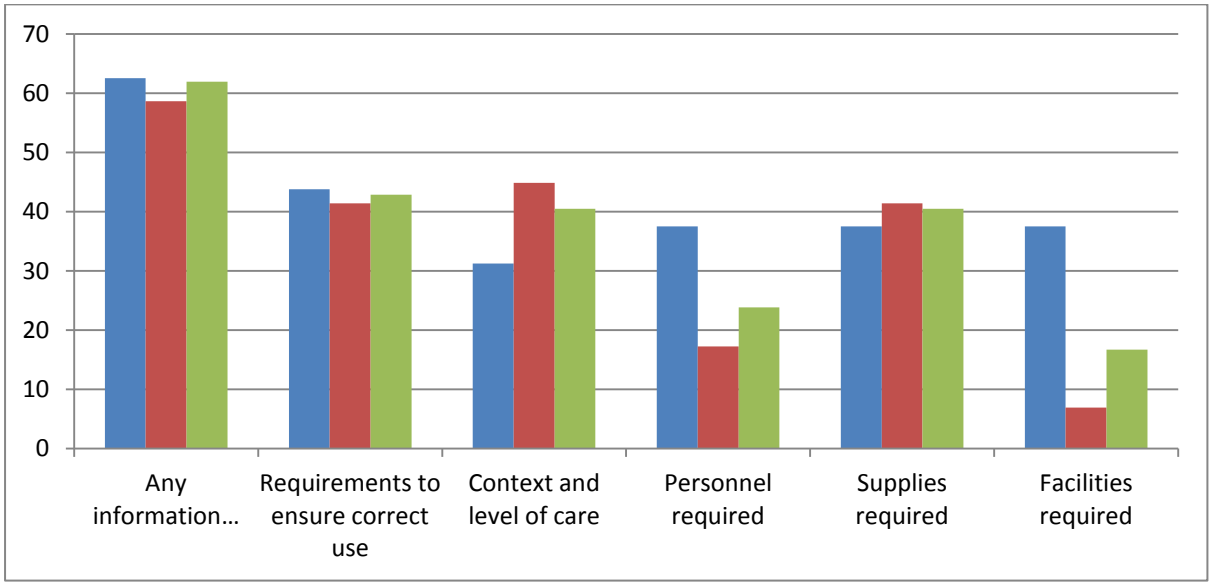
In 26 (62%) of the evidence requirements (17 used for pharmaceuticals and 10 used for medical devices) companies were asked to describe the requirements (such as equipment, infrastructure and staffing) needed to use the health technology (figure 15). The level of specificity of the questions varied, for example some evidence requirements (n=18; 43%) asked about factors required to ensure correct use for example, evidence requirements from Germany. In other evidence requirements specific questions were asked about monitoring or other treatments for example, evidence requirements from England. Also in some evidence requirements details about the restrictions and limitations for the product were requested which could have included requirements for use, for example evidence requirements from the Czech Republic.

The evidence requirements included requests for companies to describe the context and level of care (n=17; 40%), who would perform or administer the health technology (n=10; 24%) and the supplies needed to use the technology (n=17; 40%). In a small number of evidence requirements companies were asked about facilities required (n=7; 17%). For the evidence requirements for pharmaceuticals, information about supplies required was mainly restricted to specific questions about other treatments needed and assessment and monitoring requirements.

Information about requirements for use was only requested for the technology rather than the comparators. For medical devices information about the personnel required to use the device and the facilities required was more frequently requested in the evidence requirements than for pharmaceuticals. For pharmaceuticals this information may be available in the SPC, and so could be taken by agencies directly

from the SPC, and for medical devices this information may be taken from documents such as user manuals.

Figure 15: Evidence requirements that included a request for information about requirements for use (% of evidence requirements with information)



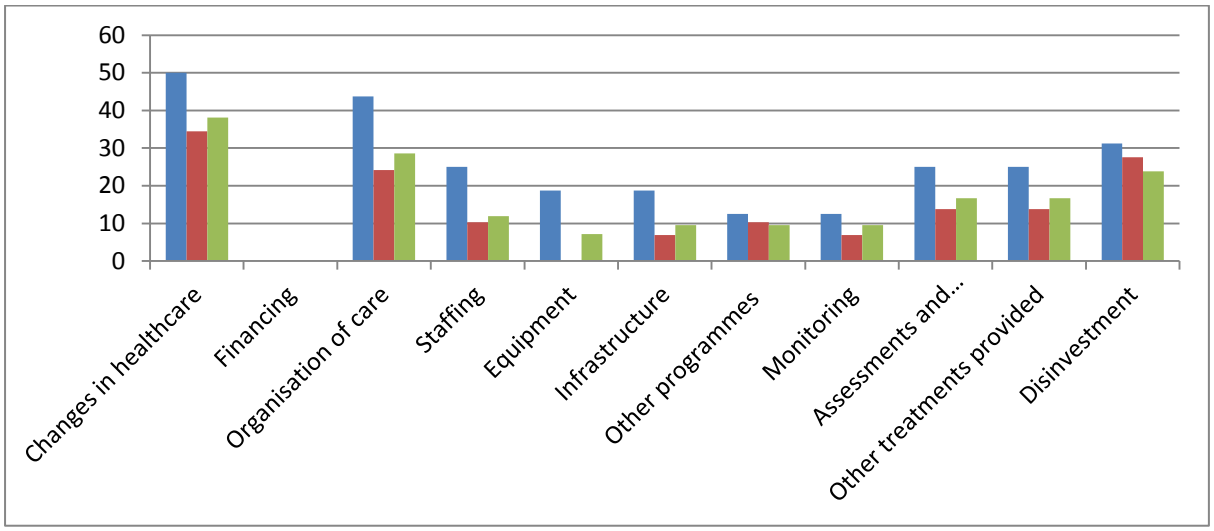
Evidence requirements: blue used for medical devices (N=16), red used for pharmaceuticals (N=29), green total evidence requirements (N=42).

Investments and changes in service delivery and organisation

In 16 evidence requirements (38%) information was requested about whether introducing the health technology would require changes to healthcare organisation and delivery (figure 16). Investments and changes in healthcare were not always clearly distinguished from the requirements for use, that is, the resources needed to use the technology, which may or may not require additional investment or changes in healthcare delivery.

The questions in the evidence requirements tended to be general about changes to the organisation of care (n=12; 29%), but in some cases more specific questions were asked about staffing and human resources (n=5; 12%), infrastructure (n=4; 10%), monitoring (n=4; 10%), assessments and investigations (n=7; 17%) and other treatments (n=7; 17%). Questions about changes in healthcare provision were more frequently requested in evidence requirements for medical devices than pharmaceuticals.

Figure 16: Evidence requirements that included a request for information about changes in service delivery and organisation (% of evidence requirements with information)



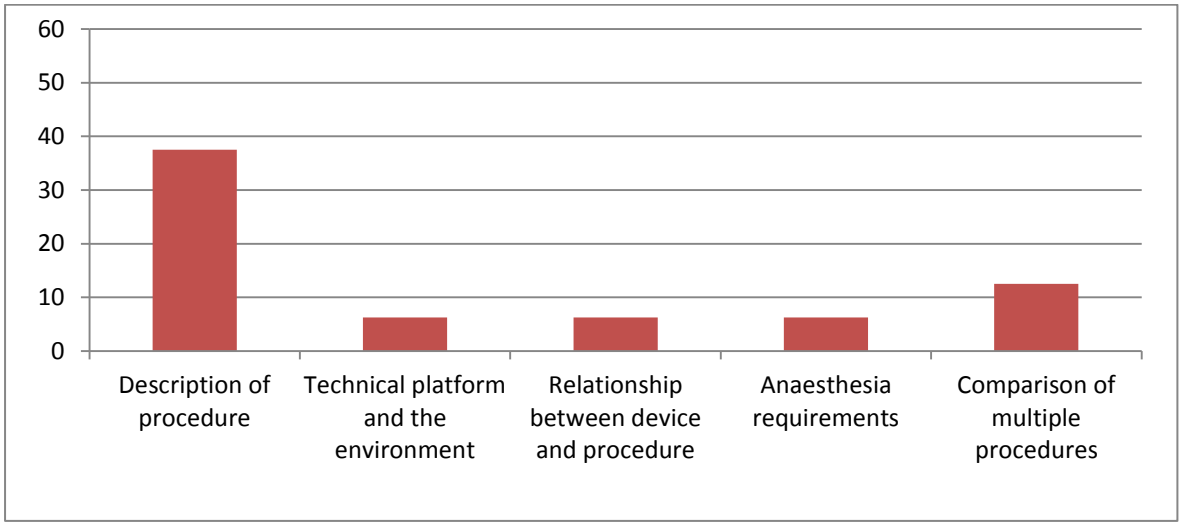
Evidence requirements: blue used for medical devices (N=16), red used for pharmaceuticals (N=29), green total evidence requirements (N=42).

In 10 of the evidence requirements (24%) information about disinvestments that could be made as a result of introducing the technology was requested. Information about disinvestments was varied, in some evidence requirements companies were asked whether there were any tests or programmes that would no longer be needed if the technology was introduced (for example, Austria), in others companies were asked more generally about whether there would be any disinvestments (for example, England; medical devices). The evidence requirements from Poland specified that if the company's budget impact analysis showed that there would be an increase in costs associated with introducing the technology, then a separate 'rationalisation' analysis was required that would demonstrate how public funds could be released that would cover the increase in the costs associated with the technology.

Procedures used with the technology

For the evidence requirements for medical devices, in 6 (38%) information was requested about the procedures that would be used with the technology (figure 17). In 5 of the 6 this was phrased as a general request for a description of the procedure. However, the evidence requirements from France included a specific section outlining in detail the requirements for describing procedures that were used with a medical device, covering a detailed description of each of the stages of the procedure, the technical platform, relationship between device and procedure, anaesthesia requirements and the similarities and differences between procedures when multiple procedures could be used.

Figure 17: Countries requesting information about procedures used with the medical device (% of evidence requirements with information)



Summary of description and technical features of the technology

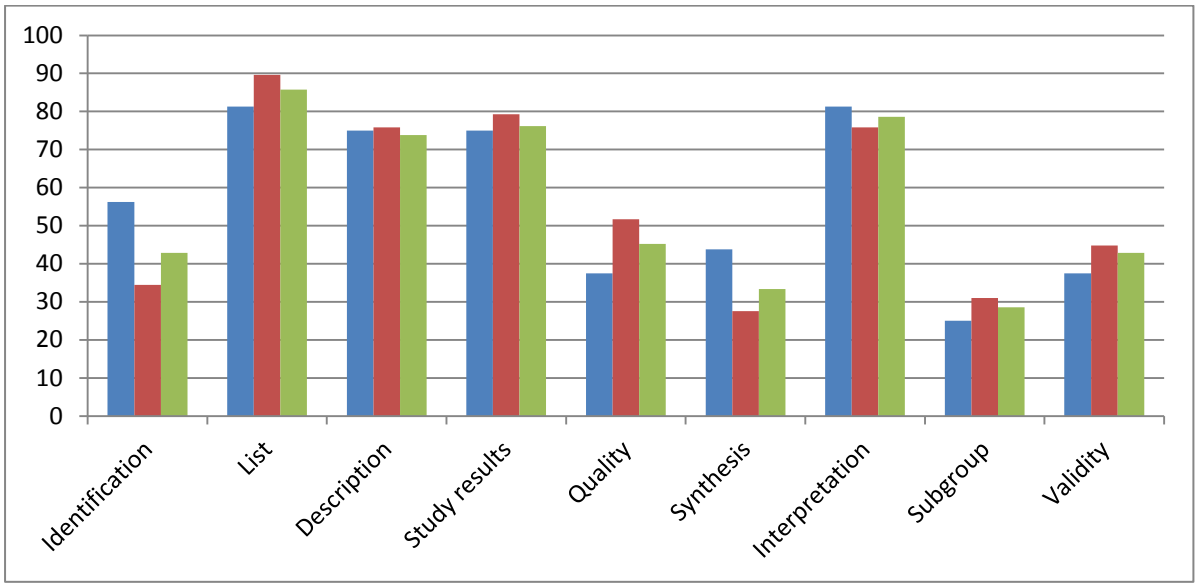
- In all of the evidence requirements one or more pieces of information relating to the description and technical characteristics of the technology domain of the HTA CORE model was requested.
- The information requested differed depending on whether the evidence requirement was for pharmaceuticals or medical devices. This may be expected given the different characteristics of these health technologies, different regulatory frameworks and routes to market access.
- The information requested focused specifically on the technology rather than the comparator, which may be expected in a company submission of the evidence.
- The evidence requirements were not solely focused on information relevant to the country of application; in over half of the evidence requirements the regulatory and/or reimbursement status in other countries was requested.
- For features of the technology the most frequently requested information was the names and codes of the product. For pharmaceuticals the most frequently requested information also included details about the active substance, package contents, administration and dosing, and for medical devices a detailed description of the device and how it was used.
- The most frequently requested information about regulation and reimbursement was the regulatory status of the product and indication under assessment, and the reimbursement status of the product in other countries.

Clinical effectiveness

All the evidence requirements included one or more requests for pieces of clinical information. However, the exact requests varied in the level of comprehensiveness, for example the evidence requirement from Luxembourg requested that if available a comparative study was provided, the Swiss evidence requirement for pharmaceuticals requested 3 publications, while the evidence requirement from Belgium for pharmaceuticals requested a complete list of evidence.

The most commonly requested information was a list of the relevant evidence (n=36; 86%) and/or a summary or interpretation of the clinical evidence (n=33; 79%). Requests for a description of the studies and for the study results were also frequently requested (n=31, 74% and n=32, 76%, respectively). In less than half of the evidence requirements information about methodological aspects was requested, such as the process used by companies for identifying studies (n=18, 43%), synthesis methods used to derive the summary of clinical effectiveness (n=14, 33%) and discussion of validity of the evidence base (n=18, 43%) (figure 18). For assessing study quality, although a number of agencies asked for consideration of study quality (n=19, 45%) few of these asked companies to provide full critical appraisal of each study in the submission (n=4; 21% of those requesting consideration of quality). These differences are likely to reflect the different agency processes and the extent to which the company submission forms the main source of evidence in an assessment, or if it is used to inform or support an independent assessment of the evidence carried out by the agency.

Figure 18: Evidence requirements including a request for information in each module (% of evidence requirements with information)

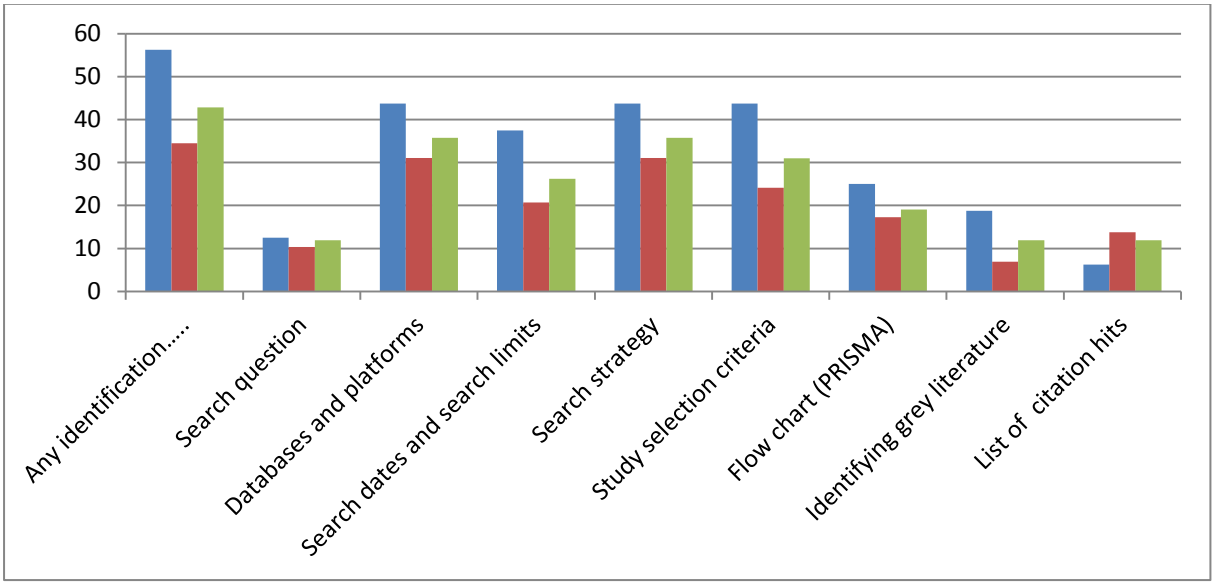


Evidence requirements: blue used for medical devices (N=16), red used for pharmaceuticals (N=29), green total evidence requirements (N=42).

Methods of identifying evidence

In under half of evidence requirements companies were asked to describe the process they went through to identify relevant evidence (n=18; 43%), but in those evidence requirements the questions were consistent (figure 19). The information requested focused on the databases and platforms used (n=15, 36%), search dates and limits applied (n=11, 26%), search strategies used (n=15, 36%), study selection criteria (n=13, 31%) and a flow chart (usually a PRISMA chart; n=8, 19%). Fewer countries asked that companies also outline the question guiding the searches (n=5, 12%), the methods of identifying unpublished 'grey' literature (n=5, 12%) and to provide a list of the citation hits, that is, the study titles identified in the search process (n=5, 12%). In a small number of evidence requirements it was specified that companies complete a systematic review, but the evidence requirements did not include specific headings for search information (for example, Belgium; medical devices evidence requirements). In some further evidence requirements systematic searches were requested as part of the development of the health economic analysis, but they did not specifically request this information for the clinical effectiveness part of the submission (Belgian and Danish pharmaceutical evidence requirements). The Scottish evidence requirements specified the presentation of systematic searches for comparator technologies used in indirect comparisons, but not for the technology under assessment.

Figure 19: Evidence requirements including a request for information about identifying evidence (% of evidence requirements with information)



Evidence requirements: blue used for medical devices (N=16), red used for pharmaceuticals (N=29), green total evidence requirements (N=42).

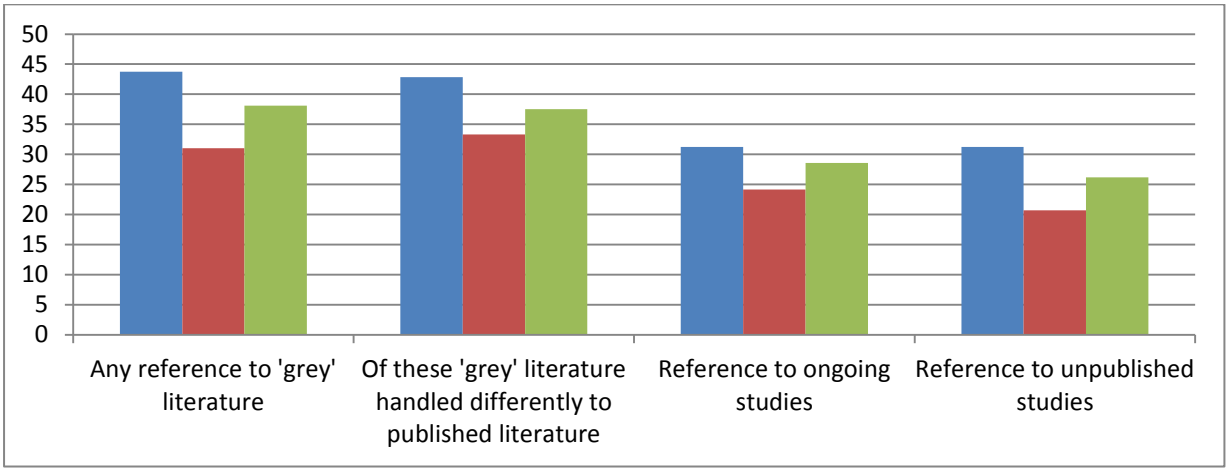
For identifying studies, information about searching when given as a percentage is more frequently requested in the medical device evidence requirements than in those for pharmaceuticals. However, the absolute number of evidence requirements

that include a request for information about searching is similar for pharmaceuticals and medical devices.

Unpublished and ongoing studies

In 38% (n=16) of the evidence requirements information from companies about unpublished literature or ongoing studies ('grey literature') was requested. In 38% (n=6) of these cases the unpublished or ongoing studies were incorporated into submissions differently from the published literature (figure 20). When unpublished or ongoing studies were presented differently from published literature the information requested from companies was less detailed for example, a list of ongoing or unpublished studies rather than an analysis of any data that may be available. For example, the pharmaceutical evidence requirements from Scotland and Ireland both included a table to list ongoing studies, whereas in the medical device evidence requirements from England and from Germany it was requested that the studies be presented in the same way as the published literature. References to 'grey' literature were more common in the evidence requirements for medical devices than pharmaceuticals.

Figure 20: Evidence requirements including a request for information about unpublished and ongoing studies (% of evidence requirements with information)

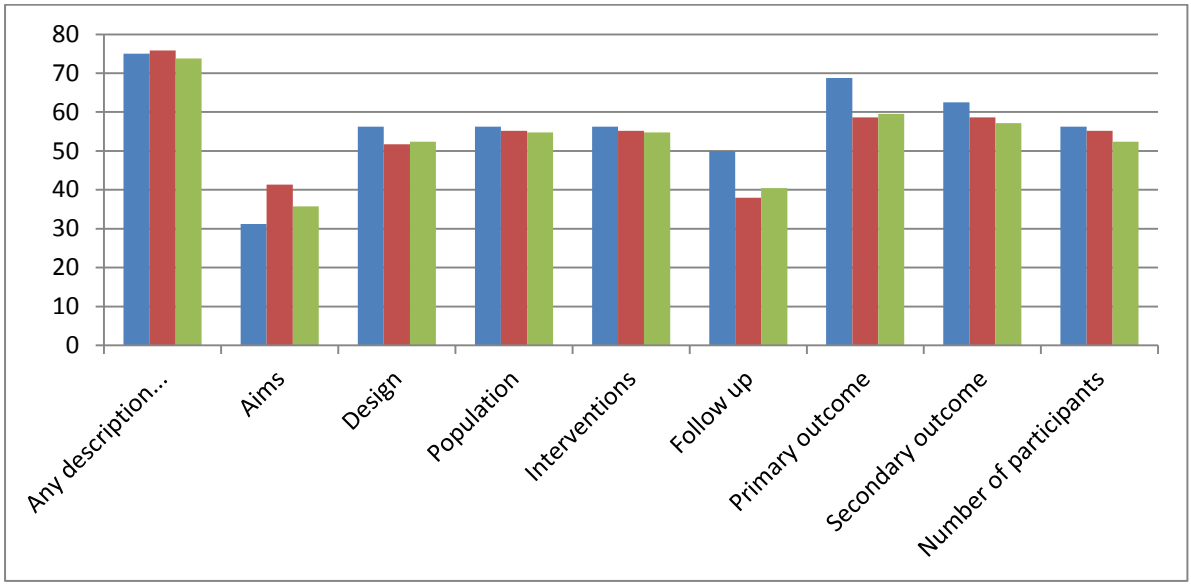


Evidence requirements: blue used for medical devices (N=16), red used for pharmaceuticals (N=29), green total evidence requirements (N=42).

Description of the study characteristics

In most evidence requirements (n=31, 74%) companies were asked to provide study descriptions. All countries except 3 (Sweden [pharmaceuticals evidence requirements], Finland, Croatia) specified some or all of the characteristics that companies should give. This information was requested consistently and was most frequently study design (n=22, 52%), study population (n=23, 55%), intervention and comparators (n=23, 55%), and outcomes (n=25, 60%) (figure 21).

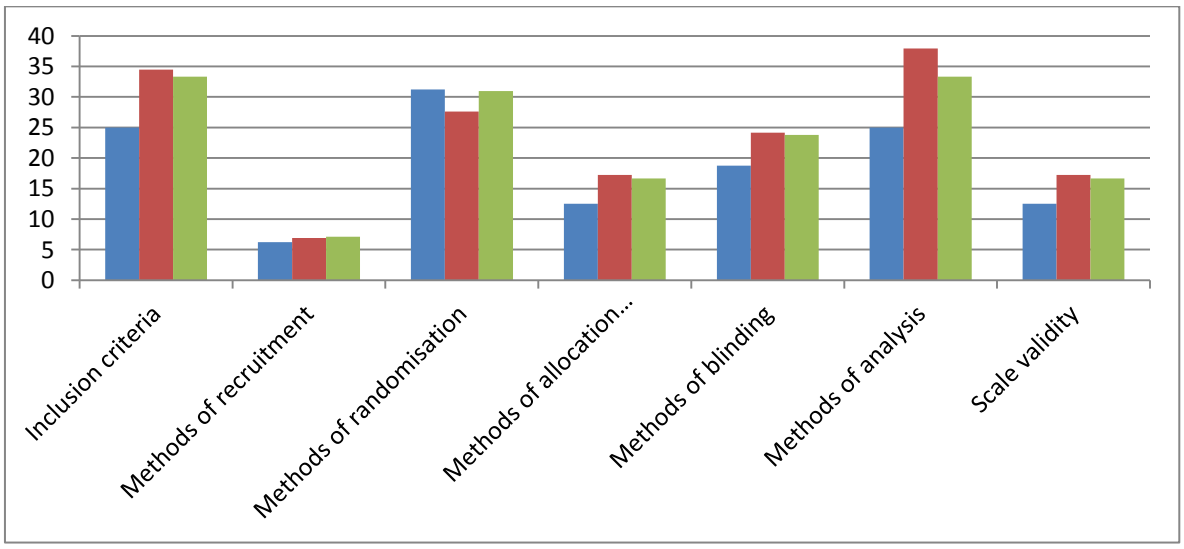
Figure 21: Evidence requirements including a request for information about study characteristics (% of evidence requirements with information)



Evidence requirements: blue used for medical devices (N=16), red used for pharmaceuticals (N=29), green total evidence requirements (N=42).

Information about the study methodology was less frequently requested than descriptive characteristics and there was variation in the requests. The inclusion and exclusion criteria (n=14, 33%), methods of randomisation (n=13, 31%) and methods of analysis (n=14, 33%) were most frequently requested, with other types of information less frequently requested (figure 22).

Figure 22: Evidence requirements including a request for information about study methodology (% of evidence requirements with information)

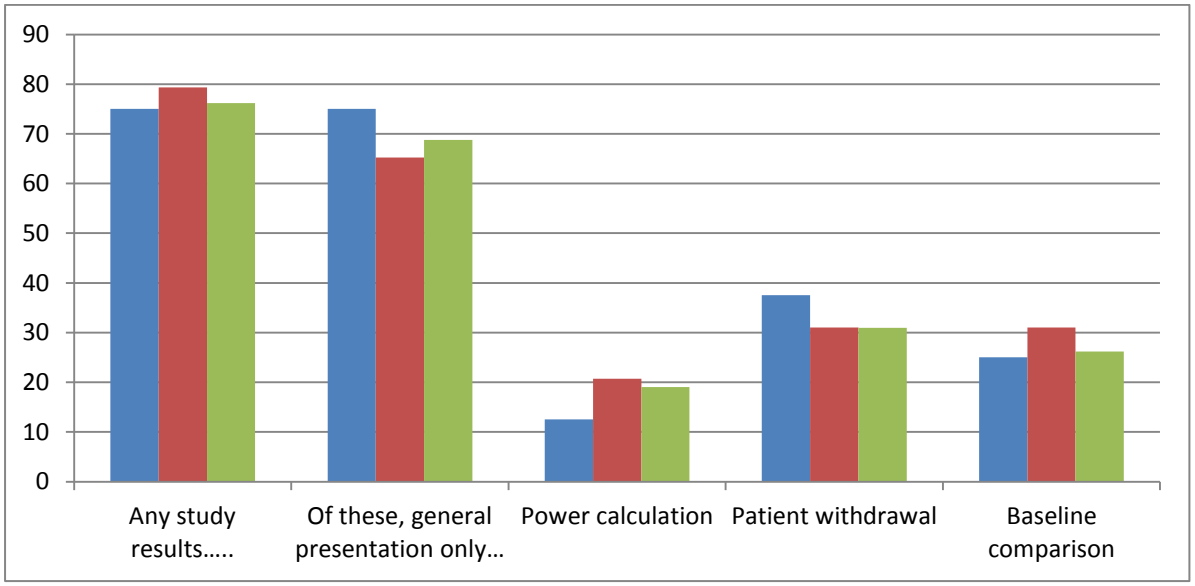


Evidence requirements: blue used for medical devices (N=16), red used for pharmaceuticals (N=29), green total evidence requirements (N=42).

Study results

Evidence requirements frequently included a request for the individual study results (n=32, 76%), but this was often a general request for results (n=22, 69% of those requesting results) rather than a request for the results to be presented in a specific way (figure 23). Evidence requirements including a request with a specific style of presentation included England, with a request for effect size, 95% confidence interval and p value, and Germany, requesting event numbers for intervention and comparator, measure of difference, 95% confidence interval and p value. Other aspects such as patient withdrawal (n=13, 31%), comparison of patients at baseline (n=11, 26%) and sample size determination (n=8, 19%) were not frequently requested. It is noted that many agencies request regulatory documents, such as the EPAR, as well as copies of published clinical studies. Therefore they may take information directly from these documents rather than asking that companies also present these data.

Figure 23: Evidence requirements including a request for information about individual study results (% of evidence requirements with information)

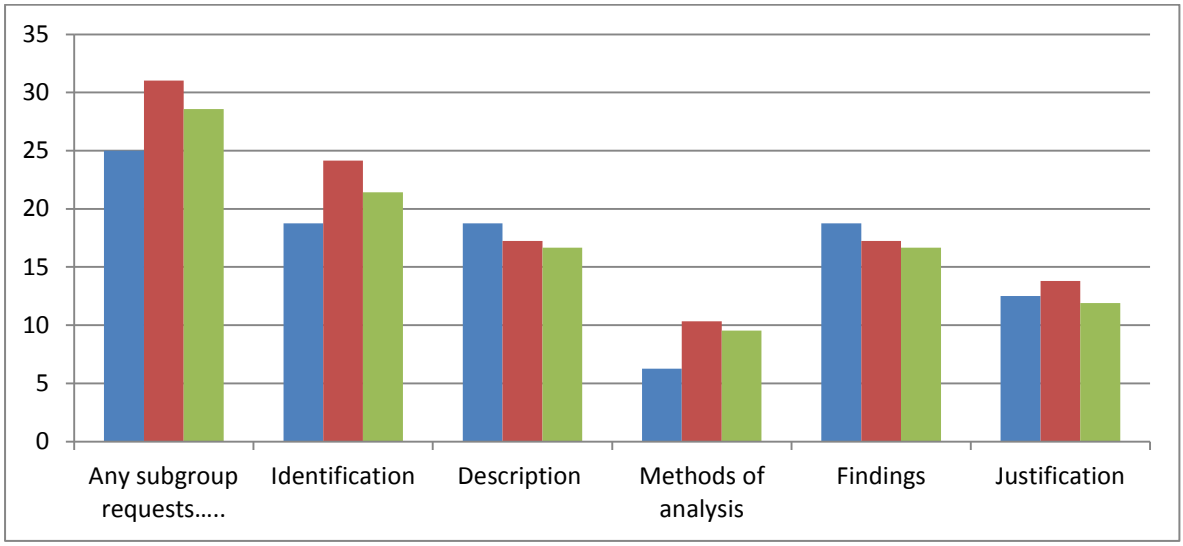


Evidence requirements: blue used for medical devices (N=16), red used for pharmaceuticals (N=29), green total evidence requirements (N=42).

Requests for subgroup data

Most evidence requirements did not specifically include a request for consideration of subgroups beyond the target population proposed by the company (figure 24). In 29% (n=12) of the evidence requirements there was a section about subgroups or a request for information about subgroups. The information requested tended to be similar across countries. The most common requests were how the subgroup was identified (n=9, 21%), a description of the subgroup (n=7, 17%) and results (n=7, 17%).

Figure 24: Evidence requirements including a request for information about subgroups (% of evidence requirements with information)

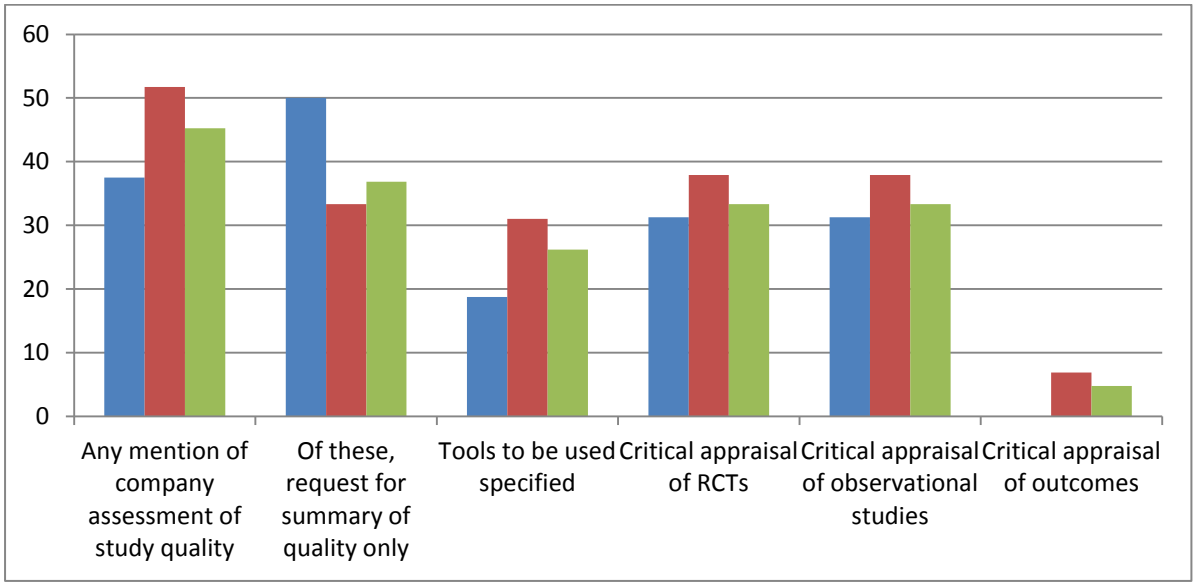


Evidence requirements: blue used for medical devices (N=16), red used for pharmaceuticals (N=29), green total evidence requirements (N=42).

Risk of bias

The evidence requirements varied in the level of detail that companies were asked to provide about study quality or risk of bias. In 45% (n=19) of the evidence requirements companies were asked to consider study quality in some way (figure 25). In some evidence requirements this was as part of a narrative (for example, Ireland asks for 'limitations of the trials that may affect the quality of the evidence'), or as a summary score for each included study (for example, Switzerland; medical devices evidence requirements). In other evidence requirements companies were asked to provide a breakdown of each of the component parts that informed the assessment of risk of bias (for example, England and Germany; pharmaceutical evidence requirements). A small number of countries specified the tools to be used in their evidence requirements, but these varied between countries for example England specified the Centre for Reviews and Dissemination (CRD) tools, and Germany (pharmaceutical evidence requirements) included their own tool. Other countries mentioned the use of hierarchies of evidence rather than specific critical appraisal tools for example, France, Netherlands, Russia and Turkey (all pharmaceutical evidence requirements). Countries rarely requested (n=2; 5%) that companies assess the risk of bias at the level of the study outcomes. In some evidence requirements the risk of bias assessment from companies was not requested, but aspects of methodology were for example, methods of randomisation or allocation concealment that would have enabled the agency to make this judgement (for example, Belgium; medical devices).

Figure 25: Evidence requirements including a request for company assessment of risk of bias (% of evidence requirements with information)

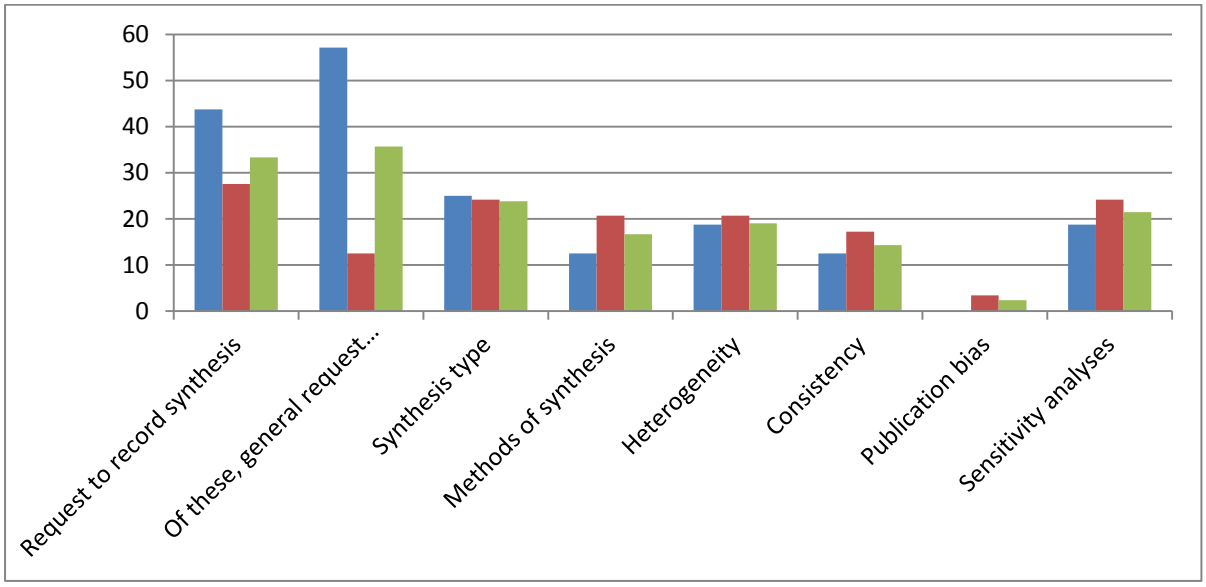


Evidence requirements: blue used for medical devices (N=16), red used for pharmaceuticals (N=29), green total evidence requirements (N=42).

Methods of evidence synthesis

The methods used by companies to derive their conclusions about clinical effectiveness were requested in a third of evidence requirements (n=14, 33%) (figure 26). In just over a third of these evidence requirements, the request was a general one (n=5; 36% of the evidence requirements requesting an evidence synthesis), as part of a request to complete a systematic review, without a specific set of questions or headings for companies to respond to (Belgium and France medical devices evidence requirements). When headings were given, companies were asked to record the synthesis type (n=10, 24%), methods of synthesis (n=7, 17%), comment on the heterogeneity of studies (n=8, 19%) and sensitivity analyses completed (n=9, 21%). The factors to consider when writing up the synthesis tended to be included in the guidance documents rather than in the submission templates and legal ordinances (for example, the documentation from Poland).The evidence requirements for medical devices were more likely than those for pharmaceuticals to include a request for a synthesis as part of a request for a systematic review without providing further headings in the evidence requirements.

Figure 26: Evidence requirements including a request for the company's process of evidence synthesis (% of evidence requirements with information)

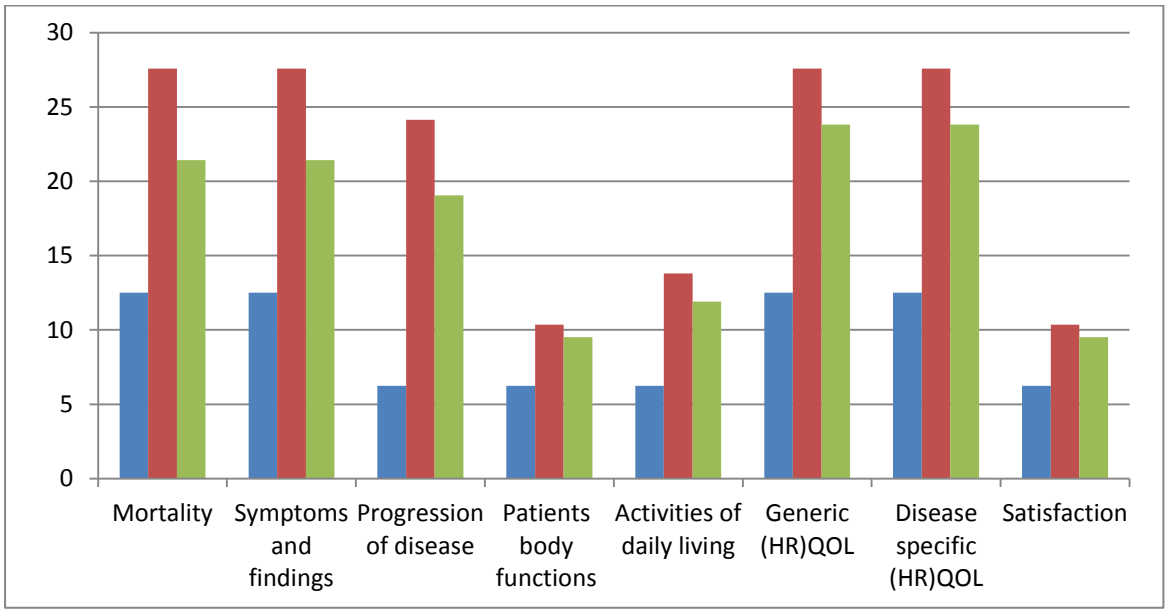


Evidence requirements: blue used for medical devices (N=16), red used for pharmaceuticals (N=29), green total evidence requirements (N=42).

Conclusions on the clinical effectiveness evidence

A summary of the evidence base or interpretation of the evidence base was requested in 79% of the evidence requirements (n=33). However, in 22 of the 32 (69%) evidence requirements in which conclusions were requested, this was only a general request, rather than a request for companies to make conclusions about specific endpoints (for example, mortality or symptoms). When companies were asked to summarise the evidence on specific endpoints, these were most frequently mortality (n=9, 21%), symptoms (n=9, 21%), progression of disease (n=8, 19%) and (health-related) quality of life (n=10, 24%). Endpoints about patients' bodily functions (n=4, 10%), activities of daily living (n=5, 12%) and patient satisfaction (n=4, 10%) were less frequently mentioned and referred to less specifically as morbidity or disability (figure 27). This does not mean that these data are not submitted to agencies or used in decision-making, rather agencies are not specific in asking that these outcomes should or should not be referred to in the interpretation of the evidence by companies. Evidence requirements for pharmaceuticals were more likely than those for medical devices to specify the endpoints companies should consider in their interpretation of the data.

Figure 27: Evidence requirements including a request for conclusions or summaries of the evidence base (% of evidence requirements with information)

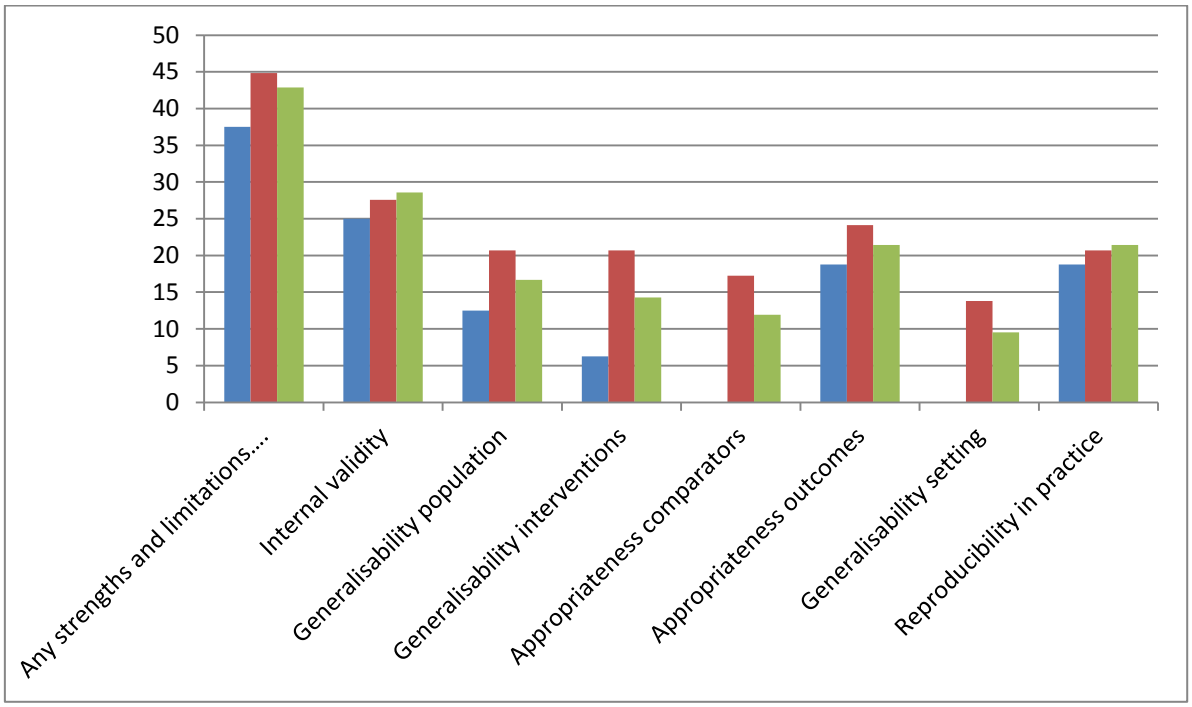


Evidence requirements: blue used for medical devices (N=16), red used for pharmaceuticals (N=29), green total evidence requirements (N=42).

Strengths and limitations

In 43% (n=18) of the evidence requirements a request for companies to summarise the strengths and limitations of the evidence base (figure 28) was included. Consideration of internal validity was requested in 12 of the evidence requirements (29%). For generalisability, relevance or external validity, some evidence requirements were more specific than others. For example, the evidence requirements from France for medical devices mentioned the transferability of the results of trials to the population in clinical practice with specific reference to the study populations, risks of misuse, ability to identify patients who will benefit, and reproducibility in practice. In contrast, the medical device evidence requirements from Germany were less specific; an assessment of the reliability of the results and of the suitability of the product for its intended use was requested. The most frequently requested factors relating to external validity were: generalisability of the populations (n=7, 17%), appropriateness of the outcomes (n=9, 22%) and the reproducibility of the findings to clinical practice (n=9, 21%). In some cases the request to consider the strengths and limitations was specifically related back to the scope of the assessment or decision problem underlying the assessment for example, the evidence requirements from England and from Norway.

Figure 28: Evidence requirements including a request for the company to consider the strengths and limitations of the evidence base (% of evidence requirements with information)



Evidence requirements: blue used for medical devices (N=16), red used for pharmaceuticals (N=29), green total evidence requirements (N=42).

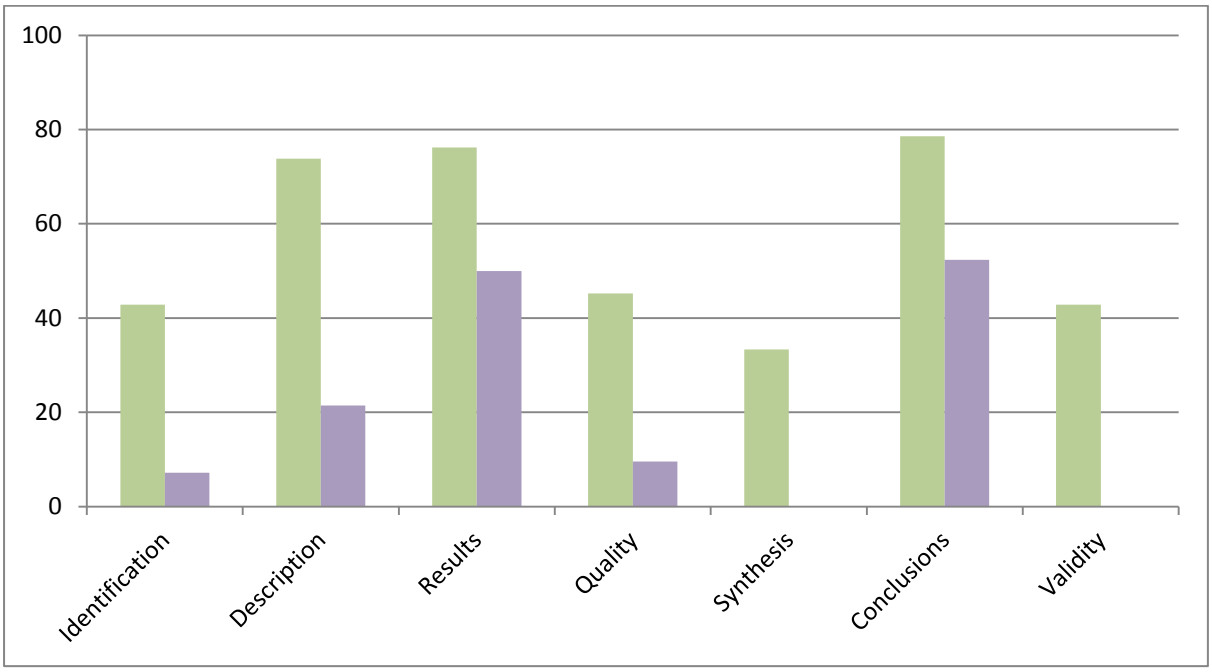
Summary

- All evidence requirements included at least one piece of information relating to clinical effectiveness, but the amount of evidence requested and level of detail that companies were asked to provide varied between evidence requirements.
- The most commonly requested items were a list of the relevant evidence and/or a summary of the clinical effectiveness evidence.
- Methodological aspects such as identification of studies, quality assessment and synthesis of evidence were less frequently requested. This is likely to be a result of different processes, with some agencies completing their own independent assessment using evidence provided by companies.
- When requested, methodological aspects were not described in detail. This may be because this information is provided in guidance documents rather than prescriptively outlined in the submission templates and checklists.
- The presentation of information requested by national agencies for pharmaceuticals was similar to that requested for medical devices. However, for the medical device evidence requirements there was more likely to be a general request for a systematic review rather than a prescriptive outline.

Safety

All the evidence requirements included some form of request to companies to provide clinical data (which may include safety data). A minority of the evidence requirements (n=9; 21%) did not include a request that companies present the clinical effectiveness data and the safety data separately. In these evidence requirements study reports or publications were requested, or a summary of trial data, or companies were asked to present trial data for all relevant outcomes without separately reporting clinical outcomes and safety outcomes.

Figure 29: Evidence requirements including a request for presentation of safety data separately from clinical effectiveness data (% of evidence requirements with information)



The green bars are the evidence requirements that included a request for information (that could relate to clinical effectiveness and safety together or separately), the purple bars are the evidence requirements that included a request for safety and effectiveness presented separately (N=42).

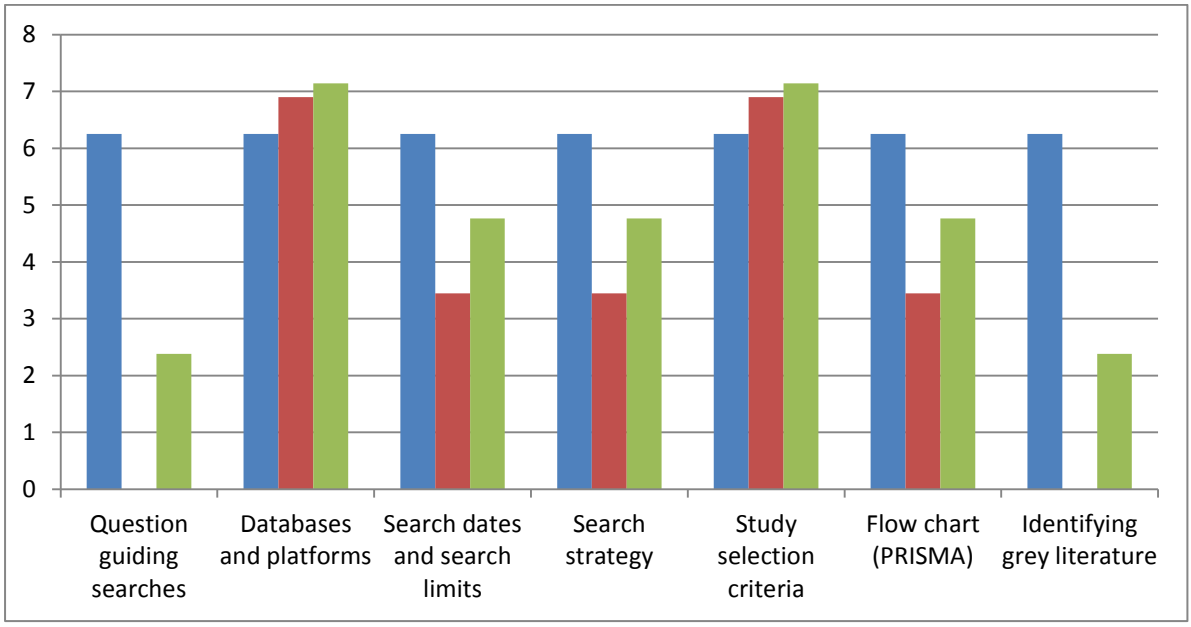
Evidence requirements differentiating between clinical effectiveness and safety did so in 2 ways, by either (1) using headings and/or questions for safety outcomes that were different from those used for clinical outcomes, or (2) including a separate section for safety outcomes but using the same structure for presentation as for clinical outcomes (for example, questions about study identification, description and quality assessment in the evidence requirements from England). When different headings and questions were used these were most frequently for the safety results data from individual studies and for the companies' interpretation and conclusions relating to safety. Sections for safety outcomes structured in the same way as clinical outcomes included searches of literature, quality assessment and strengths and limitations of the evidence base. None of the evidence requirements had completely separate presentations of clinical effectiveness and safety, for example, study safety

results could be presented separately from those of clinical effectiveness but the identification and interpretation of the studies from which the outcomes were derived were considered together (for example, England) (figure 29).

Identification of safety data

A minority (n=18; 43%) of evidence requirements included a request that companies record their searches of the literature, and of these, only 3 evidence requirements suggested that companies provide separate searches for safety data (the 2 evidence requirements from England and 1 from Ireland). Specific searches for safety data were not obligatory, and were focused on obtaining information from a wider range of study designs or a wider range of indications to supplement the information from the other studies in the submission. The type of information that companies were asked to record about the identification of relevant safety literature was the same as for clinical effectiveness for example, information about search dates (n=2; 5%), search strategies (n=2; 5%), databases and platforms (n=3; 7%), study selection criteria (n=3; 7%) and flow charts of study selection (n=2; 5%). For example, the evidence requirements from England asked companies to write up the safety searches using the same headings as for clinical effectiveness (figure 30).

Figure 30: Evidence requirements including a request for separate search information about safety (% of evidence requirements with information)



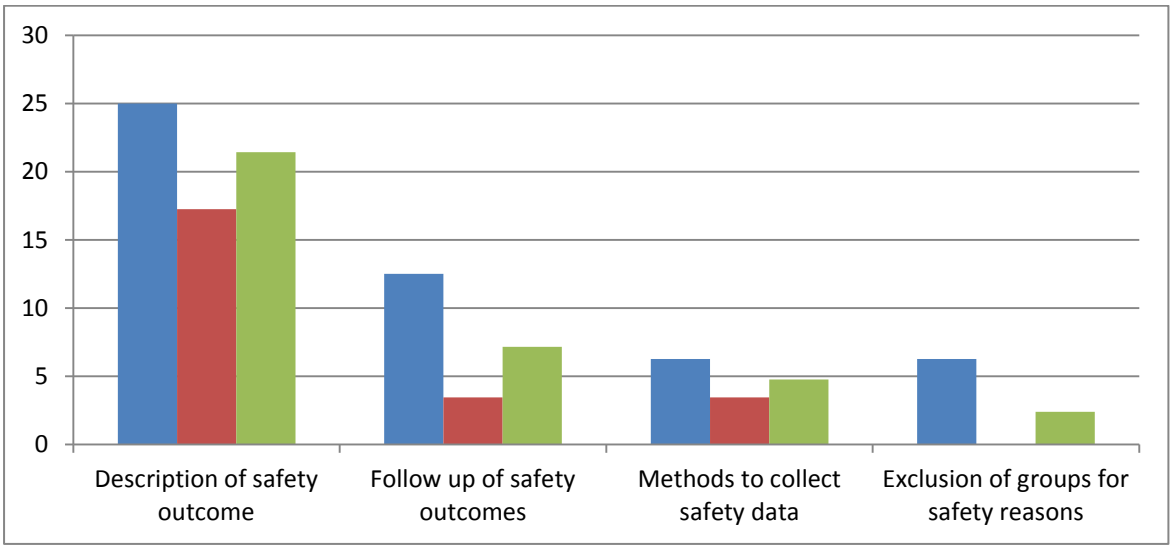
Evidence requirements: blue used for medical devices (N=16), red used for pharmaceuticals (N=29), green total evidence requirements (N=42).

Description of safety outcomes

In 21% (n=9) of evidence requirements there was a request that companies describe the safety outcome measured (figure 31). The level of requested detail varied, for example, Ireland and Scotland included separate sections or tables for safety outcomes, including a description of the outcome, while Germany included separate

columns for adverse events as part of their study description tables. For other evidence requirements the description of safety outcomes was considered as part of the request for a description of primary and secondary outcomes. In 2 of the 9 evidence requirements (both from England), there was a request that if additional safety studies are included then a description of these outcomes is included using the same reporting structure as for the clinical effectiveness studies.

Figure 31: Evidence requirements including a request for a separate description of safety outcomes (% of evidence requirements with information)



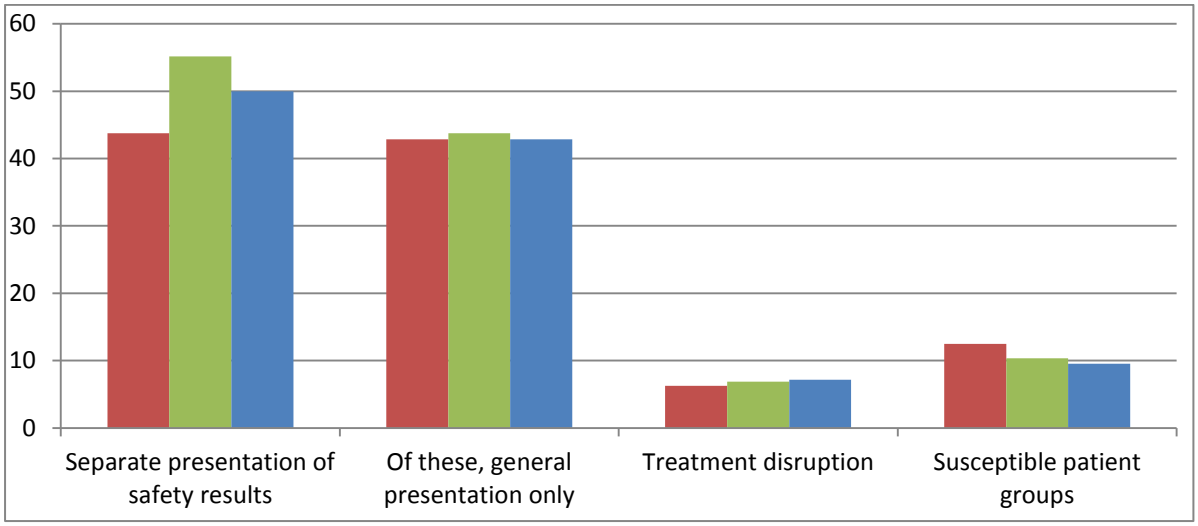
Evidence requirements: blue used for medical devices (N=16), red used for pharmaceuticals (N=29), green total evidence requirements (N=42).

Safety outcomes from individual studies

In 50% (n=21) of the evidence requirements there was a request for the safety data from individual studies to be presented separately from the clinical outcomes data (figure 32). This does not mean that these data were not requested by the other agencies, it is just that for some agencies, summaries of individual studies were requested that were ordered by primary compared with secondary outcomes, rather than by clinical and safety outcomes. Of the evidence requirements including a separate request for study safety results, 57% (n=12) specified how the data should be presented. For example, the evidence requirements from England requested that adverse events are divided into classes of event, and separated by time periods, and that for each time period the percentage and number of events in the intervention and comparator group is given as well as the relative risk and 95% CI. The table in the evidence requirements is based on the table given in the EPAR. The evidence requirements from Ireland state that results should be presented in terms of absolute and relative risk with appropriate statistical summaries, while those from Turkey specify reporting the number of events occurring in each arm of the trial. Most evidence requirements did not specifically mention other safety data considerations such as exposure to treatment, disruption of treatment (n=3; 7%) or patient groups more likely to be affected by adverse events (n=4; 10%). National agencies differ in

the extent to which safety is taken into account because of the overlap with the regulatory authorities. Some agencies may take this information directly from regulatory documents, others may take this information into account only in the context of the health economic evaluation or not at all.

Figure 32: Evidence requirements including a request for separate presentation of individual study safety data (% of evidence requirements with information)



Evidence requirements: blue used for medical devices (N=16), red used for pharmaceuticals (N=29), green total evidence requirements (N=42).

Risk of bias in safety outcomes data and studies

Studies providing safety data were critically appraised in the same manner as studies providing clinical effectiveness data. The evidence requirements from England, although including a separate section for safety data, state that when different studies are used to provide safety data from clinical effectiveness data, the relevant sections of the template for the clinical effectiveness data (for example, study identification, description, methodology, critical appraisal) should be repeated for the safety data. The pharmaceutical evidence requirements from Germany, which request an assessment of risk of bias in outcomes, uses the same risk of bias tool for all outcomes.

Synthesis of safety data

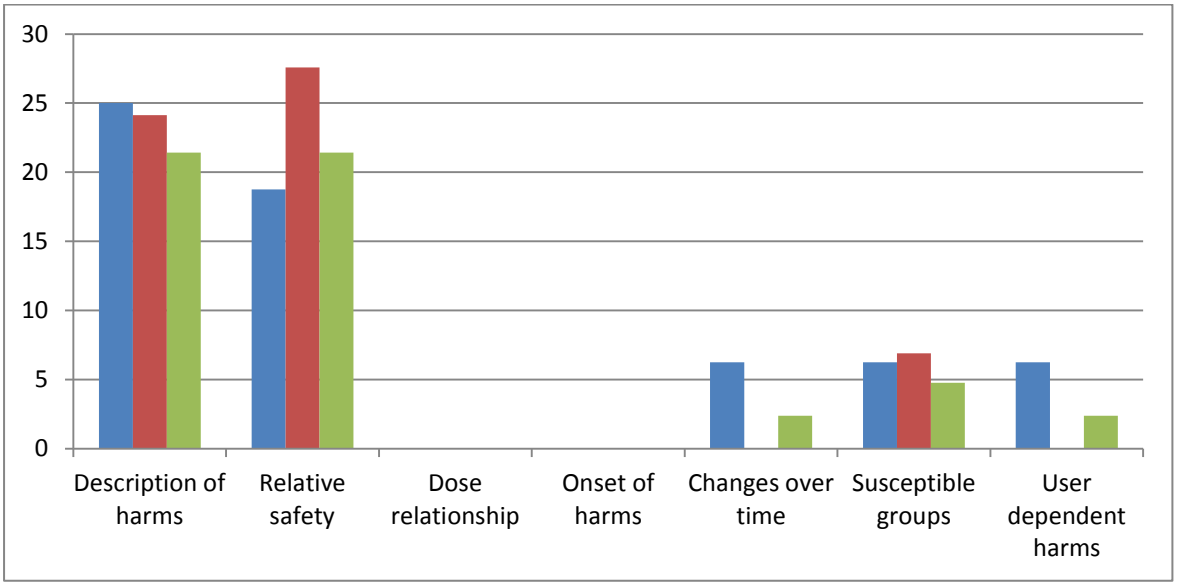
In none of the evidence requirements was there a request that companies include a separate write-up of the evidence synthesis specific to the safety data. When safety data were synthesised the presentation of the synthesis was completed using the same headings as those for clinical effectiveness.

Interpretation and conclusions about safety data

In 52% (n=22) of the evidence requirements there was a request for companies to summarise the safety conclusions separately from the clinical effectiveness conclusions. Of these 45% (n=10) included only a general request for the

interpretation or summary or discussion of the safety data. Of the 55% coded as requesting specific information relating to safety data, this was most commonly a description of harms (n=9; 21%) and/or of relative harms (n=9; 21%; figure 33). The medical device evidence requirements from France included the most detailed request for the summary of safety data, including how harms changed over time, user dependent harms and risks that the product poses to operators.

Figure 33: Evidence requirements including a request for separate interpretation and conclusions about safety data (% of evidence requirements with information)



Evidence requirements: blue used for medical devices (N=16), red used for pharmaceuticals (N=29), green total evidence requirements (N=42).

Strengths and limitations

None of the evidence requirements included a request for separate strengths and limitations for safety. In one evidence requirement specific strengths and limitations related to safety data were mentioned in guidance documents. However, this was not reflected in the template structure (Ireland).

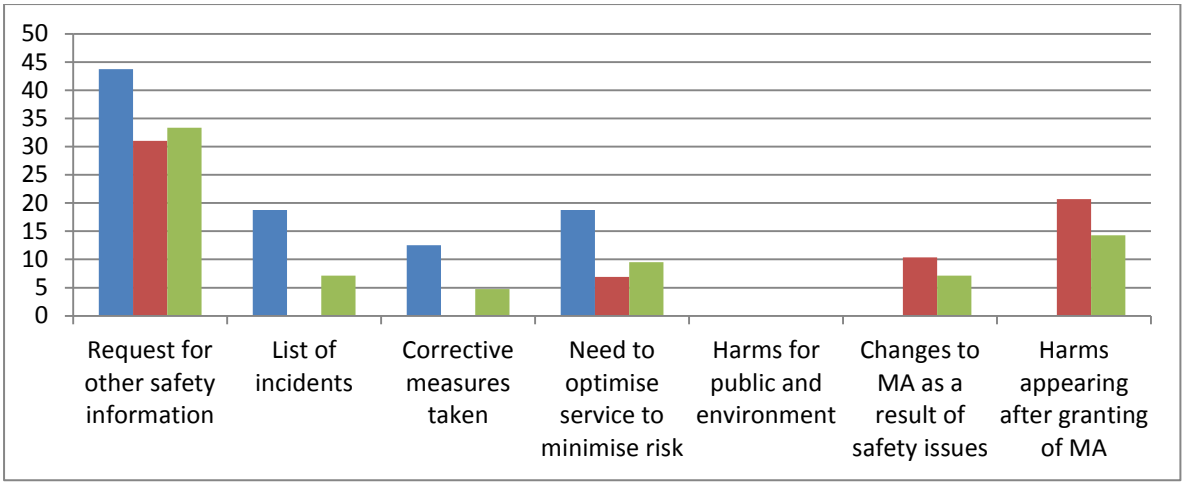
Other safety information

A third of the evidence requirements (n=14; 33%) included a request that companies provide other safety information obtained from outside of the clinical trials (figure 34). In 3 of the medical device evidence requirements (England, Germany, France) there was a request for vigilance data, for example a list of the incidents and the corrective measures taken. For evidence requirements for pharmaceuticals the information requested was for changes to the marketing authorisation as a result of safety issues (n=3; 7%) and data on harms that have come to light after granting of the marketing authorisation (n=6; 14%). Other agencies requested information for professionals from regulatory websites (Poland) or the drug safety sheet (Luxembourg). Some

agencies may have taken this information directly from regulatory sources such as periodic safety updates.

In 7% of the evidence requirements (n=4; Estonia, France [medical devices], Croatia [medical devices] and Germany [pharmaceuticals]) there was a request for information about requirements to optimise the service to minimise risks. None of the evidence requirements included a request for information about potential harms to the public or the environment.

Figure 34: Evidence requirements including a request for safety information from outside of clinical trials (% of evidence requirements with information)



Evidence requirements: blue used for medical devices (N=16), red used for pharmaceuticals (N=29), green total evidence requirements (N=42). List of incidents and corrective measures do not apply to pharmaceuticals. Changes to marketing authorisation and harms appearing after granting of marketing authorisation do not apply to medical devices.

Summary

- A minority of the evidence requirements made no distinction between presentation of clinical effectiveness and safety data for example, study reports or a summary of trial data were requested.
- When a distinction between clinical effectiveness and safety was made, this was most commonly between the safety and clinical results (n=21; 50%) and the safety and clinical conclusions (n=22; 52%).
- A smaller proportion made the distinction between other aspects for example, description of studies.
- The information requested about methodology usually had the same structure as for clinical effectiveness for example, the questions used for clinical effectiveness were also used for the safety data.
- The data requested from clinical studies was the same in evidence requirements for pharmaceuticals and for medical devices.

- A third of evidence requirements also included information about safety issues from sources outside of the clinical studies, these differed between evidence requirements for medical devices and pharmaceuticals.

Analysis of other information requests

The development of the evidence submission template focused on the health condition and current use of the technology, description and technical characteristics of the technology, and the clinical effectiveness and safety domains of the HTA CORE model. However, evidence requirements often include other information beyond these domains of the HTA CORE model. An additional analysis aimed to describe the other kinds of information requested, to establish whether the development of submission templates in these areas could be of value to national agencies making reimbursement decisions.

Methods of analysis

The documentation used in the analysis was the evidence requirements and guidance documents provided by the national agencies making decisions on the reimbursement of health technologies (pharmaceuticals and medical devices).

Data coding forms were developed in Excel. Each evidence requirement was coded independently by 2 EUnetHTA partners. The completed forms were then reconciled to create a final version of the data extraction. For each evidence requirement it was recorded whether a piece of information was specifically requested. The similarities and differences between the evidence requirements were then analysed by counting the number and range of items requested.

The analysis focused on the information relating to economic aspects, because this was the information most frequently requested in the evidence requirements. Evidence requirements requesting information about legal and ethical issues tended to ask either very general questions (for example, Switzerland in their evidence requirement for medical devices asked ‘Does the new service raise any ethical issues, if so, what are these?’), or questions that were specific to the national context for example, the evidence requirements for England asked specifically about equalities issues in the context of national legislation. Other information that could be interpreted as part of legal aspects for example, guarantees and patent information, had already been coded as part of the description of the technology. Social aspects were more frequently requested than legal and ethical aspects, but when these were requested they were again often coded as part of the analysis of other domains, for example clinical effectiveness.

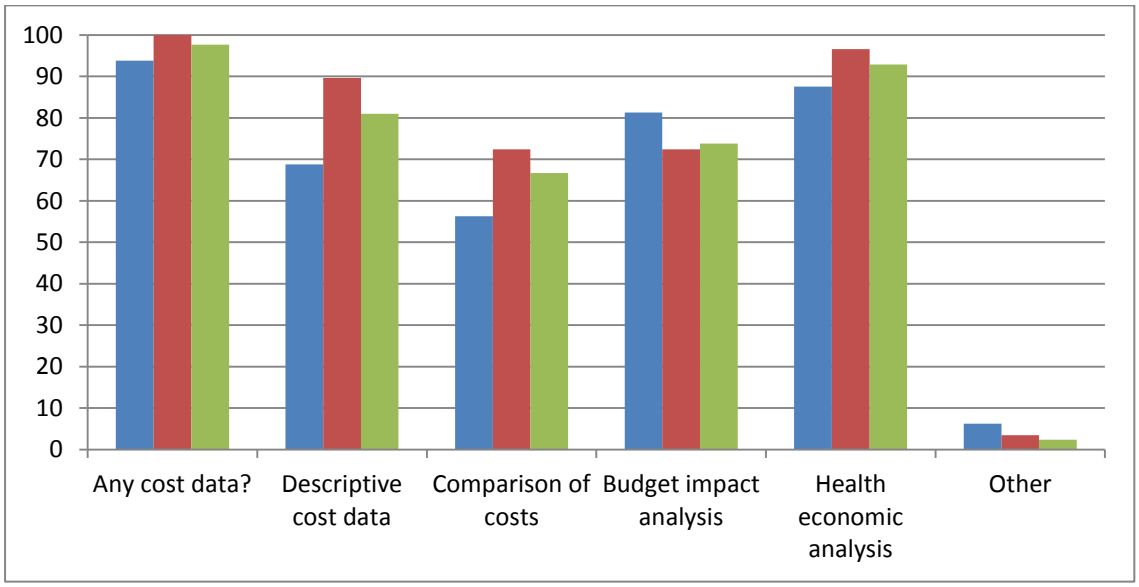
Information relating to costs

Of the 42 evidence requirements, 41 included a request for evidence about costs (figure 35). For 3 agencies this information was either all included or mainly included in a separate evidence requirement (Netherlands and Germany, pharmaceuticals; France, pharmaceuticals and medical devices). Only the evidence requirement from Germany for medical devices included no reference to including information about costs.

The kinds of cost data included were descriptive data on the costs of the technology (n=34; 81%), comparisons of the costs of the technology under assessment with alternative technologies or with the costs in other countries (n=28; 67%), budget impact analyses (n=31; 74%) and health economic analyses (either reviews or summaries of existing literature or de novo analyses, n=39; 93%). Budget impact analysis was more frequently requested in the evidence requirements used for medical devices than for pharmaceuticals (81% compared with 72%), whereas the opposite was true for the other types of information.

As with the information about clinical evidence, there was variation in how prescriptive the requests for evidence were. For example in some cases, there was a guidance document for companies to follow, but there was no pre-specified template (for example Sweden; Belgium, pharmaceuticals; Denmark). In other cases there was a prescriptive template for companies to complete (for example, England, both evidence requirements; Germany, pharmaceuticals).

Figure 35: Summary of types of cost data requested (% of evidence requirements with information)



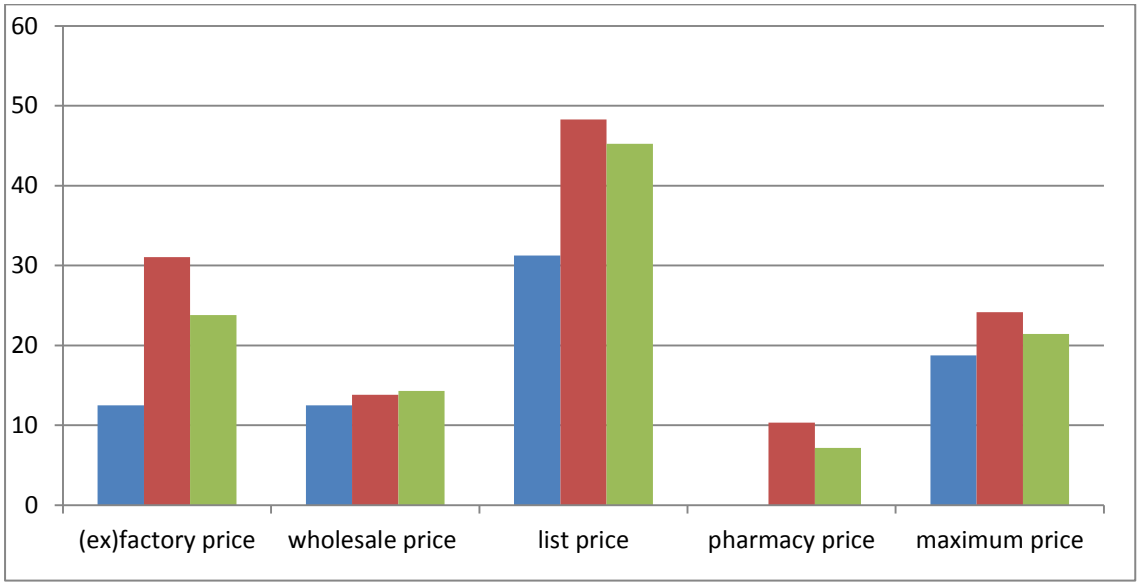
Evidence requirements: blue used for medical devices (N=16), red used for pharmaceuticals (N=29), green total evidence requirements (N=42). Descriptive cost data and comparisons of costs were coded when these are requested separately from their inclusion in budget impact analysis or health economic analysis.

Descriptive unit cost data requested

The descriptive cost data requested included list or public prices (n=19; 45%), wholesale prices (n=6; 14%), factory prices (n=10; 24%) and pharmacy prices (n=3; 7%; figure 36). Other evidence requirements included a request for information, such as the list price, as part of cost comparisons, budget impact analysis, or health economic analysis. For countries where decisions on pricing are taken as part of the

reimbursement process, some evidence requirements also included questions about the maximum price (n=9; 21%) and the proposed or requested price (n=15; 36%).

Figure 36: Summary of unit cost data requested (% of evidence requirements with information)

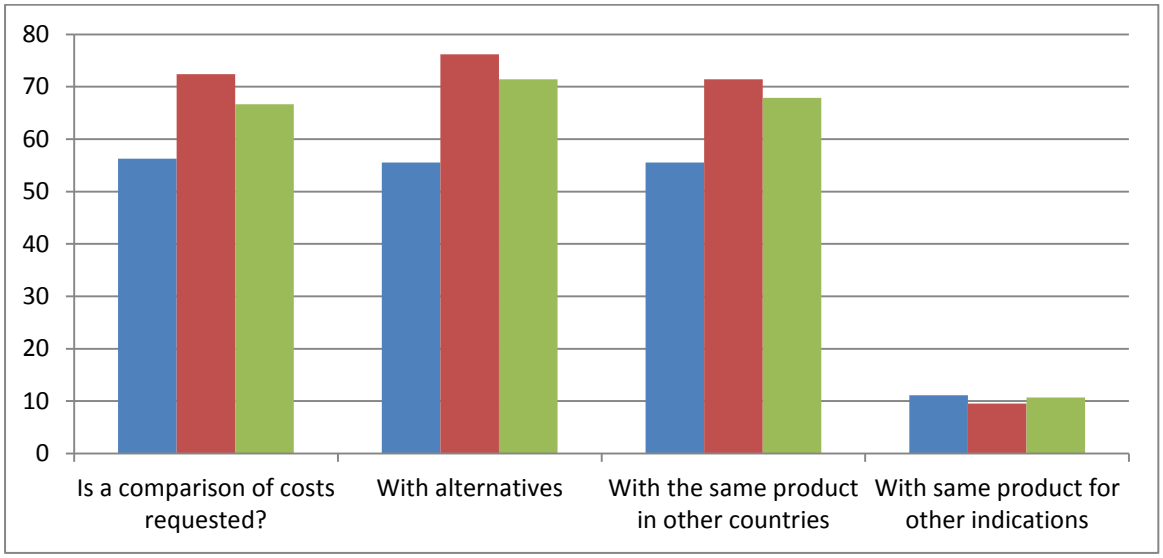


Evidence requirements: blue used for medical devices (N=16), red used for pharmaceuticals (N=29), green total evidence requirements (N=42).

Comparisons of costs

Most evidence requirements asked for some kind of descriptive comparison of costs (n=28; 67%) (figure 37). The comparison requested was either with the current standard treatment or an alternative technology (n=20, 71%), or of the cost of the same technology in other countries (n=19; 68%). In a smaller number of evidence requirements other comparisons, such as the costs of using the same product for a different indication, were requested (n=3; 11%). The basis for such a comparison was most frequently the unit cost (n=20; 48%), but could also be the daily cost (n=9; 21%), annual cost (n=4; 10%), or the duration of treatment (n=11; 26%).

Figure 37: Summary of cost comparisons requested (% of evidence requirements with information)



Evidence requirements: blue used for medical devices (N=16), red used for pharmaceuticals (N=29), green total evidence requirements (N=42).

Budget impact analysis

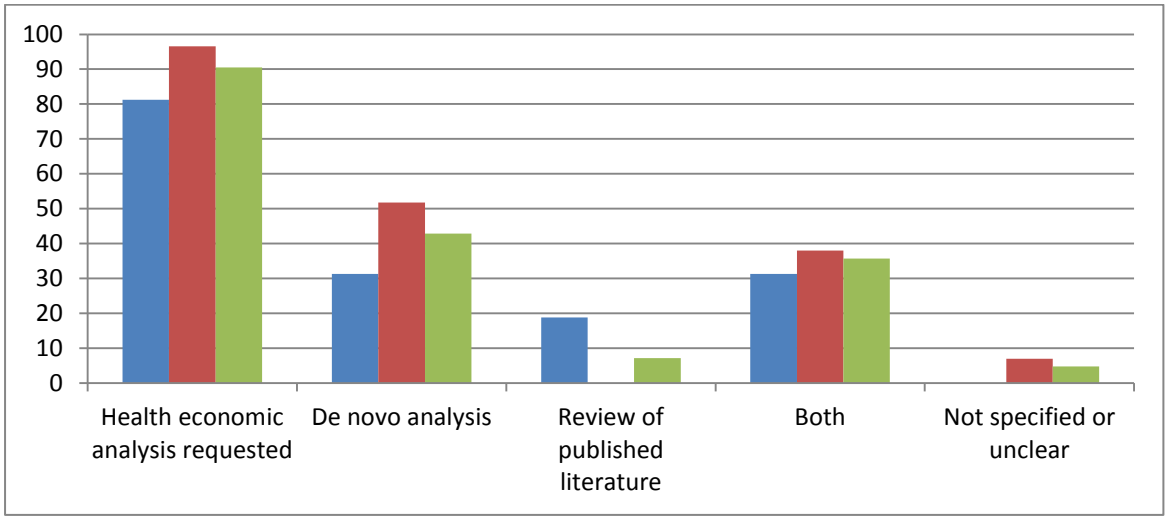
In 31 (74%) of the evidence requirements there was a request for a budget impact analysis. Companies were asked to provide information about the annual cost of introducing the technology over a time horizon of 1, 3 and/or 5 years. The costs to be included in the analyses varied and in some cases multiple scenarios were required. A scenario with drug costs only was requested in 9 evidence requirements (21%), direct costs were requested in 17 evidence requirements (40%) and in other cases some indirect costs could be included, or these could be included in sensitivity analyses (n=1; 2%).

Health economic analysis

In all evidence requirements except 4 (90%) there was a request for some health economic analysis (figure 38). However, in some (n=9) a health economic analysis was optional in some situations (for example, if the submission was for a generic product) or all situations. In other evidence requirements (n=3) the health economic analysis was a review of the literature or a request for health economic studies.

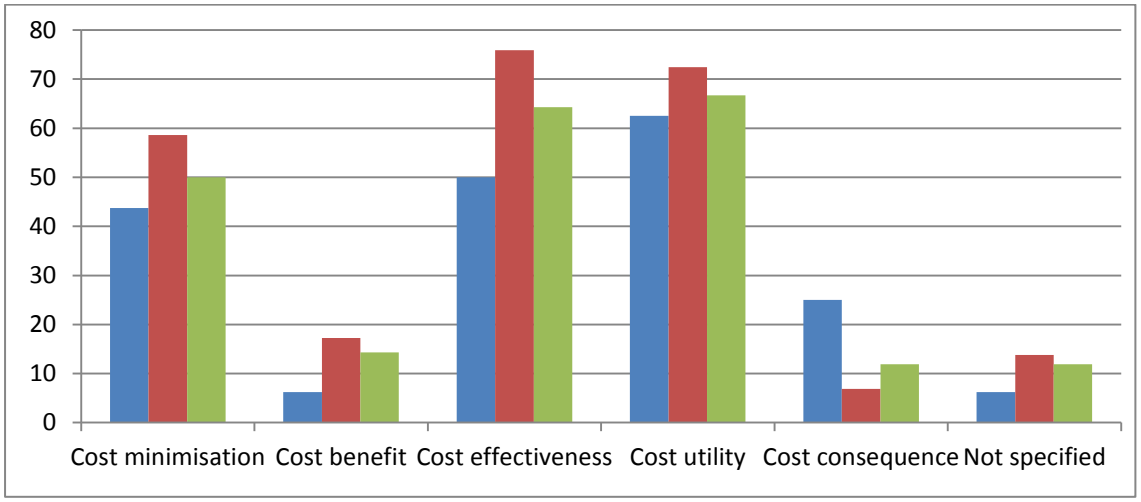
In the evidence requirements coded as requesting a de novo analysis (including evidence requirements where the analysis was optional; excluding 2 evidence requirements where the request was unclear) the range of types of analysis that could be submitted varied. These included: cost minimisation (n=21; 50%), cost benefit (n=6; 14%), cost effectiveness (n=27; 64%), cost utility (n=28; 67%) and cost consequence (n=5, 12%) (figure 39).

Figure 38: Summary of health economic analyses requested (% of evidence requirements with information)



Evidence requirements: blue used for medical devices (N=16), red used for pharmaceuticals (N=29), green total evidence requirements (N=42).

Figure 39: Summary of type of health economic analyses requested (% of evidence requirements with information)



Evidence requirements: blue used for medical devices (N=16), red used for pharmaceuticals (N=29), green total evidence requirements (N=42).

Pricing and sales information

For some reimbursement agencies pricing considerations were also reflected in evidence requirements. Some evidence requirements included a request for companies to justify their price(s) compared to other existing products (n=6; 14%). In 2 evidence requirements (Switzerland, Denmark) there was a request for companies to justify the pricing for different strengths of the same product or for different pack sizes of the same product.

In 23 (55%) of evidence requirements there was a request that companies provide information about actual or predicted sales at home (n=18; 43%), in other countries (n=1; 2%) or at home and in other countries (n=4; 10%). In some instances it was unclear if this information was being asked as part of the process of estimating budget impact, or if it was information for companies to provide separate to any budget impact.

Summary

- The company submission of evidence is rarely restricted only to information about relative effectiveness.
- A variety of other information, mainly about costs, is also requested from companies.
- The range of information requested varies. For example, cost information included unit costs, comparisons of costs, budget impact and primary and secondary health economic analysis.

Appendix 1: Evidence requirements provided

Evidence requirements in bold type were the main source of information used in the analysis. Documents in normal type were supplementary documents to support analysis of the main document.

Country	Agency	Submission template used for data extraction	Document type	English version	Technology
Austria	Hauptverband der österreichischen Sozialversicherungsträger	Arbeitbehelf Erstattungskodex *Reimbursement code*	Legal document	Provided	P
		Verfahrensordnung zur Herausgabe des Erstattungskodex nach § 351g ASVG - VO-EKO *Procedural rules for publication of the reimbursement code*	Template		
Belgium	Rijksinstituut voor ziekte- en invaliditeitsverzekering Institut National Assurance Maladie-Invalidité (RIZIV-INAMI)	**Demande d'admission au remboursement d'une specialite en classe 1 (2009)** *Request for a reimbursement admission of a specialty in category 1 (2009)*	Checklist	Provided	P
		Belgian guidelines for economic evaluations and budget impact analyses: second edition	Guidance document	Provided	P
		RECOMMANDATIONS POUR LA CONSTITUTION DU DOSSIER *Recommendations for the contents of the submission*	Template	Generated	D
Bulgaria	National Council for Pricing and Reimbursement of the Medicinal Products	**ДО НАЦИОНАЛНИЯ СЪВЕТ ПО ЦЕНИ И РЕИМБУРСИРАНЕ НА ЛЕКАРСТВЕНИТЕ ПРОДУКТИ З А Я В Л Е Н И Е** *TO NATIONAL COUNCIL ON PRICES And reimbursement of MEDICINES: Application*	Template	Summary Provided	P
Croatia	Agency for Quality and Accreditation in Health Care and Social Welfare provided documents used by the Croatian Institute for Health Insurance	**Pravilnik o mjerilima za stavljanje lijekova na osnovnu i dopunsku listu lijekova Hrvatskog zavoda za zdravstveno osiguranje, Official Gazette No. 155/2009** (Provisional translation on English language: Ordinance: Establishing the criteria for inclusion of	Legal document	Provided	P

	(Ordinances) and by Agency (The Croatian Guideline for HTA)	medicinal products in the basic and the supplementary reimbursement list of the Croatian Institute for Health Insurance (2009)			
		Pravilnik o mjerilima za stavljanje lijekova na osnovnu i dopunsku listu lijekova Hrvatskog zavoda za zdravstveno osiguranje, Official Gazette No. 83/2013; changes from Ordinance published in 2009	Legal document	Summary Provided	P
		Official Gazette No. 138/09 PRAVILNIK O MJERILIMA ZA STAVLJANJE ORTOPEDSKIH I DRUGIH POMAGALA NA POPIS POMAGALA HRVATSKOG ZAVODA ZA ZDRAVSTVENO OSIGURANJE	Legal document	Summary Provided	MD
		Official Gazette No. 43/13 PRAVILNIK O IZMJENAMA PRAVILNIKA O MJERILIMA ZA STAVLJANJE ORTOPEDSKIH I DRUGIH POMAGALA NA POPIS POMAGALA HRVATSKOG ZAVODA ZA ZDRAVSTVENO OSIGURANJE	Legal document	Summary Provided	MD
		Official Gazette No. 84/13 ORDINANCE ON ESSENTIAL REQUIREMENTS, CLASSIFICATION, REGISTRATION OF MANUFACTURERS IN THE REGISTER OF MEDICAL DEVICE MANUFACTURERS, REGISTRATION OF MEDICAL DEVICES IN THE REGISTER OF MEDICAL DEVICES AND CONFORMITY ASSESSMENT OF MEDICAL DEVICES	Legal document	Provided	MD
		The Croatian Guideline for Health Technology Assessment	Guidance document	Provided	G
Czech Republic	Ministry of Health	**Žádost o stanovení maximální ceny výrobce a výše a podmínek úhrady léčivého přípravku / potraviny pro zvláštní lékařské účely (2013)** *Request to set the maximum price of the manufacturer and the amount and terms of payment of the medicinal product / food for special medical purposes (2013)*	Template	Summary provided	P
		An application for categorization of new medical devices (hereinafter "MD") into the Reimbursement catalogue of major health	Checklist	Summary provided	D

		insurance company (hereinafter "VZP")			
Denmark	Sundhedsstyrelsen *Danish Health and Medicines Authority*	**Ansøgning om generelt tilskud eller generelt klausuleret tilskud til et lægemiddel** *Application for general reimbursement or conditional reimbursement of a pharmaceutical product*	Template	Generated	P
		Vejledning til ansøgning om generelt tilskud. *Guidelines for application for general reimbursement of medicinal products*.	Guidance document	Provided	P
		Vejledning om procedure for revurderinger *Guidelines on procedure for reassessment of reimbursement status*	Guidance document	Provided	P
		Standardised reporting structure for health economic analyses in applications for general reimbursement	Guidance document	Provided	P
England	National Institute for Health and Care Excellence	**Technology appraisals: Specification for manufacturer/sponsor submission of evidence (June 2012)**	Template	Provided	G
		Guide to the methods of technology appraisal 2013	Guidance document	Provided	G
		Medical technologies evaluation programme: manufacturer submission of evidence (March 2013)	Template	Provided	D
		Medical Technologies Evaluation Programme: Methods guide	Guidance document	Provided	D
Estonia	Tartu University Department for Public Health provided documents used by the Estonia Health Insurance Fund	**Eesti haigekassa tervishoiuteenuste loetelu muutmise taotlus** *Application form to add new health care service or to modify the health insurance service list*	Template	Provided	G
Finland	Finnish Medicines Agency Assessment of Pharmacotherapies Process provided documents used by the	**Application for reimbursement status and wholesale price for a medicinal product subject to marketing authorization.**	Template	Provided	P
		Application instructions: Reimbursement status and whole-sale price for a medicinal product subject to marketing authorization.	Instructions	Provided	P

	Pharmaceutical Pricing Board				
France	Haute Autorite de Santé (HAS)	**Dossier Type: Premiere inscription ou extension des indications d'un medicament** *Standard Dossier: First assessment of extension of indication(s) of a medicine*	Template	Provided	P
		Notice de depot: Modalites de depot d'un dossier de demande aupres de la Commission de la Transparence *Submission instructions: Procedure for submitting an application dossier to the Transparency Committee*	Guidance document	Provided	P
		Guide to the application dossier for inclusion, for modification of the conditions for inclusion and for the renewal of inclusion of a product or service under a brand name on the list referred to in Article L.165-1 to be submitted to the National Committee for the Evaluation of Medical Devices and Health Technologies (CNEDiMTS)	Template	Provided	D
		Choices in methods for economic evaluation: October 2012	Guidance document	Provided	G
		Avis d'efficience: rapport de presentation *Report for the presentation of efficiency*	Template	Generated	G
Germany	Institute for Quality and Efficiency in Health Care (IQWIG)	**Dossier zur Nutzenbewertung gemäß § 35a SGB V** *Dossier on benefit assessment according to § 35a SGB*	Template	Generated	P
		Antrag zur Erprobung von Untersuchungs- und Behandlungsmethoden nach § 137e des fünften Buches Sozialgesetzbuch Application for a testing of diagnostic and treatment methods according § 137e of the fifth book Social Code Book	Template	Generated	D
		Appendix VII to Chapter 5 - Application for a cost-benefit assessment	Template	Generated	P

Hungary	Országos Gyógyszerészeti és Élelmezés-egészségügyi Intézet - National Institute of Pharmacy and Nutrition (OGYEI formerly GYEMSZI) provided documents used by the National health insurance fund	**Requirements for pharmaceuticals (from the 32/2004. [IV.26.] MoH Regulation)**	Legal document	Summary provided	P
		Requirements for medical devices intended for patient use (from the 14/2007. [III. 14.] MoH Regulation)	Legal document	Summary provided	D
		Requirements for other medical devices and medical procedures (from the 180/2010. [V. 13] Government Regulation)	Legal document	Summary provided	D
Ireland	National Centre for Pharmacoeconomics (use guidelines produced by Health Information and Quality Authority [HIQA])	**Guidance on the Reporting Format and Layout of Pharmacoeconomic Submission to the National Centre for Pharmacoeconomics (February 2013)**	Template	Provided	P
		Guidelines for Evaluating the Clinical Effectiveness of Health Technologies in Ireland (23rd November 2011)	Guidance document	Provided	P
		Guidelines for the Economic Evaluation of Health Technologies in Ireland	Guidance document	Provided	P
		Guidelines for the Budget Impact Analysis of Health Technologies in Ireland 2010	Guidance document	Provided	P
Italy	Agenzia Italiana Del Farmaco (AIFA)	**Schema del dossier a supporto della domanda di rimborsabilita e prezzo** *Template for the file supporting the coverage and price application*	Template	Provided	P
Latvia	National Health Service, Centre of Health Economics (VECS)	**Evidence requirement in accordance with Davinet Regulation No. 899, adopted 31 October 2006** "Procedures for the Reimbursement of Expenditure for the Acquisition of Medicinal Products and Medicinal Devices Intended for Out-patient Medical Treatment"	Legal document	Provided	G
Lithuania	Ministry of Health	**PARAIŠKA: ĮRAŠYTI VAISTINĮ PREPARATĄ Į LIGŲ IR KOMPENSUOJAMŲJŲ VAISTINIŲ PREPARATŲ JOMS GYDYTI SĄRAŠĄ (A SĄRAŠĄ)** *Application for including medicinal product into the reimbursement system*	Template	Provided	P
Luxembourg	Union de Caisses de Maladie	**Demande d'inscription d'un medicament sur la liste positive des medicaments pris en charge par**	Template	Generated	P

		l'assurance maladie au Grand Duche de Luxembourg *Application for registration of a drug on the positive list of drugs covered by Medicare Grand Duchy of Luxembourg*			
Malta	Directorate for Pharmaceutical Affairs (DPA)	**Application to the Superintendent of Public Health for the consideration of a medicinal product to be covered by the Government Formulary List as per the Government Health Services (Medicinal Products) Regulations, 2007.**	Template	Provided	P
The Netherlands	Zorginstituut Nederland	**Template pharmacotherapeutic dossier for outpatient medicines (GVS)**	Template	Provided	P
		Framework for assessing medical aids Translation of CVZ-report 'Beoordelingskader hulpmiddelenzorg'. 2008 This document has been updated. Zorginstituut Nederland provided a summary of the changes to the evidence requirements for use in the analyses.	Guidance document and checklist	Provided	D
Norway	Norwegian Knowledge Centre for the Health Services provided documents used by the Norwegian Medicines Agency	**Application standard for acceptance to the drug reimbursement scheme**	Checklist	Provided	P
		Guidelines on how to conduct pharmacoeconomic analyses (1st March 2012)	Guidance document	Provided	P
	Norwegian Knowledge Centre for the Health Services	**Norwegian guidelines for medical technologies evaluation**	Checklist	Provided	G
Poland	Agency for HTA in Poland (AHTAPol) provided documents used by the Polish Ministry of Health	**Regulation of the Minister of Health of 2nd April 2012 on the minimum requirements to be satisfied by the analyses accounted for in the applications for reimbursement and setting the official sales price and for increasing the official sales price of a drug, a special purpose dietary supplement, a medical device, which do not have a reimbursed counterpart in a given indication.**	Legal document	Provided	G

		Act of 12 May 2011 on the reimbursement of medicinal products, special purpose dietary supplements and medical devices	Legal document	Summary provided	G
		Regulation of the Minister of Health of December 20th, 2012 on the submission template for the applications for reimbursement of a drug, a special purpose dietary supplement, and a medical device	Legal document	Summary provided	G
		Guidelines for conducting Health Technology Assessment (HTA)	Guidance document	Provided	G
Portugal	National Authority of Medicines and Health Products (INFARMED)	**Requests for prior assessment of medicinal products for human use in hospital setting**	Checklist	Provided	P
Russia	National Center for Health Technology Assessment provided documents used by the Ministry of Health	**Submission template**	Checklist	Provided	P
		Regulation of the Ministry of Health on the procedure of compiling draft essential drug list	Legal document	Provided	P
Scotland	Scottish Medicines Consortium (SMC)	**New Product Assessment Form (March 2012)**	Template	Provided	P
		Guidance to Manufacturers for Completion of New product Assessment Form (March 2012)	Instructions	Provided	P
Slovakia	Ministry of Health of Slovak Republic, Section of Pharmacy and Medicines Policy	**Farmako-ekonomický rozbor lieku (na účely kategorizácie liekov)** *Pharmacoeconomic analysis of a drug (for the reimbursement process concerning a drug)*	Template	Provided	P
		Farmako-ekonomický rozbor zdravotnickej pomocky (na účely kategorizácie zdravotnickych pomocok) *Medical-economic analysis of a medical device (for the reimbursement process concerning a medical device)*	Template	Provided	D
Slovenia	National Institute of Public Health (NIPH) and the Institute of Economic Research provided documents used by Health Insurance Institute	**Priloga pravilnik zdravila HTA** *Annex rules for pharmaceuticals HTA*	Template	Provided	P
		Priloga vaprasalnik Annex questionnaire [for medical devices HTA]	Template	Provided	D

	of Slovenia				
Sweden	Dental and Pharmaceutical Benefits Agency (TLV)	**ANSÖKAN - om att ingå i läkemedelsförmånerna samt om pris på läkemedel** *APPLICATION - to be reimbursed and the price of medicines*	Template	Generated	P
		Guide for companies when applying for subsidies and pricing for pharmaceutical products	Guidance document	Provided	P
		ANSÖKAN om att förbrukningsartikel ska ingå i läkemedelsförmånerna *Application for consumable items to be included in the reimbursement*	Template	Generated	D
		Handbok till Tandvårds- och läkemedelsförmånsverkets föreskrifter (TLVFS 2011:3) om ansökan om pris och subvention för förbrukningsartiklar *Guide to Dental and Pharmaceutical Benefits Agency regulations (TLVFS 2011: 3) on applications for price and reimbursement for supplies*	Guidance document	Generated	D
Switzerland	Federal Office for Public Health	Données-clés pour une nouvelle demande d'admission (ND) d'une préparation originale de médecine classique *Key data for a new application of an original preparation of conventional medicine*	Template	Generated	P
		Handbuch betreffend die Spezialitaten-liste *Handbook for the specialties-list providing guidance for the registration of pharmaceuticals*	Guidance document	Generated	P
		Demande d'inscription (version longue) du dispositif médical ... ... sur la liste des moyens et appareils (LiMA) déposée par … … … à l'Office fédéral de la santé publique à l'intention de la Commission fédérale des analyses, moyens et appareils, sous-commission des moyens et appareils (CFAMA-LiMA) et du Département fédéral de l'intérieur (DFI) *Application for registration of medical devices*	Template	Generated	D
		Demande de prise en charge des coûts par l'assurance obligatoire des soins (AOS)	Template	Generated	D

		concernant la prestation… … …déposée par … … …à l'Office fédéral de la santé publique (OFSP) à l'intention de la Commission fédérale des prestations générales et des principes (CFPP) et du Département fédéral de l'Intérieur (DFI) *Application form for the reimbursement of medical technologies by the national obligatory healthcare insurance.*			
		Manuel pour la présentation de demandes de prise en charge par l'assurance de prestations nouvelles ou controversées *Manual for applying for national reimbursement of medical technologies that are new or controversial over the national obligatory healthcare insurance*	Guidance document	Generated	D
Turkey	Turkish Evidence-based Medicine Association (KDTD) provided documents used by the Social Security Institution	**Summary of submission template for manufacturers in Turkey**	Checklist	Summary provided	P
		Summary of submission template for medical device manufacturers in Turkey	Checklist	Summary provided	D

Key: P used for pharmaceuticals, D used for medical devices, G used for both pharmaceuticals and medical devices

Appendix 2: data extraction forms pharmaceuticals

Domain 1: Health condition

	Information requested	Reference
1.1 Target condition		
Disease characteristics *Information under this subheading includes questions or guidance requesting information about the disease or condition for which the technology is intended, including definitions of the disease, the natural course of the disease or risk factors for the disease.*		
Effect on individual *Information under this subheading includes questions or guidance about the effects of the condition on the individual, this could include information about symptoms of the disease, impact on life expectancy and consequences of the disease in terms of disability and pain. This section also includes questions about the aspect of the disease targeted by the treatment.*		
Disease burden and epidemiology *Information under this subheading includes questions or guidance requesting information about the incidence and prevalence of the disease, number of patients with the condition and burden of disease to society.*		
Other		
1.2 Management		
Current management *Information under this subheading includes questions or guidance about relevant clinical guidelines on diagnosis and management of the condition, current practice in diagnosis and management of the condition, variations in management and management at different stages of disease or for different subgroups of patients with the condition, also includes unmet needs.*		
Relevant comparators *Information under this subheading includes questions or guidance about the identification of the relevant comparators for the technology. Questions relating to the reimbursement status of comparators and licensing status of comparators should also be included.*		
Proposed and current use of technology *Information under this subheading includes questions or guidance about current or proposed use of the technology. This can include current use and variations in current use of the technology (including available guidelines on using the product), alongside requests for prescription data or average course of treatment. This section also includes questions about the proposed positioning by the manufacturer.*		
Other		
1.3 Regulation and reimbursement		
Life cycle *Information under this heading includes questions or guidance asking for information about the phase of development of the technology. Note: information about licensing status should be under 'Regulation and reimbursement: licensing status'.*		
Regulatory status *Information under this heading includes information about licensing. This includes information about the anticipated licence, or licence received, other indications that the product has, the regulatory process followed, licensing issues, continuing undertakings, other ongoing or planned*		

indications and approvals for the same product in other countries. It should also include questions relating to the company[ies] manufacturing the product.		
HTA status *Information under this heading includes decisions for the product made by other HTA bodies or other decisions by the HTA body undertaking the assessment for other indications for which the product is licensed.*		
Other		
Please indicate N/A if no questions are included. Please include questions verbatim including a reference (ref) to the question/guidance number or page number. If countries request a table is filled in please indicate table requested and describe table contents (column headings or row headings). Use 'other' for any questions that are not covered by the existing categories.		

Domain 2: Technology

	Information requested	**Reference**
2.1 Features of the technology		
Description *Information under this heading includes questions and guidance requesting a description of the technology, aim and background to development of the technology, brand name, therapeutic class, mechanism of action, biosimilar or generic status, special features of the technology including claims of innovation and also information on who will use it and where it will be used.*		
Administration, dosing, costs *Information under this heading includes information relating to packaging and administration of the technology, dosage per unit, pack size, cost per pack, average cost of treatment and availability of access schemes.*		
Other		
2.2 Investments and tools required and training and information needed		
Requirements for use *Information under this heading includes information relating to describing the equipment, staff and services etc. that are required to implement the technology including those requirements specified in the marketing authorisation. These may include location of use, the personnel who will use the technology, diagnostics or procedures that must be given with the technology as part of management or diagnosis, as well as monitoring arrangements of patients and co-prescription of other medications for the condition or to manage adverse events.*		
Investments for use *Information under this subheading includes questions and guidance requesting information about additional investments in infrastructure and staffing that will need to be made in order to use the technology (capital costs). These may include investment in machinery or premises, and investment in additional personnel.* *Information about changes in services or reconfiguration of services required as a result of introducing the product should also be included. Also include information about requirements for monitoring of the use of the technology.*		
Training and information *Information under this subheading includes questions and guidance relating to training or information required to implement the technology, this may include training of*		

personnel, patients and wider society.		
Other		
Please indicate N/A if no questions are included. Please include questions verbatim including a reference (ref) to the question/guidance number or page number. If countries request a table is filled in please indicate table requested and describe table contents (column headings or row headings). Use 'other' for any questions that are not covered by the existing categories.		

Domain 3: Clinical effectiveness

	Information requested	**Reference**
3.1 Review methods		
Identification, selection and appraisal of clinical effectiveness studies *Include under this heading any information or guidance about the review methods for the identification, selection and appraisal of studies about clinical effectiveness. Also include any text about the identification of clinical effectiveness data for comparators.*		
3.2 Relevant studies		
Description of studies *Include under this heading any questions concerned with the description of identified relevant studies.*		
Individual study results *Include any text asking for the results from individual studies.*		
Ongoing studies *Include any questions or guidance relating to ongoing or planned studies, for which results are expected in the future.*		
3.3 Pooling study data		
Pooling study data *Include under this heading any questions concerned with methodology used to pool study results. This might be meta-analysis, mixed treatment comparison or other indirect comparison, or narrative synthesis methodology.*		
3.4 Conclusions		
Mortality/morbidity/QOL/patient satisfaction *Include under this heading any information seeking summary measures of mortality, morbidity, quality of life and patient satisfaction outcomes. Where an agency requests a general interpretation or conclusion about the findings also include this information here.*		
Strengths and limitations *Include under this heading questions or guidance relating to the strengths, limitations, and uncertainties of the evidence base for clinical effectiveness.*		
Representativeness *Include under this heading questions or guidance relating to how generalisable the evidence presented is to national clinical practice.*		
3.5 Subgroup analysis		
Subgroup analysis *Include under this heading any questions or guidance relating to presentation of subgroup data from the clinical effectiveness data in the submission. Include any information requested about the specification and rationale for subgroups.*		

Please indicate N/A if no questions are included. Please include questions verbatim including a reference (ref) to the question/guidance number or page number. If countries request a table is filled in please indicate table requested and describe table contents (column headings or row headings). Use 'other' for any questions that are not covered by the existing categories.

Domain 4: Safety

	Information requested	Reference
4.1 Review methods		
Is identification of safety data different from clinical effectiveness	Y/N	
If yes, information on identification/selection/ appraisal of studies *Include under this heading any information or guidance about the review methods for the identification, selection and appraisal of studies about safety. Also include any text about the identification of safety data for comparators. In some instances this may be the same as for clinical efficacy.*		
4.2 Relevant studies		
Are studies informing clinical effectiveness different from those informing safety?	Y/N	
Study description safety *Information under this heading includes questions or guidance asking manufacturers to provide descriptive characteristics of relevant safety studies.*		
Study results safety *Information under this heading relates to questions or guidance about the provision and presentation of safety outcomes data from individual studies. Relevant questions or guidance may relate to the intervention or comparator.*		
4.3 Pooling study data		
Is guidance on pooling data for safety different from clinical effectiveness?	Y/N	
If yes, information on pooling of study data *Include under this heading any questions or guidance specifically relating to the pooling of data for adverse effects.*		
4.4 Conclusions patient safety		
Patient safety *Include under this heading questions or guidance relating to the conclusions in relation to the safety of a product for the patient (either the intervention or the comparators) that may be drawn from the study results. These may be general questions or more specific questions.*		
Environmental and occupational safety *Include under this heading any questions or guidance about issues in relation to environmental or occupational safety.*		
Strengths and limitations *Include under this heading questions or guidance relating to the strengths and limitations, representativeness and uncertainties of the evidence base for safety. Also include any general questions or guidance asking for information about additional safety issues identified outside of the evidence base.*		

Other		
4.5 Action and implementation		
Safety risk management *Include under this heading any questions or guidance asking about issues relating to minimising the safety risks.*		
Regulatory actions *Include under this heading any questions or guidance asking about regulatory actions that have been taken as a result of safety information*		
Other		
Please indicate N/A if no questions are included. Please include questions verbatim including a reference (ref) to the question/guidance number or page number. If countries request a table is filled in please indicate table requested and describe table contents (column headings or row headings). Use 'other' for any questions that are not covered by the existing categories.		

Data was not extracted from:

Appendix 3: data extraction forms medical devices

	Country:		
	Data extraction completed by:		
	Types of device/service/procedure included in evidence requirement: If this is not clear state not clear		
	Is this a submission template, a checklist of documents to provide or both	Template / checklist / both (delete as appropriate)	
	What study designs e.g. RCTs, observational studies does the template include If this is not clear state not clear		
Section		Information in evidence requirement	Reference
Health problem and use of technology			
1.1	Overview of the disease Definition of disease and ICD Risk factors, prognosis, causes Description and overview of disease		
1.2	Effects of disease on information and society Symptoms of disease Effect of disease on life expectancy Burden of disease Aspect of disease targeted by device/procedure Estimates of incidence and prevalence		
1.3	Target population Description of population to be reimbursed Size of target population		
1.4	Current clinical management Current diagnosis and management of disease Requests for clinical guidelines Comparators or alternatives to device Unmet needs Variations in treatment Change to care pathway if device introduced		
1.5	Current use of technology and comparators Existing use in clinical practice of device Existing use in clinical practice of comparators		
1.6	Reimbursement status of technology and comparators Reimbursement status of device Reimbursement status of comparators NB: this is in any country		
	Other Any information not categorised relevant to		

	health problem and current use of the technology		
Description of the technology			
2.1	Features of the technology and comparator Names, Codes Class Mechanism of action History of development Description of device Package contents Package inserts, catalogues		
2.3	Approval of technology and comparator CE mark Indications and contraindications Date of receipt of CE mark Approval in other countries Claimed benefits		
2.4	Manufacture and distribution Manufacturer Details of distribution Availability Launch date		
2.5	Guarantees, warranties, life, replacement Availability and length of guarantee / warranty Duration of life of device Shelf life Information about replacements Technical maintenance and support		
2.6	Quality control and follow-up Declarations of quality Medical surveillance measures in place		
2.7	Cost information Unit costs of the device Costs of the device in other countries Maintenance costs Hire/rental costs Comparator costs		
2.8	Using the technology and comparator How to use the technology Instructions/direction for use, user manuals Personnel, equipment, supplies required Training and information required Monitoring requirements Other treatments required Diagnostic processes		
2.9	Investment and changes in service provision Additional investments needed to implement Services no longer required Opportunities for disinvestment		
	Other Any information not categorised relevant to description of the technology		

Clinical effectiveness			
3.1	Identification of studies How studies of clinical effectiveness of the technology and comparators were identified.		
3.2	Description of studies Descriptive characteristics of the included studies e.g. aim, population, intervention, outcomes measured, comparator. Justification of excluded studies.		
3.3	Individual study results Requests for presentation of individual study results Patient flow and withdrawal through studies		
3.4	Study quality Requests for the assessment of individual study or endpoint quality (e.g. bias assessment) or requests for ranking of evidence e.g. level of evidence or hierarchies of evidence) Record the name of any specific tools used.		
3.5	Ongoing studies and unpublished studies All information about the identification, description, and presentation of data from ongoing and unpublished studies		
3.6	Pooling study data Requests to synthesise the evidence either quantitatively or narratively including methods and presentation of outcomes of synthesis		
3.7	Conclusions General conclusions or specific conclusions in relation to mortality, QoL, function, patient satisfaction etc. This could also be referred to as interpretation of the evidence base, or summary of the clinical effectiveness or benefits.		
Filter question	Does the conclusion or summary of clinical effectiveness come from a formal study synthesis?	Yes/No/NA (delete as applicable, use N/A where not requested in evidence requirement)	
Filter question	Is the conclusion or summary of benefits considered separately from harms?	Yes/No/NA (delete as applicable, use N/A where not requested in evidence requirement)	
3.8	Strengths and limitations Requests for assessment of strengths and limitations of the evidence base. May include internal validity / weight of evidence base or representativeness / external validity		
Filter question	Are the strengths and limitations considered separately for benefits and harms?	Yes/No/NA (delete as applicable, use N/A where not requested in evidence requirement)	
3.9	Subgroups All information relating to clinical effectiveness in subgroups of patients		

	Other Any information about clinical effectiveness not categorised.		
Safety			
Note: for safety, only data extract information that is additional for safety. Where the same methods of study identification are used for safety and efficacy do not duplicate the information between the safety and effectiveness sections.			
Filter question	Is the identification of safety data different from that of clinical effectiveness?	Yes/No/NA (delete as applicable, use N/A where not requested in evidence requirement)	
4.1	*(If yes, complete)* Identification of studies How studies of adverse effects of the technology and comparators were identified.		
Filter question	Are the studies that inform the clinical effectiveness different from those informing the safety aspects?	Yes/No (delete as applicable)	
4.2	Description of studies *(include only safety specific information)* Descriptive characteristics of the included studies e.g. safety endpoints, measurement of those endpoints, definition of endpoints. Justification of excluded studies.		
4.3	Individual study results *(include only safety specific information)* Requests for presentation of individual study safety results.		
4.4	Study quality *(include only safety specific information)* Requests for the assessment of individual study or endpoint quality (e.g. bias assessment) or requests for ranking of evidence (e.g. level of evidence or hierarchies of evidence). Record the name of any specific tools used.		
Filter question	Is the guidance on pooling data for safety different from that of clinical effectiveness?	Yes/No/NA (delete as applicable, use N/A where not requested at all in evidence requirement)	
4.5	*(If yes, complete)* Pooling study data Requests to synthesise the evidence either quantitatively or narratively including methods and presentation of outcomes of synthesis.		
4.6	Conclusions patient safety Either general conclusions or specific conclusions. This could also be referred to as interpretation of the evidence base, or		

	summary of the adverse events or harms. In some instances it may be descriptive rather than resulting from a formal synthesis of the evidence.		
Filter question	Does the conclusion or summary of adverse effects/harms come from a formal study synthesis?	Yes/No/NA (delete as applicable, use N/A where not requested in evidence requirement)	
4.7	Environmental and occupational safety Any requests about ensuring the safety of the environment or people using or working near the device.		
4.8	Strengths and limitations *(include only safety specific information)* Requests for assessment of strengths and limitations of the evidence base. May include internal validity / weight of evidence base or representativeness / external validity		
4.9	Safety risk management Any requests for information about managing risks to patients, healthcare workers, public etc.		
4.10	Vigilance reports Requests for information about incidents and adverse events identified through sources other than clinical studies (e.g. regulators, surveillance databases, manufacturer returns)		
	Other		
	List of supporting documents or information requested by agency:		
	Data not extracted from:		
	Notes, comments, clarifications:		
Please indicate N/A if no questions are included. Please include questions verbatim including a reference (ref) to the question/guidance number or page number. If countries request a table is filled in please indicate table requested and describe table contents (column headings or row headings).			

