KCE REPORT 283

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

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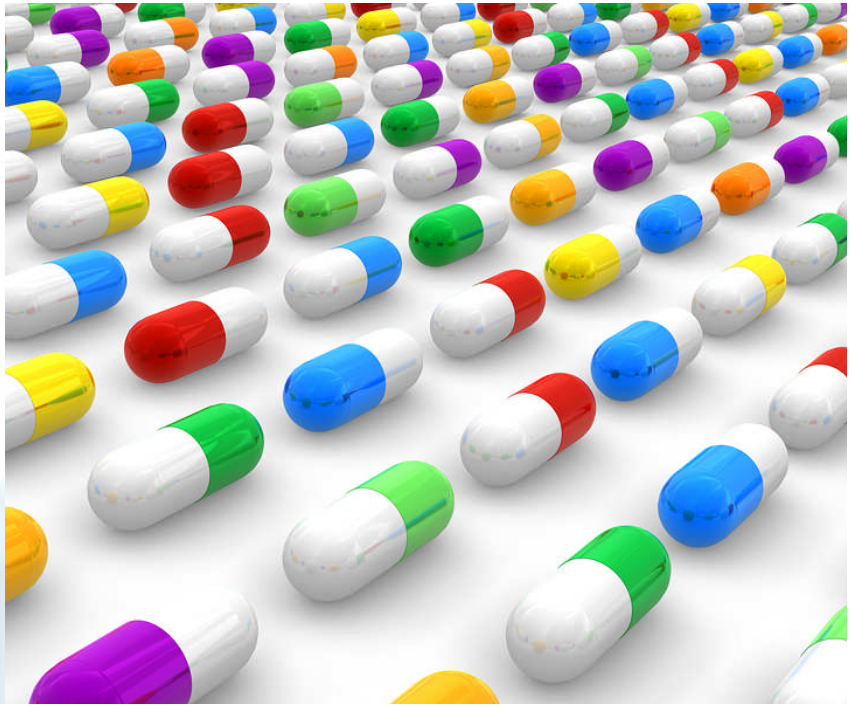

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HEALTH SERVICES RESEARCH

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
ADTC	Area Drug and Therapeutics Committee
AHRQ	Agency for Healthcare Research and Quality (USA)
AIFA	The Italian Medicines Agency
AMGROS	Danish pharmaceutical procurement service of the five regional authorities
AWCDG	All Wales Cancer Drugs Group
AWMSG	All Wales Medicines Strategy Group
AWPAG	All Wales Prescribing Advisory Group
AWTTC	All Wales Therapeutics and Toxicology Centre
BeNeLuxA	Belgium, The Netherlands, Luxemburg, Austria
BNF	British National Formulary
CHMP	Committee for Medicinal Products for Human Use-EMA
DBC	Diagnosis-Treatment Combination (Diagnose-Behandel Combinatie)
DCD	Data Capture Document
EAA	Early Awareness and Alert Systems
EBE	European Biotechnology Enterprises
ECRI	Emergency Care Research Institute: an independent, non-profit international health services research organization (USA)
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
ENG	England
EUnetHTA	European Network for Health Technology Assessment
EuroScan	International Information Network on New and Emerging Health Technologies

FA	Financial Arrangement
FDA	United States Food and Drug Administration
FTE	Full-Time Equivalent
GVS	Geneesmiddelenvergoedingssysteem (Dutch outpatient pharmaceuticals reimbursement system)
UKMI HSME	UKMi Horizon Scanning & Medicines Evaluations
UKMI HSMEWG	UKMi Horizon Scanning & Medicines Evaluations Working group
NIHR HSRIC	Horizon Scanning Research & Intelligence Centre (England)
HSS	Horizon Scanning System
HTA	Health Technology Assessment
IHSCP-SC	Italian Horizon Scanning Project Scientific Committee
IHSP	Italian Horizon Scanning Project
IHSP-DT	Italian Horizon Scanning Project Database Team
IHSP-ET	Italian Horizon Scanning Project Evaluation Team
INHS	Italian National Health Service
IT	Italy
KCE	Belgian Health Care Knowledge Centre
LBI-HTA	Austrian Ludwig Boltzmann Institute (Austria)
LNDG	London New Drugs Group
MA	Market Authorization
MHRA	Medicines and Healthcare products Regulatory Agency (England)
MPP	Medicines Prescribing Program (England)
NA	Not Applicable
NDO	New Drugs Online: database for new medicines (UK)
NHS	National Health Service (UK/England)

NHSC	National Horizon Scanning Centre (England) – see NIHR HSRIC
NHSE	National Health Service England
NICE	National Institute for Health and Care Excellence (England)
NIHR	National Institute for Health Research (England)
NL	The Netherlands
NMG	New Medicines Group (Wales)
NPIR	New Product Information Report (Italy)
NT Council	New Therapy Council (Sweden)
NZA	Dutch Healthcare Authority (Nederlandse Zorgautoriteit)
PCORI	Patient-Centered Outcomes Research Institute (US)
R&D	Research & Development
REA	Rapid Relative Effectiveness Assessment
RIZIV -– INAMI	National Institute for Health and Disability Insurance – Institute National d'insurance Maladie-Invalidité – Rijksinstituut voor ziekten en Invalideverzekering (Belgium)
SCT	Scotland
SKL	Swedish Association of Local Authorities and Regions (SALAR) (Sveriges Kommuner och Landsting)
SMC	Scottish Medicines Consortium
SPS	Specialist Pharmacy Service
SSR	Servizio Sanitario Regional/Regional Health Service (Italy)
SWE	Sweden
TLV	The Swedish dental and pharmaceutical benefits agency (Tandvårds- och Läkelmedelsförmånsverket): A state authority, which decides prices and subsidies on pharmaceuticals
UK	United Kingdom

UKMi	UK Medicines Information
US	United States
VWS	Ministry of Public Health, Welfare, and Sports (Volksgezondheid, Welzijn en Sport) also referred to as Ministry of Health (the Netherlands)
WAL	Wales
WMP	Welsh Medicines Partnership

SCIENTIFIC REPORT

1 SCOPE AND OBJECTIVES OF THE STUDY

The Belgian, Dutch, Luxembourg and Austrian governments have declared their intention to collaborate on drug policy, including the topic of horizon scanning of pharmaceuticals for Health Technology Assessment (HTA) and price negotiations[a]. The collaboration is currently known as the BeNeLuxA Collaboration Initiative. KCE was appointed to lead the task force for developing a Horizon Scanning (HS) methodology and a possible model for a joint Horizon Scanning System (HSS).

The aim of the current study is to develop a systematic approach to HS of pharmaceuticals that can facilitate collaboration with other interested countries. The objectives were defined as:

- To compare HSSs for pharmaceuticals internationally
- To develop a model for a joint HSS, based on the comparison with HSSs in other countries;
- To develop a methodology for HS that satisfies the needs of the countries collaborating in the joint HSS;
- To assess the feasibility of the proposed HS methodology for Belgium.

The scope of this study is limited to horizon scanning of pharmaceuticals.

The scope of the current report was adapted to fit the task force's needs, i.e. focusing on the development of a methodology for the identification and compilation of information about new pharmaceuticals expected to have an impact on the health system, that can be shared between the collaborating countries. Out-of-scope are emerging medical devices or health care interventions.

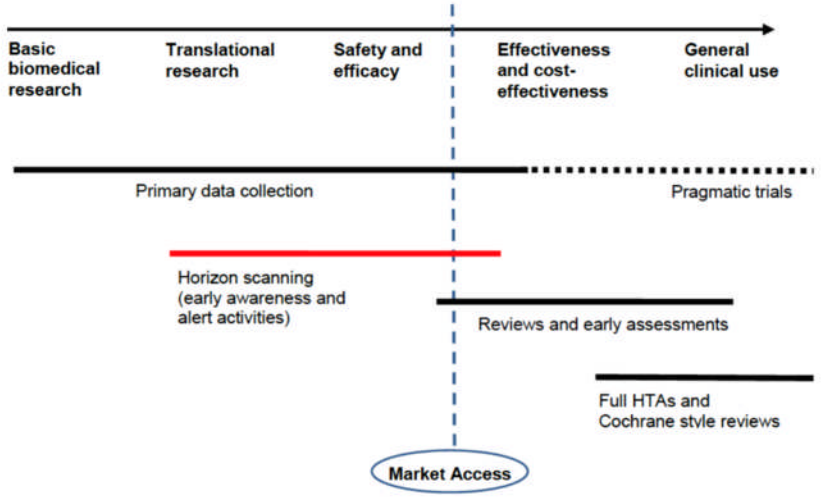
[a] Belgium and the Netherlands signed a declaration of intent on 20 April 2015 to negotiate the reimbursement of orphan drugs with the pharmaceutical industry. The Grand Duchy joined this initiative on 24 September 2015. Austria joined on 17th of June 2016.

2 WHAT IS A HORIZON SCANNING SYSTEM?

Horizon scanning systems (HSSs), or alternatively called early awareness and alert systems (EAA) or early warning systems, aim at identifying, filtering, and prioritizing new and emerging health technologies with a considerable predicted impact on health, costs, society, and the health care system in order to inform policymakers, purchasers, and health care providers (for health service research prioritization, financial or operational planning) or facilitate early access (by facilitating controlled diffusion of technologies).[1] Public and private entities (e.g. governments, payers, health systems, venture capitalists, technology developers) around the world are already using formal or informal health care horizon scanning programs for a long time.[2] The scope of HSSs can vary from medical devices or pharmaceuticals only to a very broad range including pharmaceuticals, devices, diagnostics, surgical interventions, medical procedures, hospital care, community care programs and public health interventions.

HSSs typically situate their research before market access and precedes HTA evaluation and reimbursement decisions, although HSSs are not necessary directly linked to these processes (Figure 1). As such a HSS enables proactive planning and/or decision-making regarding the use and reimbursement of new pharmaceuticals based on early estimations of budget impact and clinical effectiveness.

Figure 1 – The place of horizon scanning systems in the continuum of HTA activities

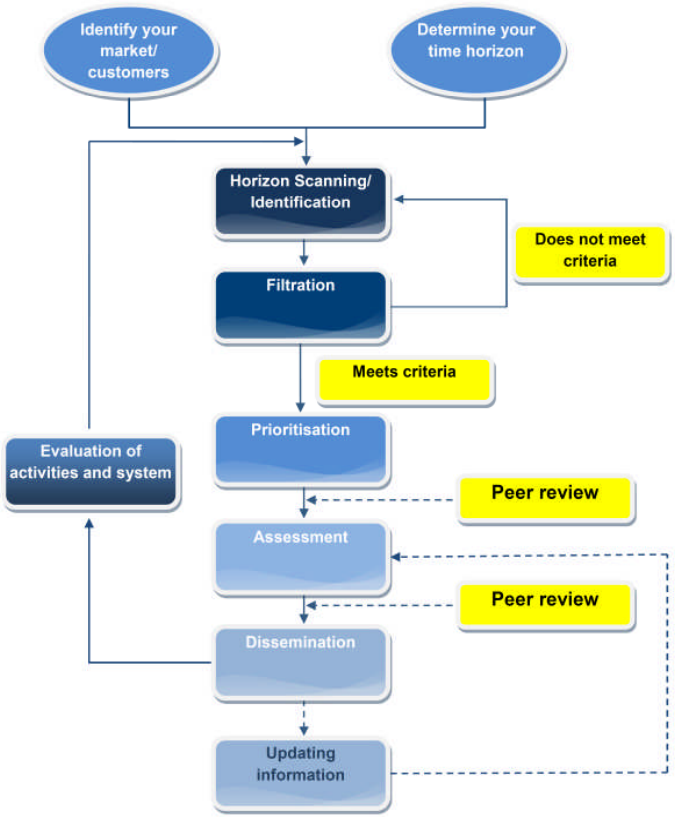


Source: EuroScan, 2014[1]

The main activities of HSSs are (Figure 2):

- Identification of new and emerging technologies (sometimes referred to as horizon scanning)
- Filtration and prioritization of the identified technologies
- (Early) assessment of the prioritized technologies or a group of technologies based on the available data or predictions about the product.

Figure 2 – Schematic overview of a horizon scanning process



Source: EuroScan, 2014[1]

Customer and time horizon

To set up a HSS, the first step is to determine the customer: who is going to use the output of the HSS and for what purpose? The customer will determine the time horizon used in the HSS i.e. the time frame before expected market authorization or market entry in which the new products need to be identified and available information or estimations about the product collated and assessed. The earlier the identification and assessment needs to be, the higher the uncertainty about the data. As such, there is a trade-off between an early time horizon, possibly needed for long-term planning, and a lower uncertainty about the information about the product.

Identification

In an active identification step, drugs in development are identified by systematically screening relevant primary and secondary sources at predefined time intervals. Primary sources of information include developers, patent applications and clinical trial registries (can give direct information on the developmental process). Secondary sources include third parties not directly involved in the development of the product (e.g. regulatory agencies (EMA/FDA)), clinical experts, conference proceedings and commercial websites.

Primary sources can provide information early in the development cycle, while secondary sources are often later in providing, sharing or updating information. Some HSSs do not use an active identification process but rely mainly on tertiary sources, i.e. other horizon scanning agencies that have already prioritized the information and perhaps even carried out an assessment.

Filtration and prioritization

In the filtration step only those products that are relevant to the scope of the HSS or to the customer are selected. Furthermore, the selected products are prioritized for assessment or evaluation based on the system's capacity or customer's preferences. Further information about a technology may be required to enable its prioritization.

Some systems apply explicit filtration and prioritization criteria, while others use more implicit criteria. How these filtration and prioritization criteria are taken into account is country- and customer-specific. In general, criteria aim to answer the following questions:

- Is the technology relevant for the healthcare system?
- Is the technology new, equivalent to existing technologies or is it an established technology intended for a new indication?
- Is the technology within the time horizon of interest and likely to enter the market?
- Does the technology have a potential financial, clinical, and/or organisational impact??

Prioritization can be performed at a point in the development cycle where the amount of information available about the product is still limited. Even with limited information or evidence, estimations can be made to determine whether a technology has the potential to have an impact on the health care system. Some HSSs use company input to get information and estimations about the products, while others choose not to have company contact. Information can also be collected through stakeholders such as clinical experts, sickness funds or payer, patients' associations.

The collated information is used to predict the clinical (clinical benefit, safety), financial, organizational (infrastructure, staffing, equipment) and societal impact of the product based on the expertise of HSS staff or other experts/stakeholders. While HSSs' staff often performs filtration, the prioritization can involve (clinical, scientific or HTA) experts, decision makers or patients' associations whose opinion is included though formal scoring systems, majority vote or by consensus.[1]

Early assessment

Most HSSs compile available information about the prioritized products in an early assessment document, which is not to be confused with a more formal HTA. For the early assessment, the following choices have to be made in advance depending on the customers' need: volume and format of the output, frequency and timing of reports (e.g. in relation to fixed dates for decision making), content and parameters, style (e.g. report, newsletter, database), size, format (e.g. paper, electronic), data inputs (e.g. confidential information from manufactures or publically available sources), and access to output (confidential, limited to stakeholders, or public).[1]

A search strategy should be developed to ensure consistency in the retrieval of relevant information. Potential data sources are: registries of clinical trials, commercial pharmaceutical databases, registration and licensing sites, relevant scientific conferences, bibliographical databases and clinical experts.

The output parameters can be related to the technology, patients and settings, evidence and policies, and expected impact. The horizon scanning staff or clinical experts critically review the available information and predictions.

The dissemination strategy is of vital importance to a HSS: it ensures that the information produced is reaching the customer at the right time.[1]

Updating Information

A HSS's output is actually a snapshot of the status of a product at a specific point in time. Due to the nature of horizon scanning (HS), the information found is often incomplete and dynamic and is likely to change or expand before the technology is fully implemented. New results or studies can become available, especially for products that were identified at an early time point. Therefore, information about the products needs to be scanned iteratively. Most HSSs stop updating the information about a product once an assessment report has been completed.

Evaluation of horizon scanning methods and systems

Evaluation of HSSs serves to better customize the HS activities to the needs of the customer, but also allows optimization of resources allocated to the HSS. The structure, process, output(s) and impact of the HSS need to be put in question on a regular basis.

The impact is determined by the acceptance of the HS unit, the HSS's products and the utilization of its products, namely the HSS output(s). Evaluation methods can comprise one of the following: an internal audit, questionnaires and interviews with stakeholders, measuring access to output, analysis against external information sources to cross-check whether for example all licensed products were identified by the HSS and content analysis of external sources to assess whether the information of the HSS is used in policy documents or covered in the media correctly.[1]

Box 1 – The EuroScan Network[7]

The International Information Network on New and Emerging Health Technologies (EuroScan), established in 1997, is an association of publicly funded HS Agencies with the aim of forming a collaborative network for the exchange of information on important new and emerging health technologies, and on methodologies of HS processes. Its goals are:

- To establish a system to share skills and experience in EAA activities.
- To strengthen activities for the development of methodological approaches for the identification, description and assessment of new or emerging health technologies.
- To improve the exchange of information about new and emerging health technologies and their potential impact on health services and existing health technologies.
- To increase the impact of the EuroScan International Network's output.
- To identify relevant not-for-profit public partners in order to share the results of work with partners/members of the EuroScan International Network collaboration.
- To advise not-for-profit organisations within public administrations who wish to consider the establishment of EAA activities.

EuroScan organizes several activities including maintaining a (voluntary) depository of HS activities and HS outputs of its members, publishing methodological papers, organizing meetings, participating in HTA meetings and establishing collaboration with other international HTA organizations. All EuroScan members are encouraged to share their HS output in the EuroScan database. The contribution of the members differs, due to the different time horizons of the HSS, the depth of assessment, the consistency and timeliness of contribution. The database does therefore not give a systematic and complete overview of all technologies that are on the horizon. Although EuroScan has contributed to the formalization of HS methodologies and the exchange of experiences between the different HS agencies, it has not led to real collaboration between HS agencies in the form of joint scanning or assessment. The depository is mainly used as an identification source for other HSS.

3 METHODS

First, an international comparison of existing HSSs was performed. The methods and approaches used in each of the HSSs were studied and a needs assessment was made in order to develop a methodology for HS that would meet the needs of the collaborating countries. Based on the international comparison and the needs assessment, a possible model was proposed for a joint HSS for the BeNeLuxA collaboration. Obviously, this model would also be applicable to a wider collaboration.

Finally, a feasibility study was performed in Belgium to assess to what extent the propose model would be feasible as far as the information requirements is concerned.

3.1 International comparison

3.1.1 Data collection

Identification of existing publicly funded HSSs in other countries that focus on pharmaceuticals was done by consultation with the EuroScan secretariat. The Swedish HSS was identified during an interview with Francis Arickx from RIZIV (March 15th, 2016) (Table 1).

Table 1 – Identified HSS agencies

Agency	Abbreviation	Country
Ministry of Public Health and Welfare	VWS	The Netherlands
Swedish Association of Local Authorities and Regions	SKL	Sweden
Agency for Healthcare Research and Quality	AHRQ	United States
Italian Horizon Scanning Project	IHSP	Italy
Horizon Scanning Research & Intelligence Centre	NIHR HSRIC	England/Wales
UK Medicines Information	UKMi	United Kingdom
Scottish Medicines Consortium	SMC	Scotland
All Wales Medicines Strategy Group	AWMSG	Wales

At the time of the publication of this report, some of the Nordic countries are in the early process of (developing) HS activities regarding pharmaceuticals. In Denmark, e.g. a HSS has just been initiated at Amgros, a publicly funded organisation that negotiates pharmaceutical pricing on behalf of five regional authorities in Denmark. Norway started with HS as part of a system of managed introduction of both pharmaceuticals and other health technologies in 2015 (Mednytt). No information about their methodology was available at the time of data-collection, and therefore they are not included in the international comparison. In the future there may also be a Nordic collaboration, between Iceland, Sweden, Norway, Finland and Denmark, but this is also in the early stages of development.

For the Netherlands, the description is based on the HSS in place before the introduction of “Horizonscan+”, which has recently been developed by the Ministry of Health to timely alert and inform all stakeholders about new pharmaceuticals their possible effects. At the time of writing, little information is available about the plans for the organization of “Horizonscan+”, as the concept was still being developed.

Information about the selected HSSs was collected through a peer-reviewed and grey literature (e.g. websites) review. This information was complemented with information from semi-structured interviews (either during a site visit or by teleconference) when the information was not clear (Table 2).

A summary of the each HSSs is included in the Appendix. The HSS descriptions were validated by an expert in each country involved in the HSS (except for the US, Scotland and Wales, which were not validated).

Table 2 – Formal contacts with representatives of HSS agencies

Country	Agency	Contact type	Contact person
NL	Ministry of Health (VWS)	Site visit, telcons	Eveline Klein Lankhorst
SWE	Swedish Association of Local Authorities and Regions	Telcon	Anna Bergkvist
US	Agency for Healthcare Research and Quality	None	NA
IT	Italian Horizon Scanning Project	Telcon	Roberta Joppi
ENG	Horizon Scanning & Intelligence Centre (NIHR HSRIC)	Site visit	Sue Simpson, Kathryn Miles, Luan Linden-Phillips, Saimma Majothi & Marie Harte
UK	UK Medicines Information	Telcon	Helen Davis & Joanne McEntee
Scotland	Scottish Medicines Consortium	None	NA
Wales	All Wales medicines Strategy Group	None	NA

NL= The Netherlands; SWE= Sweden; US= United States; IT = Italy; ENG= England; UK= United Kingdom; NA: not applicable

3.1.2 Data analysis

A descriptive analysis was performed on the collected data. First, the goal and customers of the different HSSs were compared. Secondly, similarities and differences in the methodologies of other HSSs were described.

3.2 Development of a proposal for a joint HSS

A possible model for a joint HSS was proposed based on the lessons learnt from the international comparison and on a discussion with the representatives of the Minister of Public Health (the Netherlands, Luxembourg and Austria) or the National Health Insurance Institute (Belgium) of the collaborating countries about their needs regarding the HSS.

The country representatives commented on the practicality of the proposal. For Austria, the institute with experience in HS for oncology products (LBI-HTA) was asked to comment.

Finally, the proposal was presented to the Steering Committee of the BeNeLuxA initiative. The further actions were discussed as well as the implementation issues.

The proposal is taking a maximalist point of view, meaning that it is not limited to what can be established in a very short term, but already thinks ahead in terms of possible scope, objectives and outputs of the system. This implies that for the short-term implementation, choices will have to be made to ensure feasibility. This could mean reducing the number of outputs of the system, or reducing the initial scope to, for instance, only drugs that are expected to be submitted to EMA in one years' time. However, once the system is operational, new objectives may be identified and the scope could be enlarged. The proposal takes this possibility already into account.

3.3 Feasibility study

The feasibility study consisted of the following steps:

- Development of a database template for data aggregation
- Selection of a limited number of pharmaceuticals products
- Collection of information about the products through a web-based search
- Setting up company pipeline meetings with Belgian offices of the developing companies
- Setting up meetings with clinical experts through contacting the relevant medical societies
- Estimation of potential high financial impact
- Description of experiences with the data collection approaches

A survey was organized to obtain the opinions about and experiences with the process from the stakeholders that participated in the feasibility study. The appropriateness of the criteria as well as the stakeholders' views on the process of the information gathering were addressed.

Results were described narratively.

3.3.1 Selection of products

We aimed at a small sample of products (6 products), indicated for different therapeutic areas, including an orphan drug and both inpatient and outpatient drugs. First, we considered the products on the Dutch horizon list published in 2015.[3] Products were only selected when time-horizon before market authorization (MA) was estimated to be more than 12 months. Since most of the products on the Dutch horizon list (in 2015) were close to launch or launched already, we screened the UKMi Outlook Report[4] for additional suitable products. Seven products were selected. Two products were added later: one because it received attention in the media as a promising drug in an early development stage and another following the suggestion of a company. Of the 9 products, three products were finally not selected, because of negative results (withdrawal from the development process) or too short time horizon.

3.3.2 Development of a database template for data aggregation

For the development of the database, a number of factors had to be taken into account: i.e. the database would have to include a considerable number of parameters (see Appendix 8) and it would have to be reader-friendly, while at the same time enabling sorting and filtering of specific parameters. In a comparison to Excel, Access was deemed more appropriate to meet these objectives. An initial database template was developed in Microsoft Access, containing the parameters that were selected in chapter 5 (5.8).

3.3.3 Data collection on the products

A member of the research team gathered information about the products. In case information could not be found in other HSS reports (AHRQ or UKMi), the Disqover platform[b] was used to find data on clinical trials and publications in Pubmed. In addition, the EMA and company websites were searched for potential new status changes. A web-based query was performed to add information on the parameters that were lacking or to confirm development status, clinical trials and other parameters such as costs. For each entry into the database, the source was referenced. The database entry was double checked by a second researcher on readability, clarity and comprehensiveness, and was adapted when necessary.

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b http://www.ontoforce.com (see chapter 5.6.2)

3.3.4 Setting up company pipeline meetings

For the purpose of the feasibility study, the goal of the pipeline meetings with representatives of the Belgian offices of the companies was to get an idea of what kind of information a company was able and willing to share with a HSS, and to assess the added value compared to publicly available data. The responsible persons for market access or regulatory affairs of six companies were contacted. Three of them agreed to participate in a pipeline meeting[c], one did not accept the invitation and two others did not respond, even after repeated reminders. A standard non-disclosure agreement (NDA) was signed with the participating companies. In the pipeline meeting the companies were asked to present the products in their pipeline and to fill out a "data collection form" about their selected product for the feasibility study.

3.3.5 Setting up meetings with medical societies

The goal of the meeting with the medical societies was to test the format of the meeting and the feasibility of the collection of country-specific information such as: relevant guidelines, current standard of care, expected place in therapy, expected acceptance by patients/ providers, expected inpatient/outpatient status, expected patients in treatment group, expected annual cost per patients and cost on macro level, potential savings due to substitution of medicines per patients and on macro level, expected reimbursement appraisal planning (when applicable), societal need (current disease-related expenditure per patient). Country-level medical societies of the relevant specialism were chosen as they represent the whole field in Belgium. Three medical societies (Belgian Neurological Society, Belgian Society of Medical Oncology, and Belgian Society for Rheumatology) were asked to send a representative to a face-to-face meeting. None of the societies responded to the initial invitation. However, after contacting members of the board of directors directly through a member of the KCE, two of the three medical societies accepted the invitation. The third medical society did not respond, not even after several emails and telephone calls. One meeting was a face-to-face meeting, while the second was by telephone, both lasting about one hour. Experts gave input about country-specific parameters and commented on the information collected by the HS researcher.

3.3.6 Estimation of potential high financial impact

In order to identify products with a potential high budget impact, we assessed how the products scored on the cost parameters thresholds according to the Dutch methodology for assessing the financial risk (see Table 3). As such, products received a green, amber or red light on each of the three parameters, based on the HS researcher's calculation of financial risk. Products that score a green light on all three criteria are considered not to pose a financial risk. Products that score at least one amber light on one of the criteria are deemed potentially risky.

To calculate the financial risk, we extracted the following information from the filtration form:

- The estimated annual drug cost per patient
- The estimated patient numbers in treatment group (number of patients eligible for using the product)
- The estimated uptake of new product (as percentage of number of patients in treatment group)

For the cost estimation, only the estimated product cost was included. Hence the cost per patient per year was the annual drug price per patient. Similarly to the Dutch system, we subsequently calculated:

- The annual macro costs: this is the estimated total annual costs for the product in Belgium. The estimate is based on available data about patient volumes and the estimated price of the product.
- The cost per patient per year: this is based on available data on the estimated duration of the treatment (i.e. number of dosages needed) and the available product price in Belgium and abroad.

[c] Two contacts of which were referred by Pharma.be.

- The volume risk: the risk that the estimated volume of patients will increase, for example due to expansion of the indication, off-label use.

A lot of the information needed for these calculations was based on expert opinion.

Table 3 – Thresholds for financial risk used in Dutch HSS

	Cost per patient per year	Annual macro costs	Volume risk (multiplication)
'Green light' (low risk)	€ 0 – € 15 000	€ 0 - € 10 million	1 (volume stays the same)
'Amber light' (intermediate risk)	€ 15 000 – € 50 000	€ 10 - € 40 million	1 – 2 (no change to doubling)
'Red light' (high risk)	> € 50 000	> € 40 million	>2 (at least doubles)

[d] Interview with Evelien Klein-Lankhorst, Dutch Horizon Scanning System, (2016)

4 INTERNATIONAL COMPARISON

4.1 Brief description of selected HS systems

Dutch HSS

The Dutch HSS was set up in 2012, to identify inpatient and outpatient pharmaceutical products eligible for price negotiations. All new pharmaceuticals expected to be introduced on the Dutch market within two years, are included in the HS database.[d] A classification is made for potential financial risk of the products, based on a traffic light system for three criteria (annual macro cost, cost per patient per year and volume risk), with clear thresholds. During the latest scanning round published in December 2015, 28 products were identified as having a potential financial risk: 14 inpatient and 14 outpatient pharmaceuticals. Identification and information collection usually starts shortly after finished Phase III studies.

The HS database is not public, but the information gathered by the HSS is presented in regular meetings with the National Health Care Institute (monthly), and medical societies, patients' associations, hospitals, and health insurers.

For products selected for price negotiation, a technical expert meeting (involving clinical experts (specialists) in the specific field) is organized. Before the negotiation starts, the National Health Care Institute appraises the drug and advices the minister on inclusion of the drug in the basic benefits package. If this advice is positive and includes the advice to negotiate, the minister can decide on starting the negotiations.

Swedish HSS

The Swedish system started as a cooperation of four regional county councils in 2007. Since 2015, the Swedish HSS is incorporated in a bigger framework called “the Collaboration Model” (*Samverkansmodellen*) coordinated by the overarching Swedish Association of Local Authorities

and Regions (SKL) which aims at improving the horizon scanning, introduction and monitoring of new drugs. Basically, the HSS process selects inpatient and outpatient pharmaceuticals in development for a managed national introduction.[5] Based on the HSS output, it is decided whether a managed entry is recommended, which then requires a complete assessment, including a Health Technology Assessment (HTA) and a thorough collaboration with the companies to develop a guidance for patients and follow-up (about 10 products a year) or whether a price-focused introduction without a full assessment or company involvement is appropriate (about 15 products a year).[5] Price negotiations are then conducted in a "Three-party" negotiation involving the county councils negotiation delegates, the pricing and reimbursement authority TLV (Swedish Dental and Pharmaceutical Benefits Agency) and the company. About 20 products are prioritized on an annual basis.

US HSS

The HSS in the US was initiated in 2010 by federal funding to provide the comparative effectiveness research (CER) program at the Agency for Healthcare Research and Quality (AHRQ) with the relevant information to plan its research activities. The results of the HSS are publically available for use by public and private decision makers considering the adoption and implementation of a new technology. The HSS focuses on 14 priority areas set by AHRQ, and its scans not only for pharmaceuticals but also for drugs, devices, procedures, treatments, screening and diagnostics, therapeutics, surgery, and care delivery innovations. The HSS aims to identify interventions that may have the highest potential impact in each priority area within 2 to 3 years of their availability for diffusion into clinical practice. In 2014, 353 products were filtered.

HS systems in the United Kingdom (UK)

Six separate agencies with horizon scanning duties exist in the United Kingdom: Horizon Scanning Research & Intelligence Centre (NIHR HSRIC), UK Medicines Information (UKMi), Scottish Medicines Consortium (SMC), All Wales Medicines Strategy Group (AWMSG), Northern Ireland Health and Social Care Board and the NHS England Specialized Services. They have regular contact to exchange processes and experiences[e], but operate separately with their own methodologies having different customers and time lines.

NICE, SMC and AWMSG are HTA organizations which issue guidance to the NHS on the use of medicines. NICE does it for England and Wales, SMC to Scotland and AWMSG to Wales.

To facilitate data collection, a common database, called "UK PharmaScan", was developed jointly by the Department of Health and the Association of the British Pharmaceutical Industry (ABPI). Pharmaceutical companies are encouraged to enter and update key information about their products before market authorization (products in phase III or within 3 year of market authorization) in the database. Data entered are only accessible to the registered company, NHS Evidence database managers and horizon scanning organisations with strict security safeguards to ensure controlled access. Information collected includes: technology information about the product and indication, clinical trial information, regulatory information, costs and budget impact information. More and more companies are getting involved as it saves them time (compared to interacting with the six agencies separately) and it contributes to timely access of their products to patients. As there is no information available about the processes of HS by the Northern Ireland Health and Social Care Board and NHS England Specialized Services, they are not included in the international comparison.

English and Welsh HSS

The National Institute for Health and Care Excellence (NICE) issues guidance on the use of medicines, however it does not perform its own horizon scanning. Horizon scanning is provided by the Horizon Scanning Research & Intelligence Centre (NIHR HSRIC). NIHR HSRIC is the oldest HSS with a well-developed methodology for both pharmaceuticals and medical devices. For pharmaceuticals, it aims at identifying new drugs in

[e] Interview with representatives of the Horizon Scanning Research & Intelligence Centre (April 18th 2016)

development at an early time point providing an (early) technology assessment report at 18 months before the expected market authorization. The output is used by NICE for planning its HTA research activities for advice on reimbursement. The English system goes in early dialogue with the companies to obtain information about new products in development. It produces about 225 technology assessment reports each year.[f]

UK system

As one of its services to National Health Service (NHS) staff, UK Medicines Information (UKMi) provides a horizon scanning service. The UK HSS informs healthcare professionals, NHS budget holders and those involved in prescribing planning about new medicines and indications in development in order to support managed introduction/diffusion into the NHS. The annual HS series of reports, called “Prescribing Outlook” comes in three parts. “Prescribing Outlook–New Medicines” contains brief clinical and therapeutic data on medicines with launches planned in the next 24 months and on marketed drugs with new indications, plus information on predicted launch date, potential target population and estimated impact on service delivery and cost. About 170 entries were included in the 2015 issue and 140 in the 2016 issue. “Prescribing Outlook – National Developments” contains information on national guidance and targets expected to have an impact over the next 18 months. “Prescribing Outlook – Cost Calculator” uses data from the other two publications to allow crude calculations of potential costs of prescribing changes for a local population.

Welsh HSS

In Wales, the All Wales Medicines Strategy Group (AWMSG) is responsible for the HSS. The aim of the Welsh system is to select drugs suitable for the appraisal process for reimbursement. However, it only selects products that will not be (timely) assessed by NICE. As such, the Welsh system is complementary to NIHR HSRIC system.

Scottish HSS

The Scottish HSS system, performed by the Scottish Medicines Consortium (SMC) is used to support financial and service planning for managed implementation in practice by the Scottish Health Boards. Its provides an annual report which describes impact profiles of drugs expected to be associated with moderate to high net drug budget impact and/or major service implications. Additionally, the Scottish system produces financial templates with cost estimates for budgeting purposes to be used in the local Health Boards.

Italian HSS

The Italian Horizon Scanning Project (IHSP) was set up in 2006 and covers pharmaceuticals as well as medical devices with medicated coating. The HSS’s output is used to improve planning and optimize the most appropriate use of resources, as well as to inform reimbursement decisions, on both national and regional level. The Italian HSS produces three outputs for products that are in 3 different time points in their development: the “36 months report” produced annually, the “18 months report” produced twice a year and the “12 month report” (or *New Product Information Report (NPIR)*), produced *ad hoc* for every prioritized product that is within 12 months of expected market authorization. Hence prioritization is based on information in the “18 month report”. About 10 to 12 NPIRs are produced annually. The Italian HSS does not have company contacts.

[f] based on 2015

4.2 Goals of the HSS

A HSS can cover multiple objectives and goals (Table 4).

Table 4 – Primary goals of the selected HSSs for pharmaceuticals

Goals	HSS
Select products for HTA	US, Italy, England, Wales
Inform reimbursement decisions	Italy, England, Wales
Inform for managed introduction and monitoring of drugs	Sweden, Italy, UK, Wales
Inform health care providers and managers	UK, Scotland
Inform budget forecasting	US, Italy, UK, Scotland
Plan services	UK, Scotland, Wales
Select for and inform price negotiations	The Netherlands, Sweden

Select products for further research (HTA) and inform reimbursement agencies

HS can be used to plan research activities such as HTA or to inform reimbursement agencies. For countries with a negative reimbursement list[g], the HSS signals which products need to be prioritized for further research in a more in-depth HTA (cfr England), while for countries with a positive reimbursement list, the HSS output can help to put the request for reimbursement in the perspective of future developments and/or to verify the completeness of information provided in the registration dossier. This could be of particular interest in view of the debate on reporting bias of clinical trials. The English, Welsh and Italian HSSs have goals that are more traditional in the context of HTA: the HS output is used either directly or indirectly to inform or plan for reimbursement decisions at the national level. In England, the output is indirectly used for reimbursement decisions, as the HSS is used for the selection of products for a more in-depth HTA. In fact, in England entering the HSS is a pre-requisite for entering the reimbursement process ensuring that most companies are willing to collaborate with the HSS. For Italy, this is not a pre-requisite and Wales only selects products that are not assessed by NICE. In the US the output of the HSS is used to inform comparative effectiveness research investments made through its Effective Health Care Program.

Inform for managed introduction and monitoring of drugs

HS can be used to inform decisions makers on issues relevant for the managed introduction and monitoring of drugs on a national, regional or local level. For example the Swedish system includes recommendations for national or regional introduction in clinical practices (including place in therapy, target population, etc.) and for monitoring procedures. Also the Italian system guides the regional introduction process of pharmaceuticals.

Inform health care providers and managers

The UK and Scottish systems are accountable to the NHS budget holders and NHS staff with medicines management or prescribing planning responsibilities, therefore differing in their perspective as compared to for example the English HSS. They inform health care providers and managers about the potential financial and service implications of new drugs or the proper use of drugs.

[g] With a positive list, manufacturers have to submit an application for reimbursement, while in a negative list all medicines are reimbursed unless they are added to the negative list.

Inform budget forecasting modelling

Some health care systems explicitly use the output of the HSS for budget impact calculations, budgeting and forecasting purposes. For example, the UK system publishes a cost calculator each year in the form of an Excel spreadsheet to allow calculation of potential cost in a local population, which can be used for budget planning by local clinical commissioning groups. To do so, a crude estimation of the cost of a drug per 100 000 inhabitants is given. More recently others are setting up more sophisticated forecasting models that take the replacement of older drugs into account. Recently the US system published their data on their "Ultra Rapid cost analysis" in which they analysed the potential 1-year cost of 53 interventions selected by the HSS to have potential for medium to high risk of impact on the health care system.[6] Also the Italians published a forecasting model to assess budget impact of a new diabetic drug before market authorization, using diffusion modelling from antidiabetic drugs formulations already on the Italian market.[7]

Each year since 2010, the Swedish publish a forecasting model using the HSS's output that models budgets per therapeutic/pharmacological subgroup (Anatomical Therapeutic Chemical level 3).[8] Calculations are covering a two-year time frame taking into account factors that might influence drug use, such as: life cycle of medicines, patent expiries, new drugs/indications, new guidelines, organizational changes, authority decisions. Using the forecasting model, the research group could estimate that the annual increase in total expenditure for prescription and hospital drugs was predicted to be 2.0% in 2010 and 4.0% in 2011 based on the availability of new drugs, and that the increase was predominantly due to specific domains such as anti-neoplastic and immune-modulating agents as well as drugs for the nervous system, infectious diseases, and blood and blood-forming organs.[9] Although the predictions may not become reality due to health policy decisions or different pricing options, such analyses might help to gain insight in the improvement of informed decision making about the proper allocation of resources (for example across different therapeutic areas and over different years, based on the anticipated value of new products).

The possibilities for forecasting may vary substantially between countries, because of differences in data availability, such as patient populations and coverage, aggregate versus patient level drug dispensing data, measurement units of utilization and expenditure. Also the ability to forecast requires an earlier time horizon, since predictions preferably run over a 3 to 5 years' time frame.[4]

Select products for and inform price negotiations

The Dutch HSS is quite specific and focused, in that it only selects products for price negotiations on a national level. The Swedish HSS selects products for managed entry at a national level, which include but is not limited to national price negotiations. In addition, it also uses the HSS's output to formulate protocols for introduction and follow-up of new pharmaceuticals for local authorities. The protocol describes, for instance, the medicine's role in therapy, estimated costs and what practical consequences its introduction may have, such as a need for training or laboratory resources. None of the other studied systems has the explicit goal of using information to negotiate prices with the pharmaceutical companies.

Policy link of the HSSs

In the Dutch system, the HSS is an integral part of the price negotiation policy and is even coordinated in the policy maker's office. In Sweden, counties decide, based on the HSS's output, whether or not to negotiate together on prices.

NIHR HSRIC provides a HSS for NICE to decide which medicines they will issue guidance on – if NICE recommends the medicine then it must be prescribed and reimbursed in England and Wales. Many other medicines are used in England which NICE does not issue guidance on, and so for these medicines, selection of the pharmaceutical by the NIHR HSRIC is not a prerequisite for reimbursement. The UKMi supports policy decisions at a local level, by the clinical commissioning groups. The AHRQ (US) uses the output to focus research efforts without any specific policy link.

The goal of the HSS and the possible link to policy processes influences the choice on its timing, filtration and prioritization criteria, and parameters assessed.

Lessons learnt

- **The Dutch and the Swedish system use the HSS's output for price negotiations on a national level.**
- **The Swedish and Italian system also use HS for the managed introduction and monitoring of drugs**
- **The Italian, English and Welsh HSSs have links to the reimbursement process.**
- **Sweden, UK, Italy and the US use HSSs output in budgeting and forecasting analyses.**

4.3 HS unit and customer

The HS activities are performed by diverse organizations: academic institutions (English system), independent research institutes (US, Wales and the Scottish system), (local) health units (Italian and UK system), or governmental policy makers (Dutch system, the Swedish system). Customers are national or regional health authorities (Dutch, Swedish, Italian and Welsh system), HTA agencies (English and US system) or health services providers or managers (the UK and Scottish system) (Table 5).

Table 5 – Features of the included HS systems

	NL	SWE	US	IT	ENG	UK	SCT	WAL
Founded	2014	2007	2010	2006	1998	2002	2003	2002
HS unit	Ministry of Health	Fyrläns-gruppen[i]	ECRI	Local Health Unit in Veneto	Horizon Scanning Research & Intelligence Centre (NIHR HSRIC)	UKMi Horizon Scanning & Medicines Evaluations Working Group (UKMI HSMEWG)	Scottish Medicine Consortium (SMC)[ii]	All Wales Medicines Strategy Group (AWMSG)
Type	Ministry of Health	Health units of County councils	Independent non-profit research Institute	Local health unit	Academic group at University of Birmingham	NHS pharmacy-based service	HTA agency	Independent non-profit research Institute
Customer	Ministry of Health	SKL Counties Councils	AHRQ	Italian Medicines Agency: AIFA Veneto Region	National institute for Health and Care excellence (NICE) NIHR HTA programme	NHS commissioners Health care providers	Scottish Health boards	Minister for Health and Social Services
Type of customer	Ministry of Health	Association of local authorities and county authority	Research agency under Department of Health	National, local and regional authorities	HTA agency	Health services commissioners and providers	Health services providers	Ministry of Health

i Fyrlänsgruppen = A collaboration group between the Skåne Region, Stockholm County Council, Västra Götaland Region and Östergötland County Council, which carry out investigations for all county councils as part of the Collaboration; ii SMC is part of Healthcare Improvement Scotland (HIS); ECRI = Emergency Care Research institute: an independent, non-profit international health services research organization (USA).

Insourced versus outsourced HSS

For the Dutch, the Swedish and the UK system, the HSS is an "internal" affair since the coordinating agency and the customer are one and the same. Moreover, in the Dutch system, the same staff is performing both the HSS and the price negotiations. However, there are plans to externalize the HSS towards disease-area working groups (e.g. oncology, cardiovascular diseases) as explained in the "Horizonscan+" vision (see Appendix 1.1). Other systems have outsourced the HS activities to third parties (Table 5). For example, the Horizon Scanning Research and Intelligence Centre (NIHR HSRIC) (England) and ECRI (US) are commissioned for a period of 5 years by respectively NIHR and the AHRQ. Interestingly, those systems have more formalized, and better-documented, methodologies and processes compared to other systems. One can speculate that this might be because HSSs with external customers are accountable to their external customers and that the need for formalized methodologies is lower when the scanning is done within the customer-organization. External teams might also be concerned with their professional image towards other external agencies and therefore be more explicit about their procedures and methodologies to demonstrate the quality of their working procedures. On the other hand, outsourcing can have an impact on sustainability. Since December 2015, the activities of the ECRI (US) have been put on hold because the commissioning contract was not extended[h]. In England, the contract of HSRIC with the NIHR is ending in 2017 and the activity moved to a new HSS being set up in Newcastle University.

Collaboration

In the Dutch system, horizon scanning employees are centrally located at the office of the minister's cabinet. In Sweden, the HSS's staff and responsibilities are spread across four counties. For example, the screening of sources for identification is divided over the four offices. At the UK system, the HSS's staff is provided by several medicines information centres. Thus, responsibilities and activities are shared between collaborating partners.

[h] Personal communication of AHRQ with authors

Lessons learnt

- **National HSSs have been established only in the last 18 years, with the English system being the oldest.**
- **In some countries, HS activities are organized in a collaborative way between different teams in different (parts of the) organisations working for one coordinating office.**

4.4 Time horizon

The goal of the HSS, together with the type of reimbursement list a country has and the planning of national policy processes determines the timeframe at which identification of new pharmaceutical products is required. In case of a negative list, such as in the UK, the assessment needs to finish by the time the product comes to the English market. In case of a positive list, such as in Belgium, the assessment for reimbursement only starts once a reimbursement request is submitted by the company, i.e. after market authorization. Hence, in England the identification starts at an early time point: the English system needs the data early, since the subsequent reimbursement assessment is a lengthy process (± 18 months) that aims to finish around market authorization of the product. The Dutch, Swedish, and UK system have a relative short time horizon, while the English, Italian and US system identify at a very early time point in the development of pharmaceuticals (e.g. 36 months before market authorization) (Table 6, Figure 3). The Dutch HSS starts identifying relatively late in the development process, because the HSS's output is only used around market authorization date and the Dutch HSS process is less time consuming since it relies on the output of the US system.

Table 6 – Time horizon of HSS in months before market authorization

	NL	SWE	US	IT	ENG	UK	SCT	WAL
Time horizon[i]	10-12	12-24	24-36	24-36	36	12-24	12-24	12

[i] *Months before expected market authorization[10-16] and personal communications[i]*

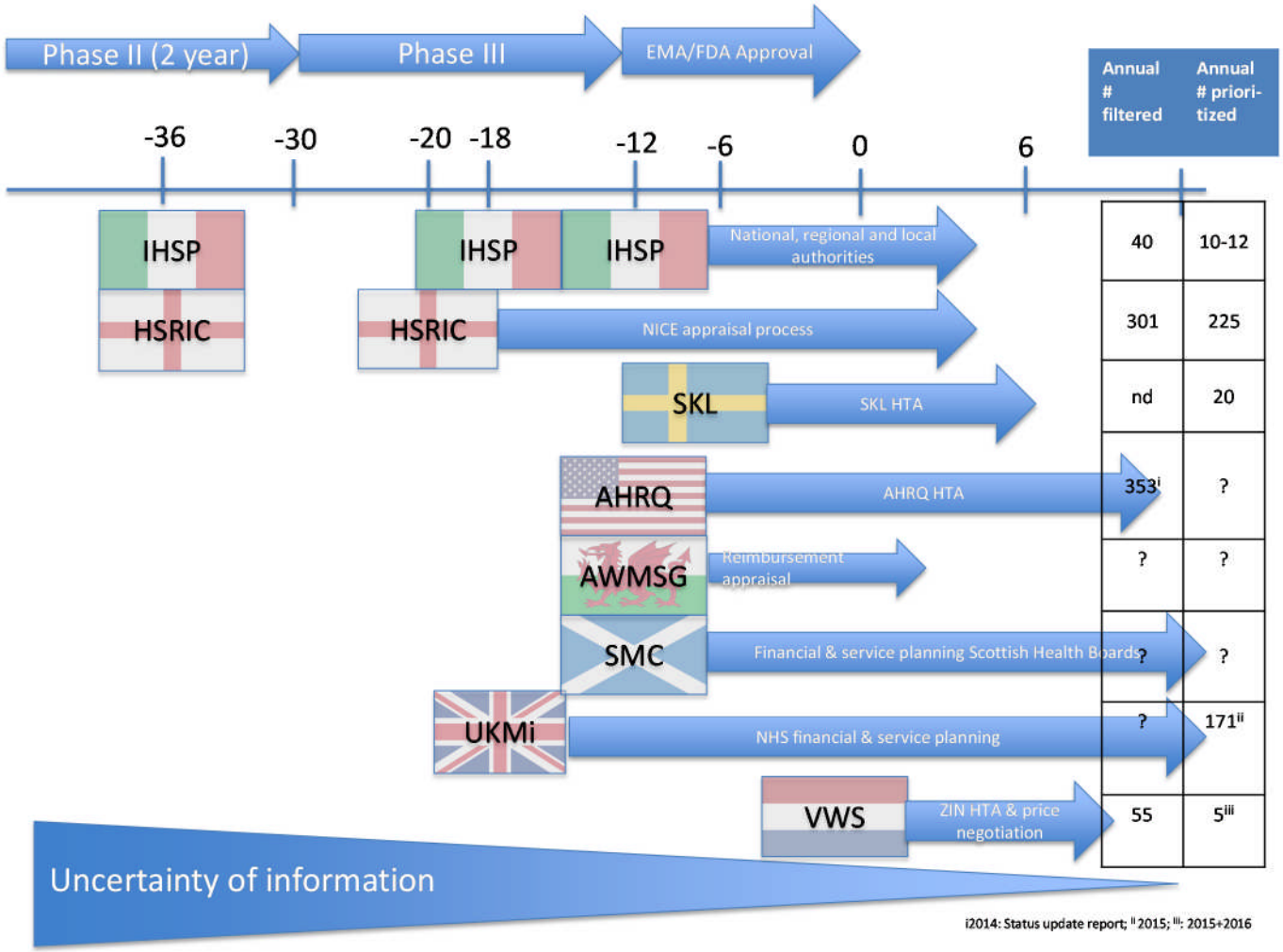
Box 2 – HS is a balancing exercise between early information and certainty of information

A HSS presents a trade-off between the value of early, uncertain information due to the lack of considerable evidence, versus the value of certain, but late information. The latter may be of limited relevance to decision makers due to the need for earlier decisions. In addition, there is a trade-off between missing an important technology and selecting an unimportant technology. This relates to making a type I and type II error in predicting (i.e. selecting) which technologies will be relevant, and refers to the proportion of technologies that have been wrongly selected as significant (i.e. false positives) and wrongly sorted out as insignificant (i.e. false negatives).[17] Some systems implicitly prefer a high sensitivity (i.e. low type II error, high positive predictive value), while others value a higher specificity (low type I error).

The English system has explicitly stated high sensitivity (i.e. lower occurrence of false negatives) to be a key performance indicator. This choice will have a great impact on the number of technologies identified and the resources needed to scan. The earlier the system identifies a technology, the more uncertainty there is about clinical and financial impact and the higher the risk that the product will not make it to market approval launch.

[i] Interview with Anna Bergkvist from the Swedish Association of Local Authorities and Regions, Region Skåne (May 3rd 2016); representatives of the Horizon Scanning Research & Intelligence Centre (April 18th 2016); Joan McEntee, & Helen Davis from the UKMi (May 6th 2016)

Figure 3 – Time lines and context of HS systems



The flag represents the timing of the output(s) of the HSS, while the arrow shows the timing of the process in which the HSS output is used.

Lessons learnt

- **The goal and the context of the health system, for example the timing of the HTA assessment, influences the time horizon of a HSS.**
- **There is a trade-off between early information, with more data based on estimations rather than evidence, and late information, with more certainty about the data.**
- **The Dutch and Swedish HSSs have similar time horizons, which are relative short compared to other HSSs.**
- **For the goal of price negotiations, the time horizon of the Dutch system -i.e. products that are in late Phase III, 12 to 10 months before expected market authorization- is appropriate.**

4.5 Identification

The aim of the identification step is the same for all systems: to identify new pharmaceuticals that could enter the European market within a pre-defined time horizon. As such, identification could be organized on a European level since most new drugs in development are not country-specific and market authorization (MA) is likely to happen on a European level. A systematic screening of pre-defined sources is used for identification (Table 7).

Active identification

The Dutch system is unique in the sense that it does not systematically scan primary or secondary sources itself, but uses the output of other HSSs (US and UK). The identification of the Dutch system is thus mainly based on a list of selected products, which has already been filtered and prioritized in the US system. This list contains only high impact products, as judged by US experts in a scoring system. Arguably, the Dutch system relies on the goal, quality, and output frequency of the other HSS. The consequences of such identification process in comparison with other HSS that do their own scanning have not been evaluated. Recently, the AHRQ has stopped producing high impact reports and the future of their scanning system is uncertain[j]. As a consequence, the way of identifying new products needs to be changed. The Dutch HS staff has indicated that they will now use the UK system (UKMi) only (personal communication). How this might impact their HS activities and output remains to be evaluated. The Dutch system also uses secondary sources in an ad hoc manner by requesting input for identification during the regular, formal meetings with medical societies. All other systems actively scan a wide range of sources.

Sources for identification

Most HSSs scan primary, secondary and tertiary sources. Company contacts are important sources of primary information, therefore some HSSs choose to make direct contacts with the companies by organizing yearly pipeline meetings (e.g. English and Swedish HSS). In such meetings, the companies highlight important new upcoming products, provide estimations about the product (including price ranges and expected market launch date) and filter out potential products which are no longer relevant to include, e.g. when research is discontinued.

The English, UK, Scottish and Welsh system also use UK PharmaScan, which contain data input from companies. Ideally, the British HSSs can rely on UK PharmaScan alone, and processes are set up to do so. However, the data in the UK PharmaScan are often not kept up-to-date and are hence incomplete.[10] Other HSSs do not formally involve companies because of resource constraints or potential biases (e.g. incomplete, uncertain, or inaccurate information) (US and the Netherlands). The Netherlands asks companies to provide information to the Ministry of Health very early in the process, but did not formalize companies' involvement in the remainder of the HS process. To obtain useful information directly from companies,

j The latest information suggests that ECRI is continuing its scanning activities, but they are not producing high impact reports anymore. According to the source, there are customers for the ECRI scanning activities other than AHRQ including UKMi (personal communication)

confidentiality issues need to be resolved. Often this is done in the form of a standard confidentiality agreement developed by the HSS organization specifying that confidential data from companies are not shared in publically available reports. Mutual trust is a pre-requisite for a successful collaboration between HS staff and companies, which may result in a win-win situation: earlier access for companies and more accurate information for the HSS.

Most organizations do not publicly share the detailed list of sources or their systematic approach[k]; however, on average the same types of information sources and web-sites are used (Table 7).[18] A list of examples for each category of sources as used by the US system is included in Appendix 3. These lists, however, are not exhaustive and sources are adapted frequently. A description of the methodology used for selecting sites or sources to screen is not available. Robert et al. (US) selected the sources by compiling sources from other HSSs and discussed them within a Delphi panel.[19] Douw *et al.* described a more systematic approach for selecting and developing their own customized internet search strategies for oncology for the development of a Danish HSS.[18] The authors first developed a checklist of in- and exclusion criteria focused on content, user-friendliness, quality, reliability, and efficiency of searching the web specific for HS. Subsequently, they scored a list of sources against these criteria and selected 18 web-sites in a prioritized order. Smith *et al.* also developed a set of criteria to evaluate the value of information sources.[20] The main criteria were coverage (approximate percentage of relevant information in source), efficiency of information search (estimated time to identify one potentially significant health technology or other relevant information) and quality of information (accuracy, objectivity, reliability)[l]. In the Dutch system, the reason for choosing AHRQ was a pragmatic one as its methodology is well described and the scoring by clinical experts considered relevant.[m]

In terms of frequency of scanning, most sites are scanned weekly or monthly.

The type of identification explains the differences in workload. The active screening of a pre-defined set of sources is more resource intensive than a non-active scanning approach. Contact with companies can be a time-consuming approach; however, it helps to establish trust so the companies will share more information about their drugs in development. Finally, screening for pharmaceuticals in development is usually performed without using a particular search strategy. Sometimes a search strategy per indication can be applied.

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k Some agencies regard this as the intellectual property of the system (Interview with Marie Harte from the Horizon Scanning Research & Intelligence Centre (April 18th 2016))

l Other criteria were: Accessibility of information (level of effort required, e.g., automatic email alerts, Internet sites or email alerts that require link/registration, printed sources/manual scanning), contact point, cost level, frequency of scanning, memory (News archive).

m Interview with Evelien Klein-Lankhorst, Dutch Horizon Scanning System, (2016)

Table 7 – Reported systematically scanned resources

	NL	SWE	US	IT	ENG	UK	SCT	WAL
Primary sources								
Trial registries					✓			
UK PharmaScan					✓	✓	✓	✓
Company meetings (regular)		✓			✓			
Company meetings (ad hoc)		✓			✓			
Company websites		✓		✓		✓	✓	✓
Company application form							✓	
Press releases			✓	✓		✓		
Secondary sources								
Scientific journals		✓	✓	✓	✓	✓	✓	
Regulatory authorities (EMA, FDA)		✓		✓	✓	✓	✓	
Experts	✓	✓		✓	✓	✓		
Medical and pharmaceutical media[i] and news sources	✓		✓		✓	✓		
Tertiary sources								
Other horizon scanning organizations	✓			✓	✓	✓	✓	✓[ii]
EuroScan database		✓	✓					
Grey literature			✓					
Blogs			✓	✓				
Databases			✓					

Sources:[13];Joppi, 2009 & 2013 [21, 22]; NN, 2008[15]; Wettermark, 2015[8];UK Medicines Information, 2012[23];UK Medicines Information, 2007[24];Scottish Medicines Consortium, 2015[10]; Interview with Anna Bergkvist from the Swedish Association of Local Authorities and Regions, Region Skåne (May 3rd 2016); Interview with Joan McEntee, & Helen Davis from the UKMi (May 6th 2016); Interview with representatives of the Horizon Scanning Research & Intelligence Centre (April 18th 2016)

[i]such as Adisinsight (http://adisinsight.springer.com), Fierce (http://www.fiercepharma.com); SCRIP (https://scrip.pharmamedtechbi.com); [ii]AMWSG is scanning UKMi NDO database

Collaboration and automation

As HSSs use comparable sources, there is considerable duplication of work performed by the different HSSs. Sweden and the UK system have spread the workload by dividing the responsibility of screening specific sources to each of the four counties or participating centres, respectively. For systems that use a similar time horizon, a collaborative effort on identification could be organized on a European level in order to reduce resources needed from the governmental, HS unit, and company perspectives.[4]

None of the systems have reported the use or the development of automatic search engines or semantic search platform (such as, for example, the DISQOVER®[n] technology of Ontoforce), which could make searches with search strategies more efficient.

Lessons learnt

- **The Dutch system does not use an active scanning approach but uses the output of other HSS.**
- **The Swedish, English and others organize regular pipeline meetings with companies for identification purposes.**
- **Company contacts could give relevant information early on, provide more realistic price indications or filter out noise.**
- **Local input from experts for identification purposes is typically organized in an informal way along the other steps of the HSS.**

4.6 Filtration

Filtration is defined as the process that selects those products that are within the scope and time horizon of the HSS and relevant to the customer. Hence, filtration helps reducing the potential number of technologies on which to start collecting more in-depth data information. Because the Dutch system builds on data of another HSS, data on the product is already readily available. Other systems filter before a substantial amount of data on the product is collected or available. Indeed, filtration is usually based on the insight and knowledge of technological changes of the HSS's staff, without in-depth information on the specific drug.[13] The Dutch system, as well as the US system, consults external experts in the filtration stage, but the selection is finally made by the HSS team. In the Dutch system, filtration is carried out in regular meetings with experts. The US system involves a majority voting process in a topic selection meeting for filtration. In the other systems, filtration is completely internalized within the HSS team. Reported filtration criteria are presented in Table 8.

[n] http://www.ontoforce.com/technology/

Table 8 – Explicit filtration criteria

	NL[i]	SWE	US	IT	ENG[iv]	UK	SCT	WAL
Within pre-defined time horizon	✓	✓	✓	✓	✓	✓	✓	✓
Filter out products that are on the market	✓							
Health benefit		✓	✓			✓		
Potential safety issues		✓						
Number of patients (Large patient population)		✓	✓				✓	
Health care cost	✓		✓				✓	
Annual macro cost	✓						✓[iii]	
Cost per patient	✓		✓					
Volume risk	✓							
Innovation		✓	✓					
Morbidity		✓	✓					
Individual burden of disease			✓					
Population burden of disease			✓					
Government priority areas			✓		✓			
Cancer-related					✓			
Unmet medical need			✓					
Off-label use			✓					
Medical society meeting			✓					
Change in delivery mode			✓					
Impact on access		✓						
Potentially legally, ethically, or politically interesting		✓						
Organizational consequences							✓	
Care change from secondary to primary care setting							✓	
Anticipated impact on health system	✓			✓				
Risk assessment in High Impact reports (AHRQ)	✓							
Work program (NICE)								✓[ii]
Potential high media/patient interest		✓						

[i]The column for NL does not include filtration and prioritization criteria that are performed by AHRQ prior to the Dutch filtration with the explicit criteria mentioned in these table. [ii]Products will not be included in AWMSG HSS (Wales) pipeline if they are mentioned in the NICE work program and a technology appraisal is expected within 12 months of market authorization .[iii]Predicted net drug budget impact for NHS Scotland of >£500K per annum. [iv] Additional filtration is undertaken by NICE.

All systems first filter products that have their anticipated MA date within a pre-defined time horizon (see 4.4). In order to be filtered into the Dutch system, the products need to be included as a "high risk" in the US HSS and hit the threshold on one of the defined cost parameters for the Netherlands. The strong focus on cost in the filtration stage is not used in the Swedish system or any other system. In other systems, when one of the explicit filtration criteria in addition to anticipated MA date is met, the product is included. For the Dutch system, the potential for high cost is estimated in a crude way in the filtration stage[o], which include price assumptions (multiple sources) and volume estimates provided by clinical experts. The worst-case scenario is always used, i.e. probably overestimating the cost impact, in order not to filter out anything with a potential impact. The Italian system does not contain explicit filtration criteria, except from expected MA date: an experienced HS staff pharmacist judges the product for the anticipated pressures on the Italian health system.

Lessons learnt

- **All HSSs select products that are within a pre-defined time horizon.**
- **Most HSSs include further explicit criteria for filtration. The criteria relate to costs, clinical benefit or unmet medical need. The Dutch system only considers products with high financial impact, which is consistent with its purpose.**
- **The Dutch HSS uses explicit thresholds on cost criteria in the filtration process, which benefits the transparency.**
- **Filtration criteria and threshold levels need to be adapted to the national context.**
- **The Dutch system prioritizes on the basis of crude annual cost estimates, which are based on price estimations, and expert opinions.**
- **The Italian HSS does not use explicit filtration criteria except for the expected European MA date.**

4.7 Prioritization

Due to limited resources and time, it is not feasible for a HSS to assess all filtered drugs. Methods must be developed for selecting those technologies that are in most urgent need of evaluation. The general objective of the prioritization effort is to define the potentially most significant emerging technologies in which to invest scarce assessment resources. Because the process of selecting technologies by agreement is susceptible to subjectivity, using tools is important to enhance accountability in the selection process. These tools may include a checklist of explicitly defined prioritization criteria and/or documentation of the decision-making process.

HSSs make predictions about the impact of health technologies, mainly build on a narrative review of efficacy and safety data from clinical studies in the output or assessments. Packer *et al.* referring to the NIHR HSRIC experience, state that most impact predictions have to use proxy indicators and estimations, both often based on the HS staff's experiences with similar developments in the past, especially when the output report has to be delivered in an early stage of the technology's development.[25]

Explicit versus implicit criteria

Most HSSs have explicit prioritization criteria, but prioritization is often also influenced by less well defined criteria (implicit criteria) such as prior knowledge of other technologies (organizational memory) and awareness of policy related priorities. In Sweden, the prioritization is done by the HS working group, based on their experience without any pre-set criteria. While being less transparent, this method is also less resource intensive.[1] In the Dutch system, other implicit criteria are taken into account for prioritization, besides the explicit cost parameters, such as perception of chances on success for price negotiations on a regional or national level or advice of medical societies (i.e. an evaluation of the 'market' situation and to establish if there are any market failures such as a monopoly).

[o] The cost of the product is judged on price information available, or price of a similar product, and on treatment schemes. In a subsequent step, a rude estimate on patient populations (proposed by experts) is multiplied by the expected cost for disease per patient.

For example, the product can be deprioritized because prices are already fixed in a decentralized manner.

The prioritization criteria differ between systems (Table 9), depending on the goal, the perspective of the customer and the context of the health care system. Although health care costs are the most predominant criterion together with organizational consequences (i.e. used in 66.6% of the studied HSSs with explicit criteria), the Dutch system is the only system using solely explicitly cost parameters for prioritization. This can be explained by its goal of using the information for price negotiations only. Health care costs are usually assessed at a population level meaning the estimated annual cost per patient times the number of patients. Cost-effectiveness was not mentioned as an explicit criterion in any of the HSSs studied. Other important criteria are health benefits, innovativeness (used in 50 % of the studied HSSs with explicit criteria), followed by the number of patients and impact on access.

Table 9 – Criteria for prioritization

	NL	SWE	US	IT	ENG[iii]	UK	SCT	WAL
Implicit criteria	Yes	Yes[i]	Yes[i]	No	Yes	No	Yes	No
Organizational consequences								
• Health care utilization			✓	✓		✓	✓	✓
• Infrastructure			✓				✓	
• Impact on system of care delivery/services			✓			✓		
• Improved disease management[i]			✓			✓	✓	✓
Impact on health care costs	✓		✓	✓		✓		✓
• Population level	✓		✓			✓		✓
• Patient level	✓							
• Volume risk	✓					✓		
Innovativeness				✓		✓		✓
• First in class/limited alternatives				✓		✓		✓
• Unmet clinical need						✓		✓
• Patient/clinical demand								✓
Health benefits	✓		✓	✓				
Number of patients						✓	✓	
Impact on access			✓					
Added value of national guidance[ii]								

[i]e.g. expert opinion; [ii] For example, significant controversy on the interpretation of evidence; iii prioritization is undertaken by NICE.

Methods for making decisions on prioritization

Different methods are used for prioritization (Table 10) such as a majority vote, a consensus meeting or a qualitative or quantitative scoring method. The Dutch system uses a qualitative scoring system for three well-defined cost criteria by applying a “traffic-light” approach: each criterion receives a green-, orange- or red-light rating depending on predetermined thresholds. The products are subsequently ranked according to the amount of red lights. Ambiguities are addressed during meetings with the National Health Care Institute, but the HS team finally decides which products are selected for price negotiations.

Table 10 – Prioritization methods

	NL	SWE	US	IT	ENG	UK	SCT	WAL
Prioritization tool	Scoring system: "traffic-light approach" by internal HS staff	Majority vote	*Majority vote *Scoring for high impact	Consensus meeting	Consensus meeting	Scoring system	Consensus meeting	No prioritization done; when necessary consensus meeting
Prioritization participants	Internal HS staff	2-3 internal clinical experts	*Internal HS staff *External clinical experts	Scanning committee	NICE	Internal HS staff	NHS clinical experts	Internal HS staff
Final decision level	Internal	External	Internal	Internal	External (NICE)	Internal+ external	Internal	External (expert panel)
Clinical expert involvement	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes

The US system uses a formal 4-point scoring system on each of the criteria (no impact, small impact, moderate impact and large impact), but leaves room for comments from the clinical experts, who are scoring the products. For the total score, each criterion is weighted equally. However, for the final prioritization ranking, the comments made by clinical experts are taken into account by the HS staff. As such, it is possible that a product with a higher score will not be prioritized. UKMi also uses a scoring system, however the relative weighting of these factors are not made public.

In most systems, (internal and/or external) clinical and non-clinical experts are formally involved in the prioritization process, except in the Dutch system. However, in the latter, input from clinical experts is certainly considered in an informal way during discussions with medical societies. The input of clinical experts is, moreover, key in terms of estimating the volume of patients and therefore in estimating the budget impact.

The final decision on prioritization can be organized internally (i.e. HS staff) or delegated to external parties. The prioritization process in England is completely externalized to NICE in a closed process.

The reasons for prioritization should be clearly stated to enhance transparency and consistency. In the English system the decision and rationale are communicated to NIHR HSRIC. In case patient associations complain, NICE can revise its decision. The Dutch system keeps track of the basis for decision in an excel database. Other systems are less clear about how they made their prioritization decision for specific drugs.

Lessons learnt

- **Health care cost is the dominant criterion for prioritization, but it is not used in all HSSs.**
- **Prioritization criteria and thresholds need to be adapted to the national context.**
- **Both explicit and implicit prioritization criteria can be used; explicit methods require more resources, but increase accountability.**
- **Making the implicit criteria more explicit would enhance transparency and reproducibility.**
- **The prioritization can be done internally (the Dutch, Italian and Scottish system) or externally (the English, Swedish, Welsh system).**

4.8 Early assessment

In some HSS, an early assessment report is produced in which predictions and the available information related to the pharmaceuticals (epidemiological, cost) is collated and critically assessed by experts.

The Dutch system does not produce formal assessment reports, but describes the estimated impact on costs and other variables in a database. Its output is an Excel database in which the data are collected, including a one-sentence advice on whether to include the product in a price negotiation. Most parameters are covered very briefly (1 or 2 sentences or written in bullet format).

The depth and resources needed for the assessment depend on the format, which can range from “rapid” (1 to 2 pages, can be done within 24-48h) to “brief” (4-6 pages, can take 0.5 to 2 weeks) to “in-depth” (up to 40 pages, can take 4-6 months) reports. The format and frequency of outputs tend to correlate with output timing and the needs of the customer.

The output characteristics of the selected HSS are presented in Table 11. The early assessment report from the Swedish system is quite extensive and takes 3 to 6 months to complete. Table 12 gives an overview of the parameters described in the main assessment report. The Italian system works with three outputs at three different time horizons (36, 18 and 12 months before expected market authorization) with an increasing depth of information.

Table 11 – HSSs' output characteristics

	HSS's outputs	Frequency	Format*	Main target audience	Output timing*
NL	Excel database	NA	Excel format	Ministry of Health	0
SWE	"Early assessment report"	Quarterly	Brief to in-depth	All counties in Sweden	6
US	"Potential high impact reports"	Twice a year for each priority area	Brief	AHRQ & Public	6/12
IT	"36 months report"	Annually	Rapid	HTA agency (international and national)	36
	"18 months report"	Twice a year	Brief	Internal	18
	"NPIR" – 12 months report	Ad hoc	In-depth	HTA agency (national, regional and local)	12
ENG	"Filtration form"	Ad hoc @ 36 months	Rapid	HTA agency	36
	"Technology briefing"	Monthly	Brief	HTA agency & public	18
UK	New Medicines pages of the SPS website	Daily	Rapid	NHS employees	Phase III and higher only, except orphan and biosimilar medicines
	"New medicines newsletter"	Monthly	Rapid (list)	Public	Phase III and higher only, except orphan and biosimilar medicines
	"Prescribing Outlook"	Annually	Rapid (1p)	Public	24
SCT	"Forward Look"	Annually/ adapted quarterly	Brief	Scottish NHS &public	12 or shorter
WAL	Confidential report	Ad hoc	No data	Reimbursement agency	0

**Rapid: a brief 1-2 page overview; Brief: a brief overview of 4-6 pages; In-depth: an in-depth overview that can be longer than 40 pages. NDO= New drug Online, NPIR= new product information report;* in months before expected market authorization or clinical phase status; Output of the Welsh and Italian systems were confidential and as such not accessible. NA: not applicable*

Table 12 – Assessment parameters in main output

	NL	SWE	US	IT	ENG	UK	SCT
HSS output	VWS database	"Quarterly report"	"Potential high impact report"	"New Product information report"	"Technology briefing"	"Prescribing Outlook: New Medicines"	"Forward Look"
Source and date of scan	✓						
Clinical Indication	✓	✓	✓	✓	✓	✓	✓
Technology description[i]	✓	✓	✓	✓	✓	✓	✓
Product potential by expert opinion	✓	✓	✓	✓	✓		
Developers	✓		✓	✓	✓	✓	✓
Estimated market authorization	✓	✓	✓	✓	✓	✓	✓
Regulatory status	✓				✓	✓	✓
Treatment duration or treatment volume[ii]	✓						✓
Patient background	✓		✓	✓	✓		✓
Clinical need and burden of disease	✓	✓		✓	✓	✓	
Current treatment options/comparators	✓			✓	✓	✓	✓
Guidance and related advice						✓	
Efficacy and safety	✓			✓	✓	✓	
Ongoing trials and evidence development		✓	✓		✓	✓	
Competitors in development	✓	✓			✓		✓
Estimated costs	✓	✓	✓	✓	✓	✓	✓
Estimated budget impact	✓						
Estimated clinical impact	✓	✓	✓	✓	✓		
Potential staffing and infrastructure implications		✓	✓		✓		✓

Potential patient and clinical staff safety issues		✓		✓
Coverage, coding, and payment status	✓	✓	✓	
Probability of success			✓	
Information other markets	✓			✓
Possibility to monitor post-launch			✓	✓

[i]Technology description includes product and compound name, type/class of product, mode of administration, mono or combination therapy, landscape: future indications & competitors; [ii]Expected volume, off-label use, future expansion; Wales was excluded because no information was available

Collaboration

Parts of the assessment, for example collating information regarding the technology itself (innovativeness, indication(s), clinical data, expected MA date, etc.) are similar for all HSSs, while country-specific information (for example information about patient population, costs, unmet medical need, impact on current care and on health services) needs to be addressed or complemented with national data or estimations. Collaboration on technology assessments among HSSs is not present at the moment, because of the different scopes and policy-objectives of the different systems and countries. Avoiding duplication of efforts is however desirable, given the scarcity of resources available and the large number of new pharmaceutical products on the horizon.

In a previous evaluation by Vondeling and Sandvei of the use of a joint database of European HTA agencies on planned and ongoing assessments, it was concluded that it did not diminish the work load or avoid duplication.[26] This might have to do with the fact that there was no formal collaboration agreement between the countries, and that the effort was therefore a bottom-up exercise.

Recently, collaborative efforts on assessment were organized again: five collaborative assessments, in the form of Rapid Relative Effectiveness Assessment (REA) of Pharmaceuticals, were produced under the EUnetHTA Joint Action 2 (2012-2015). After a collaborative workshop with 12 agencies, the Austrian HSS for oncology drugs (Austrian Ludwig Boltzmann Institute (LBI-HTA)) initiated several collaborative assessments (see text box below). These assessments were, however, done in a later stage than the HS phase. Some take-away experiences from the collaborations were: different time horizons of agencies lead to differences in collected information, relevance of topics/criteria might differ between HSSs, repeated collaboration leads to increased trust/confidence, challenges with different methodologies/technical aspects can be resolved, and ultimately collaboration leads to reduced work-load for each of the participants.[27] More formal agreements about collaboration may have a better chance of success, given that a consensus about scope and time-horizons could be reached form the start of the collaboration. Solutions ought to be sought in how to match the identification and selection processes within the different national and regional contexts.

Box 3 – Collaboration of the Italian HSS with the Austrian Ludwig Boltzmann Institute (LBI-HTA) on assessment [37, 38]

Since 2012, the Italian HSS has been writing collaborative assessment reports on oncology products with the LBI-HTA from Austria. On the basis of this collaboration, nine joint reports were produced until 2015, when the LBI-HTA left the EuroScan networkp. The overall collaboration experience was positive and working with the LBI-HTA went smoothly. Because the time horizon of the Italian HSS was earlier then LBI-HTA's, most of the information was already present from the 18- or 12-month Italian reports although the information needed to be updated. The most important factor was reaching consensus on a common assessment template, which was finally based on a template proposed by EUnetHTA and the European Public Assessment Reports (EPAR) for human medicines published by the European Medicines Agency (EMA). These reports (+/- 14 pages) are publically available on the LBI-HTA website (http://hta.lbg.ac.at) within 100 days of a positive decision from the Committee for Medicinal Products for Human Use (CHMP). In Austria, these assessments serve as decision aids for funding agencies and the decision-making network, called "HTA in hospitals". As such, these assessments are rather a HTA "light" report then a real HS output, as the clinical evidence is also appraised and assessed.

Experience of LBI-HTA on collaborations

LBI-HTA has been working jointly on fourteen reports, which were produced with six other agenciesq. Usually 2-5 researchers and 2-3 agencies were involved in each report. Each report took on average three months to complete.

Different types of collaboration:

"**Sharing of results**" approach: The report of one agency is shared and adapted to the other agency's format. For example, a EUnetHTA core model "Joint Assessment on Ramucirumab (Cyramza®) in combination with Paclitaxel as second-line treatment for adult patients with advanced gastric or gastro-oesophageal junction adenocarcinoma" was published in March 2015. The report was adapted to the LBI-HTA output format, local and country-specific information was added, and the systematic search was updated in just 8 working days.

"**Standard approach**": one agency is responsible for the literature review (incl. data extraction) and a first compilation of the report; the second agency checks the literature search /data extraction and comments on the draft.

Lessons learnt

- **Several but not all HSSs produce in-depth analyses to assess the financial, clinical, organizatorial and societal impact.**
- **Collaborative assessments are feasible; however the templates and methods for collecting data must be aligned.**

p LBI-HTA is currently re-focusing and the future collaborations are unclear (Interview with Roberta Joppi, Mario Negri Laboratory of Drug Regulatory Policies, Italy, May 19th 2016)

q IHSP, LBI-HTA, Czech agency for Health Technology Assessment and Tariff System, Arzneimittelkommission der Deutschen Ärzteschaft, UVEF, HTA Centre Bremen, Unità Di Valutazione Dell'efficacia Del Farmaco (Veneto, Italy)

4.9 Involvement of experts and other stakeholders

Experts are consulted to give country-specific estimations on product-, care- or disease-related parameters, to check the accuracy of data and information (Dutch system, UK system), predict the impact on the health system for prioritization (US and Swedish system), assess the product, as well as to comment and amend the assessment before publication (peer review) (Swedish and Italian system). This is organized through written forms or group meetings, or both. Involving external (clinical) experts is common among HSSs, with the exception of the UK system, which uses mainly internal HS staff (pharmacists).

Few studies researched the value of involving (clinical) experts in the HSS. A study by Douw *et al.* indicates that experts' information may be valuable as part of a process aimed at efficiently selecting technologies that have an impact on the health system.[28] In this study, experts correctly predicted that a specific set of 19 oncology drugs would not have an impact in the Danish Health system; however, they missed 3 out of 8 products, which did have an impact.

However, there is a tendency to involve more multidisciplinary experts or stakeholders other than clinical experts in the HS process such as other health care system specialists (including HTA experts), hospital management, payers and insurers and patients' associations (Dutch and the US system). First, because the products need to be assessed from different perspectives: for example a patient might assess clinical benefit different as compared to a clinical expert. Secondly, involvement in the selection process and assessment creates transparency and more likely support for decisions taken and policies made.

Lessons learnt

- **(Clinical) experts' involvement is important in all HSSs, as peer review and as source for data and estimations on the product or country-specific parameters.**
- **Experts can also be involved in prioritization (the US and Italian HSS) or assessment phase (Swedish and Italian HSS).**
- **A broader range of stakeholders might be involved to obtain information from different perspectives, to enhance transparency and create better support for decisions made.**

4.10 Dissemination

The accessibility of the HSS's output may vary depending on the goal and customers of the HSS (Table 13). While the Dutch system has internal customers, dissemination is intuitively of less interest and therefore rarely actively pursued, other than in regular meetings with stakeholders. The "horizonscan+" initiative, which has recently been conceptualized, envisions a broader use of the HSS and the public availability of the HSS data.

The US, UK and Swedish system publish their output on their website, while the Italian system restricts its output to its customers. Confidential company information is omitted in the disseminated output of the English and UK system.

Active dissemination methods through media channels such as reports, newsletters, journals or websites and social media are time consuming and require a certain level of communication skills. Involving stakeholders such as clinical experts in the process of HS will help to disseminate the results in a more passive way into smaller target groups such as clinical professionals and patients. Indeed, experts can help to manage expectations of future treatments towards peer professionals, patients or other stakeholders.

Table 13 – Dissemination of HSS outputs

	NL	SWE	US	IT	ENG	UK	SCT	WAL
Access	Restricted	Open[i]	Open[ii]	Restricted	Open[iii]	Open & Limited[iv]	Restricted	Restricted

"Open" means public access; "restricted" means only accessible to customers and selected stakeholders while "limited" means that part of it is open for public.
[i] http://www.janusinfo.se/Nationellt-inforande-av-nya-lakemedel/Nationellt-inforande-av-nya-lakemedel/Horizon-scanning/ ; [ii] http://effectivehealthcare.ahrq.gov/index.cfm/who-is-involved-in-the-effective-health-care-program1/ahrq-horizon-scanning-system/ ; [iii] http://www.hsric.nihr.ac.uk/ ; [iv] www.sps.nhs.uk

4.11 Updating Information

The Dutch HSS does not systematically track and update the information of the products after the initial identification, other than the inclusion of information actively given by medical societies. Other HSSs track the product until the assessment report is delivered to the customer (English system, the Swedish system). The Italian system updates the information and reports on regular time points (-36, -18 and -12 month) according to newly available data. The Scottish system provides quarterly updates of prioritized drug reports. With the UKMi system, the New Medicines pages of the SPS (Specialist Pharmacy Service) website is updated daily with newly available information, and medicines are tracked for 2 years after launch. The US system tracks products up to 2 years after market introduction.

4.12 Evaluation of HS systems

Very few data are available regarding the evaluation of the performance of the HSSs. Most evaluation research is done in light of a new HSS to be established like in Denmark or in the US.[29, 30] For the Netherlands, an evaluation report from an independent research company was published in the pilot phase of the price negotiations, in which the process of the Dutch HSS was briefly touched upon. Only the English HSS has a regular monitoring and audit of its processes and outputs. The audit looks at process-related and final output in a random selection of briefings[r]. External organizations are also involved in the performance review process. The findings of the review are incorporated into an improvement plan for the English system. The US system recently published an evaluation report.[31] The evaluation of the accuracy, completeness, credibility and usability of the potential high-impact intervention reports was done by means of expert and stakeholder surveys. The HS staff assessed the activities to collect and synthesize expert comments for the high impact scoring.

[r] The audit looks at completeness of the search record, recording of the company contacts, information, and comments sent, recording of any expert contact details, clear and correct recording and filing of the information retrieved and received, a clear statement of the innovation of the technology in the briefing, and sources of information are fully referenced, and clarity on which information is confidential.

Lessons learnt

- **Dissemination is used to create awareness about and share information on new products. The HSSs vary in type of dissemination and in access to the HSS's output, which depends on resource availibility and the HSS's goal.**
- **Informal dissemination is an important channel to manage expectations of future treatments towards peer professionals, patients or other stakeholders**
- **In most HSSs the collected information is updated on a regular basis.**
- **Only the English system has an established evaluation procedure.**

4.13 Conclusion

Various publicly funded HSSs for pharmaceuticals exist; they differ in their place in the decision- and policy-making process. The output of the HSSs is used for different objectives, ranging from input for price negotiations, information for HTA, reimbursement agencies and health care providers, to input for managers for budgeting purposes. As such, different choices are made with respect to scope, time horizon, filtration and prioritization processes and resource allocation. However, the aim of the identification is the same for all systems: to pick up data on new and emerging pharmaceuticals with a potential (financial, clinical or organizational) impact on the health care system.

From the international comparison, different methodological options emerged to organize each step of the HSS (Table 14). For the set-up and implementation of a new HSS, choices between these methodological options need to be made. Identification can be done by actively scanning a range of primary and secondary sources, by using the output of other HSSs or by notification from companies or potential adopters. The latter requires fewer resources but creates dependency on quality and output frequency of the other system.

Involvement of companies ensures product data from the primary source, but it is very resource intensive and can be biased. Filtration and prioritization criteria can be explicitly taken into account creating transparency and reproducibility. On the other hand, it may slow down the HS process. Clinical experts and other stakeholders can be involved to get field-specific information or opinions about potential impact, while creating support and understanding about the HSS and related policy-making processes.

On an organizational level, international collaboration may be worthwhile. It can increase efficiency of HS efforts by dividing tasks and sharing data. Identification of emerging and innovative pharmaceuticals for example, is not country-specific and can therefore be centrally organized to avoid duplication of efforts. While harmonized criteria can be formulated for filtration and prioritization processes, country-specific goals and preferences should be addressed locally.

Table 14 – Methodological options for different phases in the HS process

Phase in the HS process		Methodological options	
Identification	International collaboration	Yes	No
	Active Scanning	Yes	No
	Company input	Yes	No
	Expert input	Yes	No
Filtration	International collaboration	Yes	No
	Criteria	Explicit	Implicit
	Company input	Yes	No
	Stakeholder input	Yes	No
Prioritization	International collaboration	Yes	No
	Criteria	Explicit	Implicit
	Company input	Yes	No
	Stakeholder input	Yes	No
Dissemination	Early assessment	Yes	No
	Public availability	Yes	No

5 PROPOSAL FOR A JOINT BENELUXA HORIZON SCANNING SYSTEM

A collaboration of the Belgian, Dutch, Luxembourg and Austrian (BeNeLuxA) health authorities on horizon scanning for potentially high impact pharmaceuticals is planned.

The objective of the collaboration is to conduct a joint horizon scanning in a way that enables all participants to make their local decisions on the basis of the jointly collected information, and to identify possible topic on which they could work together. The aim is thus to gather timely information on pharmaceuticals that are expected to have a high impact in terms of costs, organization services and clinical benefit relative to existing pharmaceuticals before market entry. For this purpose, pharmaceuticals in development have to be identified, and data collected. This would enable the collaborating countries to decide whether a pharmaceutical is of particular relevance for their country in order to take any particular action regarding further evidence-development, regulation of use or reimbursement.

The gathering of information on new pharmaceuticals needs to be timely and useful for each country's own decision-making processes. Based on a review of current HSSs' methods and outputs, consultation with HS experts, and input from 'customers' (representatives of the four countries), the initial consensus for output of a collaborative BeNeLuxA HSS is to produce a list of emerging and new pharmaceuticals, with available cost data and data related to expected added clinical impact. A joint filtration process can be developed to narrow down the number of pharmaceuticals for e.g. further assessment. This list can also be used by the individual countries for further filtration and prioritization. In this proposal, we describe the procedure to arrive at a joint list of products that are expected to come to the market in the near or less near future and are expected to have a high impact.

The proposal is rather ambitious, in the sense that it cannot be realized in one year's time. However, very concrete steps can be taken in the short run, to already start with an operational HSS that serves certain but not all needs. In the longer term, more countries may wish to step into the HSS or use its' output. This may create opportunities that are not feasible in the short run. By not focusing on the short term possible achievements, the proposal will

not be short-lived. It should be noted that the system will also learn by doing. Flexible application of the proposal is recommended, with continuous reflection on the efficiency and usefulness of the produced outputs for the health care decision makers.

5.1 Objective of the collaborative HSS

The international comparison illustrated that HS can serve several aims (see 3.1.2.). The BeNeLuxA collaboration initiative (further referred to as "the collaboration") expressed the wish to have a HS output that can be used for a broad range of objectives covering different frames of the policy making process in the different countries. The main objectives of the HSS are:

- to inform decision makers on emerging new pharmaceuticals for reimbursement decisions and policy development;
- to inform decisions makers on issues relevant for the managed introductions and monitoring of drugs;
- to facilitate estimation of budget impact and budget planning;
- to allow the selection of pharmaceuticals for (international collaboration on) HTA, registers, price negotiations and early dialogue with industry;
- to plan health care services

In the next sections a system is described that could meet these objectives. Selection for HTA, for instance, requires a level of evidence that needs to be collected in later stages of development of the new product, whereas for budget planning data need to be collected or estimated early in the developmental process. Therefore, a broad approach is chosen with regard to the time horizon and the parameters used to collect information about the identified products.

5.2 HS process

A HS process roughly has three phases: an identification phase, a filtration phase and a prioritization phase (Figure 4).

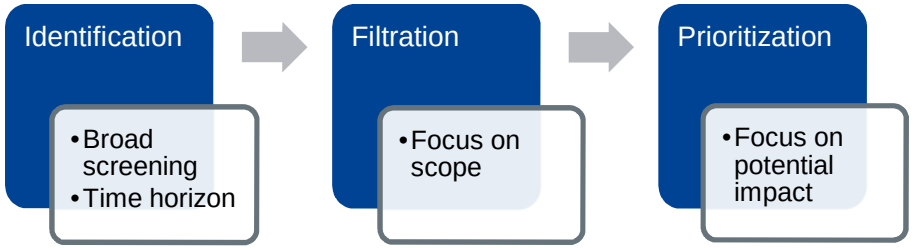
The identification phase implies a broad screening of the horizon. For a feasible identification, a time horizon should be specified. This could be expressed in months, but more relevant is to express the time horizon in terms of the development phase of products to include in the HSS. The identification of new and innovative pharmaceuticals is not country-specific and can therefore be organized jointly. The methodology for identification is described in paragraph 5.6.

The filtration phase implies the removal of products that are not within the scope of the HSS. A clear scope is hence important for an effective filtration. The filtration can be organized jointly as well, if there is an agreement amongst the collaborating countries about the scope.

The prioritization phase requires an assessment of the relative urgency of action on each of the products in the filtered database. For this, more information may need to be collected. The narrowing down of the number of pharmaceuticals for country-specific prioritization, is briefly discussed in paragraph 5.11. Country-specific prioritization needs to be organized on a national level and is therefore not considered part of the joint HSS.

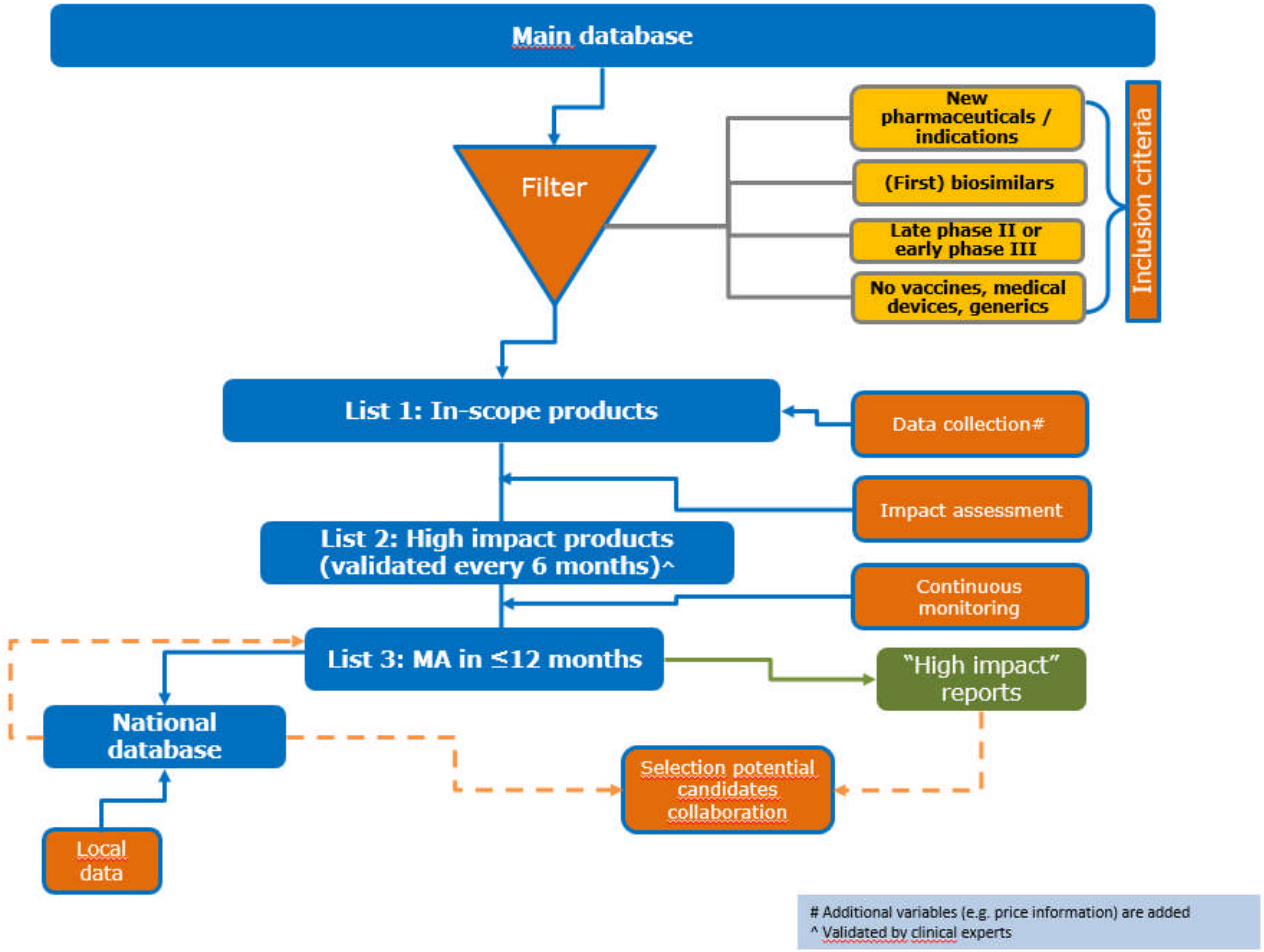
A final phase could be added in the context of an international collaboration such as BeNeLuxA: the "selection for joint activity". Joint activities could encompass joint HTAs, joint negotiations, and exchange of (strategic) information.

Figure 4 – Horizon scanning process



A more detailed presentation of the HS process is shown in Figure 5. The main database is the result of the identification phase. Filtration is presented as a filter applied to the main database, using the inclusion criteria defined based on the scope of the HSS. Subsequently, three lists are produced (as described in paragraph 5.5), varying in terms of the stage of development of the products included in it and hence the level of evidence available for each of them. The lists can be used for national prioritisation and selection of products on which to collaborate internationally.

Figure 5 – Proposed methodology for a joint HSS



Based on an informally shared viewpoint on a possible international HS database from the Bureau Financial Arrangements for Pharmaceutical Products of the Dutch Ministry of Health, Welfare and Sport (Buro Financiële Arrangementen Geneesmiddelen, Ministerie van Volksgezondheid, Welzijn en Sport, Nederland).

5.3 Organization of a joint HSS

The establishment or appointment of a "joint HS unit" for the collaboration (further referred to as the "HS unit") is proposed, which will be the designated team to execute phases 1 and 2 (identification and filtration) of the HS process. The HS unit is centralized, but financed by the collaborating countries.

The HS team within the HS unit will scan for new pharmaceutical products in early stages of drug development and track the data that become available on these products. When a product is further in the development process, the HS team will collect more (country-specific) data and input from clinical experts.

The following paragraphs (5.6 to 5.9) describe the responsibilities and activities of the HS unit in more detail. Rather than to detach competent people from each of the countries to a (virtual or physical) HS unit to be supervised by the collaborative countries, the collaboration could prefer to designate a third party as the HS unit, in charge of the operational activities of phases 1 and 2 of the HSS. This will prevent logistical and/or political issues, possibly arising with managing an international institute.

The HS unit will receive a yearly allowance to perform its activities according to a pre-defined methodology as proposed in paragraphs 5.6 to 5.9 and will be held accountable for the output deliverables. Eligible parties for the HS unit could be academic institutions, not-for-profit agencies (such as the ECRI Institute that scanned for the US HSS) or consultancy firms with a background or expertise in HS. A European tender needs to be organized to commission the HS unit for a certain period of time (for example at least 5 years), while safeguarding the continuity of the system and the expertise build up in the system. Collaborations with existing initiatives elsewhere in Europe should also be considered. Duplication of work should be avoided in this area to make sure efficient use of HS resources.

- **Outsourcing of the operational activites of the HS unit is preferred: a third party is to be designated as "joint HS unit".**
- **A European tender needs to be organized to commission the HS unit for a period of at least 5 years.**
- **The tender contains the outline of the methodology for the scanning and necessary competencies.**
- **Collaboration with existing HS initiatives elsewhere in Europe should be considered.**

5.4 Scope

The scope is related on the four countries' expectations and usage of the output of a joint HSS in relation to their policy cycles regarding new pharmaceuticals. As such the scope of the joint HSS is defined as:

Both emerging inpatient and outpatient pharmaceuticals
with a potentially high financial, clinical and/or organizational impact on the health system.

The scope also includes the first biosimilar for a biological product, cellular therapies and/or gene therapies that will be licensed as medicinal products by the EMA. Prophylactic vaccines, generics and medical devices with medicinal coating are out-of-scope for the time being. Expansion of the HSS in the future can be envisaged, once experience with the smaller scope is built up.

5.5 Time horizon

To accommodate for the different objectives and time horizons the four countries might have, the system is designed to produce **three lists**, similar to the Italian HSS (see Appendix 1.4):

- **LIST 1**: A list of pharmaceuticals within the scope of the HSS at the end of phase II trials, OR at the beginning of phase III trials in the specific indication, OR that have obtained orphan drug status or have applied for or obtained fast track status through other means (e.g. conditional MA). The drugs with an orphan designation or fast track status will already be identified while still in phase I. The list includes a brief description of the product (see 5.8.1), such as name of the molecule, manufacturer and targeted indication (about 36 to 20 months prior to MA).
- **LIST 2**: A list of pharmaceuticals nearing the end of phase III trials or with positive intermediate trial results, with an expected high impact on the health care system (about 18 months prior to MA).
- **LIST 3**: A list with more specific data for expected high impact pharmaceuticals in the final stages of development, i.e. just before MA application, phase III studies are finalized (about 12 months prior to MA).

List 3 will contain less products than list 2 and list 2 less than list 1, because some products will be abandoned by the company (e.g. because of negative trial results) and will not be submitted for market authorization, others will be filtered out during the filtration phase of the HSS. Hence, the lists do not correspond one to one with the three phases of the HS process (as shown in Figure 4). List 1 results from the identification and a first filtration based on scope, List 2 results from List 1, filtered for low-impact and abandoned products and List 3 selects products on List 2 that are close to MA request.

For some products, the timing for inclusion on list 2 and 3 may be the same; e.g. for products in a fast track at EMA. List 3 still needs to be prioritized. Therefore, List 3 should not be regarded as the outcome of the prioritization phase.

5.6 Identification

For the identification phase, an active scanning approach is proposed, i.e. the HS unit actively scans information sources to identify emerging and new pharmaceuticals instead of using the output of an existing HSS. This enables tailoring the scanning to the scope and time-horizon that is appropriate for the customer, in this case being the collaborating countries. Establishing a system that scans actively, instead of using existing HSS outputs , will, however, include a learning period, and maybe more resource-intensive in the beginning, but will be more timely and sustainable in the long run.

An active identification process enables to tailor the scanning to the scope and time-horizon of the customer and it is sustainable (independent on the output of other HSSs).

5.6.1 Identification through pre-set list of sources

An adapted version[s] of the extensive list of information sources of the AHRQ could be used for identification (Appendix 4). In the first phase of implementation, the list of sources can be pilot tested. In addition or alternatively, a Delphi panel could be organized to select a subset of sources from the adapted AHRQ list deemed appropriate for the EU context.

EMA pre-submission data are currently not accessible to non-regulatory bodies. It would be worthwhile to explore with EMA what the possibilities are to share the information about, e.g. expected submissions, with the HS unit.

[s] US-specific sources or sources with a focus on medical devices are deleted from the original AHRQ list, while European counterpart such as EMA-related sources are added. Finally pharma-intelligence sources and drugs in development databases commonly used by other HSS systems are added.

Identified products (*leads*) should be stored in a database –the "main database" in Figure 5 - which includes the date and source of identification.

New and emerging products are identified through scanning a pre-set list of sources.

5.6.2 (Semi-)Automation of the scanning process

The identification process is currently done by humans in all observed HSSs, i.e. each source is checked separately by a dedicated person. This is, however, a very intense and time-consuming process. Technologies exist that could aid the search process. For example, the American FUSE (Foresight and Understanding from Scientific Exposition) intelligence program analyses language in patents and papers to identify technologies that will become game changers in three to five years from now.[32] The University of Newcastle was recently elected to host the next horizon scanning unit for England as they plan to use more automated and robotic methods for identification (personal communication), however there is as yet no information available how they will approach this.[t]

For the current HS proposal, there are opportunities for automation of collecting data at different levels:

- on identification: scanning several sources at the same time
- on data collection for each product

A possible technology that could be adapted to the needs of the HSS is the DISQOVER platform. DISQOVER, developed by ONTOFORCE[u], is an open-access, web-based platform that delivers smart semantic search capabilities within a large range of publically available databases. The semantic search approach extents the current available search possibilities by putting the search question into the right context; therefore it is not only looking for ontologies (or key words) but also for linked data.

Currently the databases present in DISQOVER, which are relevant for horizon scanning include:

- PubMed and thus all relevant journals in the field
- ClinicalTrials.gov & EudraCT[v]
- WHO clinical trials (aggregation of 15 (trans)national clinical trial registries)[w]
- European Patent Office's (EPO) life sciences related patents: includes monitoring information of 90+ other patent registries
- US drug/medicine registries: FDA National Drug Code directory, FDA Approved Drug Products with Therapeutic Equivalence Evaluations (commonly known as "Orange Book"), RxNorm[x], DailyMed[y]
- Drug (active compound) databases: ChEMBL, PubChem, DrugBank, Unique Ingredient Identifier (UNII), …

t status: 26 October 2016

u http://www.ontoforce.com/technology/

v European Clinical trial database published by EMA (https://eudract.ema.europa.eu)

w http://www.who.int/ictrp/network/en/

x RxNorm provides normalized names for clinical drugs and links its names to many of the drug vocabularies commonly used in pharmacy management and drug interaction software

y DailyMed provides trustworthy information about marketed drugs in the United States. DailyMed is the official provider of FDA label information (package inserts). (https://dailymed.nlm.nih.gov/dailymed/index.cfm)

- Disease classifications and databases: SNOMED CT[z], ICD10, Medical Subject Headings (MeSH), MedDRA[aa], Human Phenotype Ontology, OMIM, Genetic Home Reference, …

Data from the EMA are, as of yet, not included.

A private environment can be created in which more data sources, either public open data sources or private, licensed data sources (for example from the list in Appendix 4) can be added to the search environment upon request. See for more information Appendix 1.

An automated search can make the HSS more efficient for several reasons. First, a semi-automated system could significantly improve, accelerate and simplify the identification process of new pharmaceuticals. Secondly, it could extend the collected data for each product by linking additional data sources about clinical evidence, pricing, etc. Thirdly, it can enhance the transparency and reproducibility of the searches: every search is stored and shareable with others. In addition, it will always have the most recent information, since new items that match the search are automatically added. Finally, the dashboard of the searches can be structured in such a way that it can evolve in an online platform/database with the linked information (sources), which can directly be shared with multiple stakeholders, for example the clinical experts.

A limitation of the automated search is that the vast amount of data available on the Web makes it difficult to identify which pieces of information are indeed relevant and credible to inform decisions.[33]

Additionally, the experience in a European project on scanning for emerging science and technology issues has shown the crucial value of networks and human expertise. In general, across all combined tools the value of the 'human' factor outweighed the benefits of any automation tools as these can only be put to the service of how a human mind understands, analyses and synthesizes various pieces of information.[34]

The use of semi-automated processes of scanning information sources and subsequent implementation for identification and collecting data information should be evaluated.

5.7 International filtration

Filtration of the identified pharmaceuticals is done at two levels: the international and the national level. The international-level filtration is conducted by the HS unit and filters out products that are not within the scope of the HSS. The country-level filtration is done by experts in the respective countries, based on specific aspects of the technology, e.g. whether it fits into specific government priority areas, how it fits into current care and whether it is recognized by medical societies as a technology that might be relevant in the context of their health care system (see 5.11).

For the international filtration, a set of questions can help the HS unit to determine if an identified product is representing an intervention that fits within the scope of the HSS. A possible set of questions for that evaluation is the set developed by AHRQ (see Appendix 6). When the identified product is still of interest after answering the set of questions, the product is uploaded to List 1.

The first filtration performed by the HS unit will lead to the addition of relevant new and emerging products to List 1.

Products on List 1 which are in late Phase II (or phase I for orphan drugs) or early Phase III are further researched and data on the products are collected in order to be able to assess its potential financial, organizational and/or clinical impact. List 1 gives the customer an idea of what is in the pipeline. This can be useful for pharmaceutical policy decisions.

[z] OMED CT is the most comprehensive and precise clinical health terminology product in the world, owned and distributed around the world by The International Health Terminology Standards Development Organisation (IHTSDO) (http://www.ihtsdo.org/snomed-ct)

[aa] Medical Dictionary for Regulatory Activities (http://www.meddra.org/how-to-use/support-documentation/english)

5.8 Data collection

5.8.1 Collection of minimal information to allow assessment of potential impact

For all products on List 1 (i.e. identified new products within the scope of the HSS), that are in late phase II of clinical development (or phase I for orphan drugs), a minimum of information needs to be collected to allow an assessment of their potential impact. This includes the

- international non-proprietary name,
- manufacturer,
- stage of development (clinical phase and status (initiated, late phase)),
- indication, (potential) orphan status or any further kind of designation (e.g. fast track or breakthrough therapy),
- patient population and expected place in therapy,
- comparator(s),
- mechanism of action, and
- potential outcomes (summary of the first available results; endpoints defined for the planned/ongoing phase III trials).

It might be that not all information is readily available yet at the List 1-stage but emerges as the product is developed further. Therefore, information on these data requires regular updating.

Scanners should classify the products by

- type of molecule (Biological, Monoclonal antibodies, Antibiotic,..),
- therapeutic area,
- type of technology: unique, add-on, substitute, drugs with better kinetics or new mechanism of action, and
- when unique: new substance, new indication, new combination, new formula, new route of administration, orphan drug

An estimation of the date of filing at EMA or FDA by the company should be made based on the development stage of the product.

Scanners should subsequently judge whether the product could have a financial, organizational and/or clinical impact by addressing a short set of questions (for example see). Although the answers will not be very detailed in the early phases of the product, they are helpful to filter out products that are not relevant for the HSS (e.g. a new antifungal feet cream). If the HS analyst judges that there could be an impact, the product will be included in List 2.

The datasheet with the collected information is preferable validated by one other HS analyst. In case of doubt or ambiguity, the datasheet is presented in a consensus meeting of the analysts of the HS unit.

Products on List 2 are followed-up until phase III trial results become available. When the product comes close to MA, it is included in List 3. With moving insights about the product over time, more detailed answers can be formulated on each of the questions in Figure 6, allowing for a further filtration in each step of the HS process. Filtration is an iterative process, as more information in collected and collated. Therefore, we propose to reflect on these questions before including a product on each of the three lists.

List 2 will be shared annually with the customers, List 3 will be shared bi-annually. The desired format of this list can be customized: it can be shared as a database or a customized report can be drawn directly from the database if database software is used that allows for this.

Figure 6 – Example of a questionnaire to determine potential impact

What is the potential or intended impact of the technology (speculative)?
Copy this symbol ☑ to the relevant boxes

Patients

☐ Reduced morbidity	☐ Reduced mortality or increased survival	☐ Improved quality of life for patients or carers
☐ Other, please specify:		

Services

☐ Increased use e.g. length of stay, out-patient visits	☐ Service re-organisation required	☐ Staff or training needs
☐ Decreased use e.g. shorter length of stay, reduced referrals	☐ Services – other, please specify	

Costs

☐ Increased unit cost compared to alternative	☐ Increased - more patients coming for treatment	☐ Increased - capital investment needed
☐ New costs, please specify:	☐ Savings, please specify:	☐ Other, please specify:

Source: NIHR HSRIC

Products on List 1 which have a potential financial, organizational and/or clinical impact are selected for "List 2". This list can be useful for national budgetary planning, as it encompasses products that are potentially important but not yet too close to marketing authorization to preclude anticipation.

5.8.2 Collection of extended information on pharmaceuticals with potential high impact

All products on list 2 are subsequently sorted per "therapeutic area". For a possible classification of therapeutic areas see Table 15. Alternatively, an internationally recognized disease categorization system, such as the ICD-10 chapter headings or sub-headings, could also be used.

Table 15 – Proposed therapeutic area classification

	Therapeutic areas
1	Oncology and haematology
2	Metabolic diseases
3	Chronic immunity diseases
4	Infectious diseases
5	Lung diseases
6	Neurological diseases
7	Cardiovascular diseases
8	Others

Source: Dutch HSS

More information about the products should be collected when products have preliminary Phase III results (or phase II results in case of orphan status). Necessary information includes:

- a short description of burden of disease & disease severity
- availability of other treatments: which recognized standard treatment is available; are marketed drugs and/or other medical interventions only effective in subsets of patients?
- therapeutic need (impact of disease on quality of life and life expectancy, and inconvenience of current treatment)
- dosages

- clinical trial results (safety and efficacy)
- therapeutic effect: major benefit on clinical end-points (e.g. increased survival rate and/or quality of life) or validated surrogate end-points; partial benefit on the disease (on clinical or validated surrogate end-points) or limited evidence of a major benefit (inconsistent results)
- landscape (current standard of care, other similar products (competitors) in development and their stage of development)
- expected price per country
- expected Committee for Medicinal Products for Human Use (CHMP) opinion date
- possible future place in therapy (for example transition from third line to second line of treatment) or potential for off-label use (for example in indications with same targets or indications that are already in clinical trials)
- possible extension of indication

Information can be obtained through publications of other HSSs, internet and literature searches, company pipeline meetings and clinical expert input, or –when not available through one of these sources, which might be regularly the case- data can be estimated by the HS analyst.

To do so, a data collection form is used containing the parameters needed, a description of the parameters and examples of the type of expected information to ensure consistency of data collection (for an example see Appendix 7). Cost data are preferably based on country-specific data either through company input or through estimations based on prices of comparators. The source of information should be noted. Products that are discontinued are not pursued any further and archived.

All collated information is entered into the database.

The HS analyst re-checks if the product is representing an intervention that fits within the remit of the HSS. To check if the product is expected to have an impact, a questionnaire is filled out by the analyst (see Figure 6). If there is any doubt, the product is discussed within two-weekly meetings within the HS unit and a decision to include the product in the list is made by consensus.

A list of products within 12 months of expected MA request and the available information is collated in List 3 which is produced twice a year.

Products on List 2 which have preliminary phase III results (or phase II results in case of orphan status) are selected for further information collection. They move to List 3 when the MA request is expected in 12 months' time.

List 3 is shared bi-annually with the customer.

5.8.3 Company pipeline meetings

Company pipeline meetings could provide useful information in the identification phase of the HSS, but also in later phases of the HS process. Therefore, the company meetings should aim at both identifying new products, not yet included in the HS database, as well as collecting additional information on products already in the HS database.

Company contacts could be organized at a European level by the HS unit. The contacts of the main relevant pharmaceutical companies could be identified through industry associations, such as EFPIA (European Federation of Pharmaceutical Industries and Associations) and EBE (European Biotechnology Enterprises). Annual face-to-face pipeline meetings or mailing contacts could be organized, in which companies will be asked to pro-actively share a list of new products in their pipeline. Identified products (*leads*) should be stored in a database and the date and source of identification should be tracked. This process resembles the process at EMA. It should be explored if and under which circumstances the EMA would be willing to share the results of its business pipeline meetings with the HS unit.

In addition, companies will be asked to provide input on their products that are already listed in the HS database. The most important parameters that require company input are:

- likeliness that a product is further developed

- identification of products that are/will be discontinued
- expected market authorization date,
- expected market launch dates in respective countries
- estimated price range.

Other information that is collected on products such as target population, indications or possible extension of indications, clinical trial results etc. can also be verified with companies. To facilitate the exchange of information, a "data collection form" should be developed that could be completed by the pharmaceutical companies (for example see Appendix 7). Firms should be urged to fill out the form when they have new products in development and to update the information during the annual pipeline meetings or written contacts. To stress the importance of obtaining the data, it might be useful to explain the link to policy processes and how and by whom the HS outputs will be used in the respective countries. In addition, a company can be approached ad-hoc by mail when a product is identified and more information is required.

Information collected in the database could remain confidential amongst the collaborating countries, but this should not reduce transparency of the process. For example, estimations should be based on the best information available at that specific point in time, and could be shared with the company. This can include price ranges for products or expected indications in which the products will be commercialized (when approved). If such information is not provided by the companies, the HS unit will make a "best guess" which can lead to inappropriate information and hence insufficient preparation of the health care system (i.e. insufficient budget planning, undervalue potential clinical or service impact). When the required cost data cannot be obtained from the company, cost estimations are traditionally based on cost of comparable products.

In a preliminary reaction from the association of Belgian Pharmaceutical Industry Pharma.be, companies seem positive towards a collaborative HS effort; however, they have expressed two main restrictions. First, they ask that information supplied by companies for calculating any budgetary impact remains confidential, and second, that participation in the HSS should not lead to implicit reimbursement decisions, meaning that the reimbursement dossier should be treated and assessed as a whole without prejudice.

In the feasibility study (see Chapter 6), a confidentiality agreement similar to that in other HSSs (England, Sweden) was used to ensure data provided in a confidential way would stay within the HS process.

Therefore, if it is decided to include confidential information provided by the companies in the HS database, it should be evaluated after the establishment of the collaborative HSS whether companies are willing to provide the requested data and whether the meetings have an added value. At the European level it needs to be established if the European associations (EFPIA, EBE) have the same attitude towards the joint HS activities as Pharma.be, because there might be different experiences and traditions related to collaboration with pharmaceutical companies in the different countries.

5.8.4 Country-specific data collection

In order to collect country-specific information in each country, a national HS expert should be appointed in each country. The national HS expert will search for country-specific information (relevant guidelines, incidence and prevalence data, potential savings due to substitution of medicines) and liaise between HS unit and country-specific experts/ medical societies. Medical societies can help in identifying the super-specialists in a particular field.

After finalized phase III or at the end of phase III, List 2 will be sorted per therapeutic area. After filtering out the products that were halted, discontinued or delayed in the developmental cycle, the country-specific clinical experts (whether through medical societies or by asking at least 2 experts) are asked to comment on the collated information and to collect country-specific information for products relevant to their expertise such as:

- current standard of care
- expected place in therapy (e.g. second line therapy)
- expected acceptance by patients/ providers (e.g. adherence rate)
- expected inpatient/outpatient status

- expected proportion of patients eligible for the treatment
- expected annual cost per patient
- expected reimbursement appraisal planning (when applicable)
- societal need: current country-specific, disease-related expenditure per patient & prevalence of the disease or lack of treatment

The information could be provided by e-mail or during teleconferences. The type of information required and the definitions of the terms used in the data collection forms needs to be made very clear in order to standardize the input. The information is collated by the responsible HS analyst in the HS unit that summarizes the relevant comments in bullet form. In a consensus meeting of the HS unit, the relevant comments are discussed and validated to be included in the database. Internal and external clinical experts can be asked to participate in the meeting. No prioritization is performed by the HS unit. However, the national HS expert could use the country-specific information for the national prioritization procedure.

Each product will have a link to the validated database entry. The advantages of sharing the collected country-specific data are that similarities and differences can be highlighted to facilitate further collaboration downstream the HSS.

Products in the List 3 will be followed for their timelines and EMA/FDA status until they either have approval or are denied approval, after which they are archived.

A national HS expert is appointed by the participating countries.

For products for which a MA application is pending, country-specific information is collected through local medical societies by the national HS experts for the HSS. The country-specific information is shared with the HS unit.

The products with the extended information are collated in List 3, which is shared with the customers twice a year.

5.8.5 Database

The database should consist of entries for each drug-indication combination based on a pre-fixed template containing parameters on the product that should be described or estimated along the HS process. As such, it aims to collate the information from the different sources in a shortened, concise format. The source of information should be referenced for each parameter or even a link to the source or document itself is included to provide an insight into the (un)certainty of the information provided. The database should give a clear, but easy overview of data on a product and facilitate sorting of products, while tracking changes and editing tasks in real time. A list of parameters to be included in the database is presented in Appendix 8.

Dissemination of information derived from the database and access to the database are discussed in paragraph 5.9.

5.9 Dissemination

The three HSS outputs (Lists 1, 2 and 3) could be shared at fixed time points each year (for example January (List 1 and 2); April and October (Lists 3)). The output will be a list of products with a link to the specific database entry for each product, which is accessible for the collaborating countries. Over time, the database should evolve in a real-time database, meaning that every time an entry in the internal database is updated and validated by the analyst team, the entry is accessible for the collaborating countries through a web-based database.

Access to such a database will be restricted to the responsible HS persons from each collaborating country (for example in Belgium this could be designated people from the RIZIV-INAMI and/or the ministry of Health). This can e.g. be organized through a secure website. A user agreement will have to be developed in order to make explicit the allowed use and dissemination of information derived from the database. Restriction of access will enhance sustainability (only those who are paying for the system get access) and manage unrealistic interpretation or expectations by lay people, as the information in the database is not written/appropriate for a broader public. As a consequence, the HSS's outputs are not publicly available. It could be examined though whether it would be possible and worthwhile to publish or disseminate extracts from the database more widely (e.g. with information that is publicly available) to other stakeholders who could benefit from the information (e.g. clinicians).

For each of the outputs a disclaimer should clearly mention that the datasheet contains estimations based on the available information at the time of publication and that more evidence is required to confirm the clinical, economic and organizational impact of the product.

- **The outputs of the joint HSS are published in the format of Lists, with links to the database entry.**
- **Access to the database is restricted to fixed registered parties within the collaborating countries.**
- **The database format is not appropriate to disseminate findings to a broader audience, but dissemination to specific target groups might be considered.**

5.10 Summary of proposed methodology of collaborative HSS

The features of the proposed HSS are presented in Table 16.

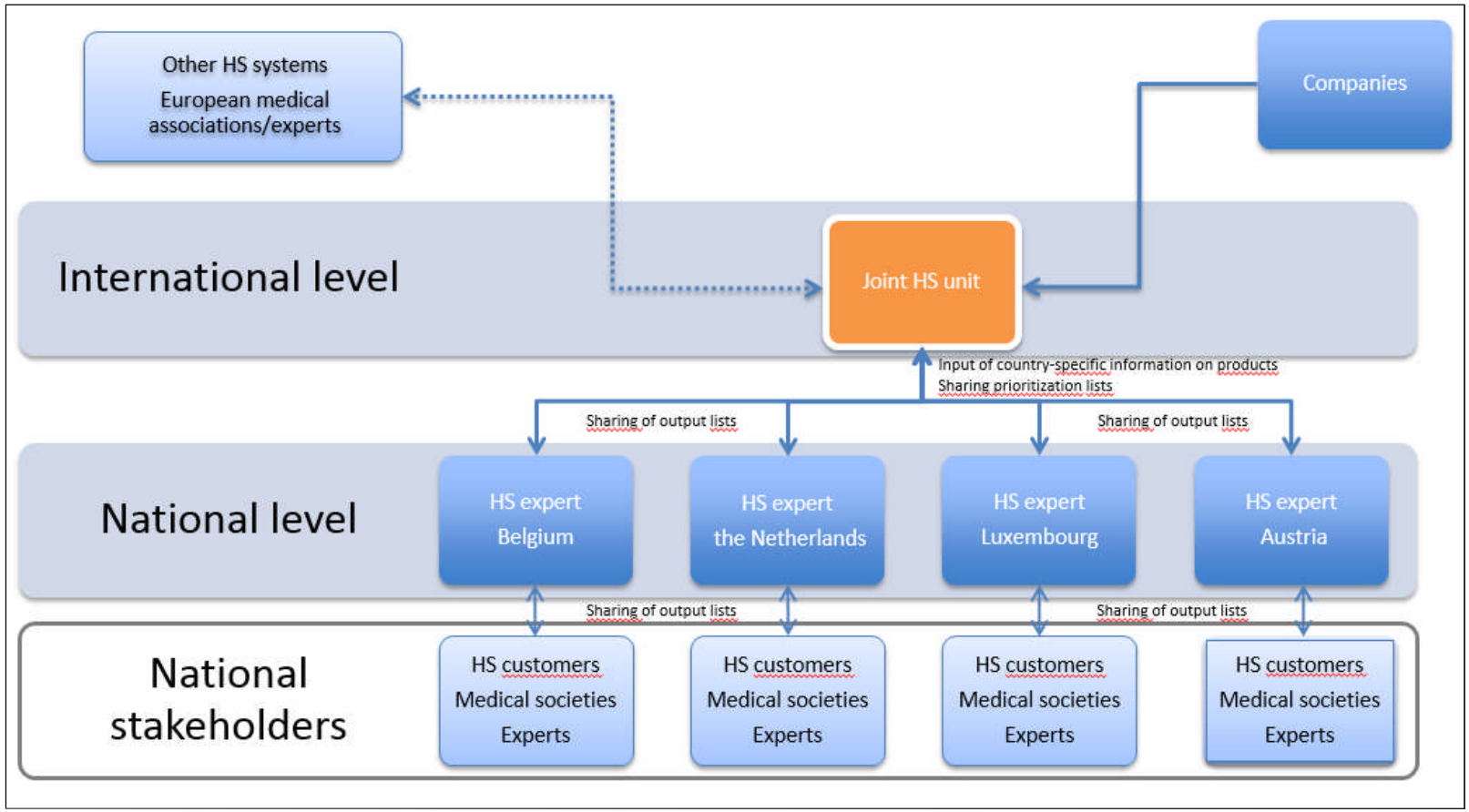
Table 16 – Features of the proposed joint HSS

Identification	International collaboration	Yes	No
	Active scanning	Yes	No
	Company input	Yes	No
	Expert input	Yes	No
Filtration	International collaboration	Yes	No
	Criteria	Explicit	Implicit
	Company input	Yes	No
	Stakeholder input	Yes	No
Dissemination	Early assessment	Yes	No
	Public availability	Yes	No

The proposal suggests to collaborate on the identification and filtration. The collaboration should provide the resources for a centralized HS unit to perform the HS activities for the collaboration, according to its needs. This HS unit could be an existing unit that is being commissioned to perform the HS for the collaboration or a newly established unit.

For the organisation structure, it is proposed to set up or commission a central HS unit that closely works together with designated national HS experts in each country. The organisational structure is presented in Figure 7.

Figure 7 – Possible organisational structure for a joint HSS



The HS unit will perform the following tasks:

- Scan the horizon for new and emerging products
- Maintain and update the HS database
- Compile three HS outputs (List 1, 2 and 3) in a timely manner
- Update data and regulatory status on a regular basis up till approval (every 6 months)
- Verify whether the products in the lists still fit the scope (initial filtration)
- Organize company pipeline meetings
- Integrate country-specific data provided by national HS experts in the HS database
- Estimate the expected clinical, organizational or economic impact to determine if inclusion in List 2 is appropriate
- Distribute Lists 1 and 2 once a year to the collaborating countries
- Distribute List 3 twice a year to the collaborating countries

The national HS experts in each of the participating countries have the following responsibilities:

- Collect country-specific information (relevant guidelines, incidence and prevalence data, potential savings due to substitution of medicines)
- Liaise between HS unit and country-specific experts and/or medical societies
- Provide input for the joint HSS
- Communicate the output of the HSS to national decision makers
- Coordinate the prioritization process

5.11 Recommendation for country-specific prioritization

Country-specific prioritization is not part of the collaborative HSS proposed in this report. Nevertheless, proposals for country-specific prioritization processes are discussed below, as each country will need to set up a systematic approach to use the HSS's output in their policy cycle or research agenda. Otherwise, the joint HSS will become irrelevant after a while. The idea is that all information necessary to perform a country-specific filtration and prioritization process is included in the joint HSS's database. In theory, country-specific filtration can be done based on each of the HSS's outputs, but it is most relevant and feasible to base it on List 3.

5.11.1 Step 1: Create filtration and prioritization criteria

Overall, HSSs in different countries tend to use similar criteria in their prioritization process, but the weighting of these criteria varies depending on the context, preferences and goal of the decision makers. Therefore, a common set of harmonized prioritization criteria can be developed for the four countries. Each country could amend these according to their needs and apply appropriate prioritization decision processes to end up with country-specific prioritization lists. For example, if a country wants to use the HS output mainly for selection of pharmaceuticals for price negotiations, financial criteria might weight more than clinical criteria.

Prioritization processes can be explicit, quantitative processes, consensus-based processes or a combination of both. Both clinical judgment and factual data will provide input to these processes (see 1.7.4).

Based on information obtained from the international comparison and expert consultation, we present below a broad range of possible criteria, which can be classified into financial criteria, clinical criteria, and organizational criteria.

The financial criteria are presented in Table 17 and are based on the formulation of the criteria used in the current Dutch HSS and in the Belgian reimbursement decision process.[35] The clinical criteria are based on the formulation of the criteria identified in KCE report 234[35] as criteria relevant to assess the added value of therapies (Table 18). The organizational criteria are based on those used by the US HSS (Table 19).

Table 17 – Proposed financial criteria for filtration and prioritization

Criterion	Aspects/dimensions
Potential of high impact on disease-related public expenditure per patient	Healthcare expenditures directly related to the current treatment (added cost or savings)
	Healthcare expenditures related to the treatment of side-effects (added cost or savings)
	Non-healthcare public expenditures (added cost or savings)
Potential of high impact on disease-related public expenditure	Aggregated cost data
Volume risk	By increase in prevalence, extension of indication, off-label use

Source: Dutch HSS (Ministry of Health) and KCE [35]

Table 18 – Proposed therapeutic criteria for filtration and prioritization

	Criterion	Aspects/dimensions
Therapeutic need	Potential of high impact on quality of life	Impact on mobility, self-care, usual activities, pain/discomfort, anxiety/depression
	Potential of high impact on life expectancy	Impact on overall survival, disease-free survival, progression-free survival
	Potential of high impact on inconvenience of treatment	Different administration route, changes in frequency of use, duration of treatment (per unit of use), duration of treatment effect, logistics, adverse effects
Societal need	Potential of high impact on prevalence of the disease	Impact on prevalence, incidence

Source: KCE[35]

Table 19 – Proposed organizational criteria for filtration and prioritization

Criterion	Aspects/dimensions
Potential impact on the healthcare delivery system	Decreased length of stay in hospital Shift in place of therapy (i.e. from 2nd line to 1st line) Shift in care settings (from hospital to home-based treatment, other departments) Changes in care process or treatment algorithm Changes in number of patients that can be treated Volume of care that needs to be delivered/can be avoided Change in infrastructure needs, such as physical resources (e.g. facility expansion or contraction, impact on use of shared resources within a facility or health system, capital equipment acquisition or obsolescence, expenditures or savings) and staffing resources
Potential for acceptance/ adoption by patients and clinicians	Convenience/ease of use and learning curve to use it, ease of acquisition, ease of compliance, degree of invasiveness, degree of physical and mental capacity required for use Anticipated side effects, risks, adverse events High Demand or expectations from patients or clinicians

Source: AHRQ

The expected impact of a product on the defined (clinical and organizational) criteria should be judged by (clinical and other) experts based on the intrinsic knowledge of the expert, and the data and estimations provided in the HS database. As such, the database should contain all information to perform a country-specific filtration and prioritization in each country. The expert comments will be used as an input in the prioritization process. In practice, two to three clinical experts per country are contacted through the relevant medical societies. These experts are asked to provide their opinion on the anticipated level of impact on clinical, financial and organizational impact of a new product based on an “expert comment form” (for example see Table 20).

Table 20 – Example of a commenting form

Criterion	0	1	2	3	Rationale
Potential of high impact on quality of life	None	Small	Moderate	Large	
Potential of high impact on life expectancy	None	Small	Moderate	Large	
Potential of high impact on inconvenience of treatment	None	Small	Moderate	Large	
Potential of high impact on prevalence of the disease	None	Small	Moderate	Large	
Potential of high impact on disease-related public expenditure per patient	None	Small	Moderate	Large	
Potential to impact on the Healthcare Delivery System	None	Small	Moderate	Large	
Potential for Acceptance/Adoption by Patients	None	Small	Moderate	Large	
Potential for Acceptance/Adoption by Clinicians	None	Small	Moderate	Large	
Other comments					

Source: adapted from AHRQ

5.11.2 Step 2: Assign teams for prioritization

Country-specific prioritization should be performed on a country level, with methods chosen by each country and performed by a designated person or team. The country-specific HS expert could be asked to coordinate the prioritization process as he/she will also collect the relevant country-specific information from clinical and other experts.

Sharing of finalized prioritization lists between the four countries is encouraged, as it would facilitate collaboration on processes downstream of the HSS (HTA, pricing and reimbursement), and thus reduce duplication of efforts.

5.11.3 Step 3: Filter relevant products

Depending on the objective and the criteria of the country, some products can be filtered out. For example, the Dutch system only takes products into the prioritization process that have at least one or more identified financial risk parameter (see above).

5.11.4 Step 4: Choose a method for priority-setting and perform prioritization

When the criteria have been defined, each country can choose how to weight them, and set thresholds (cut-off points) for impact to arrive at an overall judgment on the policy relevance of a new pharmaceutical.

Country-specific explicit priority-setting approaches

Explicit methods of priority-setting of new pharmaceuticals for a specific objective (for example price negotiations) use explicit weighting of criteria and thresholds. Depending on the objective of the use of the HS, criteria can be weighted differently. Explicit methods will lead to transparency and accountability of why a certain pharmaceutical has been selected. For explicit priority-setting, in each country thresholds need to be defined for the criteria. For example, the Dutch HS system uses specific thresholds for a financial criterion to select pharmaceuticals for price negotiation (example can be seen in Table 21). Each country can define thresholds relevant to their specific context. To quantify the priority-setting process, scores can be assigned to each criterion.

It is advised to pre-define the weighting of each of the criteria and the order of consideration. As such, a total weighted score can be calculated based on assigned scores for each criterion (for example on a Likert scale) and the weights assigned to each criterion. Products with a total score above a pre-defined minimum can be selected. Threshold needs to be decided on a country level by national decision makers.

Country-specific prioritization list

Products that are prioritized can then be placed on a country-specific "HS output" (country's prioritization list). The countries can then decide whether further information or reporting is necessary. Countries could share the prioritization list with the other collaborating countries, while highlighting for which purpose prioritization was done. For example, countries can decide to prioritize for selection of products for price negotiations or for further HTA research. This might lead to a country having several (different) prioritization lists. Based on the similarities in the country specific prioritization lists, one or several products can be further selected for a joint follow-up, for example joint assessment report writing or joint price negotiations.

Table 21 – Possible financial thresholds scheme

	'Green light' (low risk)	'Amber light' (intermediate risk)	'Red light' (high risk)
Annual macro costs	€ 0 - € X million	€ X - € Y million	> € Y million
Cost per patient per year	€ 0 – € A	€ A – € B	> € B
Volume risk (multiplication)	1 (volume stays the same)	1 – 2 (no change to doubling)	>2 (at least doubles)
Potential savings	Substantial	Moderate	None

Source: Adapted from Dutch HSS, personal communication

5.12 Prioritization for "Joint Activities"

To maximize the possibility of collaboration downstream the HSS, a common prioritization list is imperative (so-called "joint prioritization list"). Ideally, (a) country- and objective-specific prioritization list(s) should be shared within the collaboration at fixed time points in the year and integrated into the common HS database. As such, list with common prioritized products can be produced from the joint database at specific time points during the year. Joint meetings need to be organized to discuss amongst the collaborating countries for which products joint activities may have an added value. For example, collaborating countries can decide to start joint price negotiations or joint HTA on products that have been prioritized by several countries. The frequency of meetings can be tailored to the extraction of List 3 (for example two times a year, 2 months after List 3, giving time to countries to perform their prioritization).

The consensus meeting could be organized on the themes of collaboration for example:

- Joint HTA
- Joint price negotiations
- Joint assessment briefings
- Joint pharmaceutical policy

Products that are common in each of the countries' prioritization lists can be discussed during the meeting. At the end of the meeting there needs to be a consensus about whether or not to include the product in the joint prioritization list, based on clear and transparent argumentation.

Regular consensus meetings between collaborating countries can support discussion about products to be prioritized for further joint activities.

5.13 Establishment of the collaborative system

The establishment of a collaborative system requires resources. This paragraph described in general terms what is needed to start up a joint HSS and to run a joint HSS. More detailed budgetary needs will have to be discussed by the BeNeLuxA collaboration once the proposed HSS has been agreed.

5.13.1 Start-up investment

Throughout the HSS development process, but especially in the start-up phase, communication needs and costs are high. Resources are needed for setting up telephone conferences, e-meetings, face to face meetings and travelling. Relationship building with companies and medical societies at a country level to explain their role in the HS process also requires quite some time investment from the HS staff. The knowledge about indications and licensing plans cannot be accurately found outside companies and medical societies could provide names of super-specialists in a particular field; therefore it is important to invest in this relationship building.

Before the HSS can be operational, there is also a need for the development of a template for the database, search strategies, selection of sources and development of a web-based interface to allow multiple countries to access the database. (Partly) automation of the scanning process should be developed, with the help of external partners (for example Ontoforce, see also 5.6.2), which will make the scanning process more efficient. An investment is needed to train people in the process, methodology and in communication skills in order to standardize the database entries as much as possible.

Because of the time needed to set-up a list from scratch, it can take up to 6 months to have an initial database. In order not to have to wait this long, a **two stage approach** could be applied. In the first stage, a database can be acquired from AHRQ, NIHR HSRIC or UKMi to get started. The Ludwig Boltzmann Institute (Austria) has already confirmed that they are willing to share their list of oncology drugs in development[bb]. Based on these databases, the HS unit can start working. In the meantime the necessary templates and operational structures are put in place to set up an operational joint HSS for the collaboration, including the templates, pipeline meetings with companies, web-interfaces etc. This would be the second stage of the establishment process.

5.13.2 Annual budget

The required annual budget for the HSS will depend on the extent of the HS activities. Based on the scope and process described above, it is estimated that 8 to 10 full-time equivalents are required. The competences are diverse. The HS unit requires:

- A medical librarian
- Two HS analysts with HTA and/or health economics expertise or with background in pharmacoeconomics
- A pharmacologist
- A HS analyst with medical background (M.D.)
- A data manager
- A communications specialist (contacts with companies, medical societies, other experts)
- An ICT specialist
- A manager or coordinator

Also for the subscription to sources, rent and facilities an annual budget will need to be made available.

Note that outsourcing to a for-profit third party might require a premium above the costs.

5.13.3 Pilot phase

A pilot phase is proposed to gradually set up the system and compile the list and output formats. In the pilot phase, the database is populated with products in development and the above process is tested. The pilot phase is estimated to take about 1.5 year (or at least two “List 2” cycles), after which it should be evaluated. The outputs can, however, already be used by the stakeholders during the pilot phase. An evaluation framework needs to be compiled to assess:

- the process,
- the sources for identification,
- the frequency of outputs,
- the contacts with and information obtained from companies,
- the collaboration with national medical societies,
- the problems and barriers in the current HSS, and
- the number and frequency of outputs

The pilot phase could also be used as an opportunity to test whether the involvement of a financial analyst from the pharmaceutical and biotech investors in the HS identification team, for example for input on List 3, could help validate the (cost) data or to contribute to new methodologies for cost and budget estimations.

[bb] Which currently contains about 273 products (25 October 2016 personal communication).

6 FEASIBILITY OF INVOLVING COMPANIES AND CLINICAL EXPERTS IN BELGIUM

A feasibility study was set up to describe the process of collecting country-specific data for the HS process. The process follows the steps as proposed in the previous chapter, and data are collected in Belgium.

The goal of the feasibility study was to:

- investigate the feasibility of collecting country-specific data about new and emerging pharmaceuticals from clinical experts,
- investigate the feasibility of obtaining (country-specific) information from companies,
- identify the barriers and limitations of data collection and stakeholder involvement, and
- estimate the resources needed

6.1 Results

6.1.1 Selection of products

The list of the selected products is presented in Table 22.

Table 22 – List of selected products

	Name	Source	Indication	Company	Expected approval	MOA	Status
1	Aducanumab	Newspaper the Guardian (31 August 2016)	Early Alzheimer's disease	Biogen/ NeuroImmune	2022	Antibody aggregated forms of β-amyloid	Phase I/early phase III
2	Baricitinib	Dutch HSS Dec 2015	Arthritis and non-traumatic joint disease	Incyte/Eli Lily	01/03/17	Selective JAK1/ JAK2 inhibitor	Phase III finalized
3	Idalopirdine	UKMi outlook report 2015	Mild to moderate Alzheimer's disease	Lundbeck	Q2/3 2018	Selective 5HT6 receptor antagonist	Fast Track designation (FDA), failed first phase II*, phase III still running
4	Lebrikizumab	UKMi outlook report 2015	Uncontrolled asthma (Severe Type -2-asthma)	Genentech/Roche	Q4 2019	Monoclonal antibody blocking IL-13	Phases II and III
5	Ocrelizumab	Roche	Multiple sclerosis	Roche	Q1/Q2 2017	Humanized anti-CD20 antibody, inhibiting B-cells	Submitted July 2016 to EMA, Feb 2016 to FDA
6	Olaparib	Dutch HSS Dec 2015	BRCA-mutated maintenance therapy after platinum-based chemotherapy in ovarian cancer	AstraZeneca	Q32018	Inhibitor of PARP, an enzyme involved in DNA repair	Orphan status, approved FDA and EMA in 2014

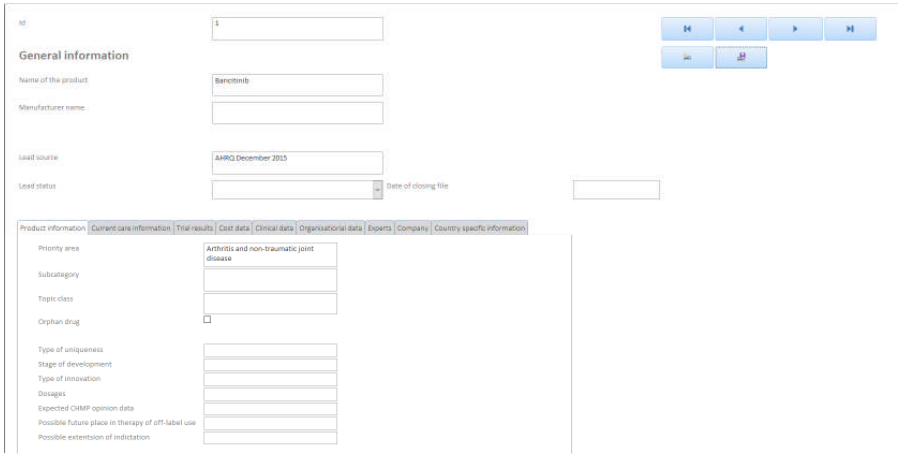
*BRCA: Breast cancer gene; MOA: mechanism of action; PARP: poly-ADP ribose polymerase; JAK: Janus Kinase; IL13: interleukin-13; DLBCL: diffuse large B-cell Lymphoma; CLL: chronic lymphocytic leukaemia; FL: follicular lymphoma; GnRHR: gonadotropin-releasing hormone receptor; mPTP: the mitochondrial permeability transition pore; *Sept 22,2016.*

6.1.2 Development of a database template for data aggregation

To give an idea towards the BeNeLuxA collaborators on the possible format of a HS scanning database and how to work with it, a data entry template was developed. An example of the template is presented in Figure 8. The parameters were classified into logical sections of information such as “Regulatory affairs & market entry”, “Technology description”, “Innovativeness”, “Burden of disease”, “Dosage”, “Clinical parameters”, “Landscape”, “Country-specific parameters” and “Detailed information about trials”.

According to the HS researchers, the format clearly enhanced the readability of the database as compared to an Excel file and helped to classify the information.

Figure 8 – Example of an input template linked to an underlying database



6.1.3 Gathering information on the products

Since the selected products were in a late stage of development, data on several parameters could be found in publicly available sources, except for: expected market launch and date in the different countries, patient volume per treatment line (i.e. first-line, second-line treatment), variation in access of current treatment, and expected unit price. Also country-specific parameters such as expected uptake, expected place in therapy, expected patients in treatment group, expected reimbursement appraisal/HTA, barriers for entering the market and potential off-label use were difficult to find in public available data.

For cost data, often an investor’s opinion could be found online about the (annual) sales estimates for the product. Sometimes, the expected price (range) (in terms of annual or monthly cost) was also mentioned or the expected premium/discount compared to comparator treatment was indicated. In one case the price of a comparable product in another indication was mentioned as reference for price. The price per unit was never found in the sources that we checked.

6.1.4 Company pipeline meetings

Ease of consulting companies

The contacts provided through pharma.be all responded positively, while others did not react or reacted very late after repeated reminders. Finally, three companies (out of 6) participated in a pipeline meeting. Two out of three companies provided the requested information during the meeting, the third company provided the data collection form by email several weeks after the meeting.

Added value of information provided by companies

Two out of three companies shared the products in their R&D pipeline, stating that the R&D pipelines could be found on their website as well. However, the extent of information and ease of access to information on the respective websites differed considerably. Although both websites provided a list of products in Phase III, more specific information such as expected year of EMA/FDA market authorization application was not always available

and not all indications[cc] were present. Moreover, the information on the website is not always updated frequently[dd], limiting the suitability for the HS data collection.

The meeting with the two companies showed that companies differ in what they want to share. One company shared data that could not be found on the website, such as the most important or promising product(s) (product(s) with possible the biggest impact or most likely to be continued in development). Furthermore, the company shared whether products were discontinued or halted in their development. This can help the HSS to focus on the products that are more likely to reach the market. As we only have a sample of two we cannot draw any conclusions as to what it is that defines whether a company shares other data than provided on website.

We compared the information provided by the companies during the meeting with the information that was gathered before the meetings by the initial information gathering of the HSS researchers (see 6.1.3). Appendix 10 gives an overview of the comparison. Most information on the products could be found by the HS researchers. However, some information provided by the company differed from the information found by the HS researchers. It concerned information about the place-of-therapy. Finally, the company was able to give additional or new information in some instance, for example more precise date of expected EMA filing, outcomes on unpublished trials, annual product costs and expected uptake of the product.

The "brief description of the product, including therapeutic or pharmacological action" gave a very wide range of information; hence the parameter needed to be refined with the inclusion of a specific example of the expected input.

Experiences and opinions of companies

The companies who participated stated that they are in favour of a HSS, especially if this could also lead to international cooperation in for example HTA. However, one company stated that they did not have a good insight in how a HSS works. The criteria and description in the data collection form were overall satisfactory. A comment was made by one of the company representatives that filling out the data collection form was very time consuming. In addition, filling out the data collection form was not possible for all products in the pipeline, because the type of information requested is not known for products at an earlier stage of development. For example, country-specific prices were not available yet, claiming that strategic pricing decisions are taken on the headquarters' level and are only communicated just before market launch to the local offices. Finally, a company indicated that it would be good to provide the filled out documents upfront to the HS team, so that interviewers can prepare better questions in the face-to-face meeting.

- **The willingness of the companies in our sample to meet was limited: only 3 out of 6 invited companies participated.**
- **Companies can provide useful information on pipeline products, such as their expected impact, companies' development priorities or product discontinuation.**
- **Companies can provide useful information on product parameters such as submission dates, place in therapy, comparators, and costs.**
- **Some parameters can be excluded from the data collection form as the data can be easily found through other sources.**
- **For cost parameters, companies can provide an estimate of the annual product cost per patients.**

[cc] We could not find the specific indication provided by the company in the company meeting of one of the selected product.

[dd] For example, the last update for stage of development was July, 19th, 2016 (website assessed on December, 2016). Negative results, available through the web search, were not updated in at least one of the selected products.

6.1.5 Meeting with medical societies

The goal of the meetings with the medical societies was to get information of the country-specific parameters and to get an expert opinion about the potential impact of the products. To do so, a researcher presented the data collected on the product(s) and asked the expert to comment on the country-specific parameters.

Ease of consulting the medical societies

None of the societies responded after first contact. After contacting members of the board of directors directly through KCE staff, two of the three medical societies accepted the invitation. A third medical society did not respond, not even after several emails and telephone calls. One society was consulted in a face-to-face meeting, while the other was consulted via telephone, both meetings lasting about one hour.

Added value of information provided by medical societies

The clinical experts of the two societies judged the products' place in therapy (i.e. appropriate target patient population, first, second or third line, substitution of other product). According to one expert, the current place in therapy does not solely depend on the characteristics of the product (e.g. mechanism-of-actions, efficacy, side effects) or clinical trials, but also on the cost of a drug. For example, whether Baricitinib becomes a first-line or second-line treatment depends on the price the company will charge. According to the expert, companies will have to make a strategic choice between volume and price.

Clinical experts gave insights into the context of the novel treatment by providing information on the current standard-of-care, the medical need in (specific) patient population(s) and the estimation on the volume of patients in each treatment line.

Experiences and opinions of medical societies about horizon scanning

The clinical experts were positive towards HS. However, they warned that a HSS should not only cover therapeutics in development but also uncover areas that show a lack of (successful) development or research. For example, within the field of rheumatology there is a great need for new developments for treatment of juvenile idiopathic arthritis[ee]. One expert stressed that it should be warranted that independent, investigator-initiated research into new treatments should also be covered in the new HSS.

The last decades, several medical specialties were further "subdivided" in so-called subspecialties. For example, in neurology some neurologists are further specialized in and only treat neurodegenerative diseases (e.g. multiple sclerosis, Alzheimer's disease), while others only treat traumatic brain injury, epilepsy, etc. The medical societies mentioned that they could assist in identifying the respective clinical experts in the various sub-domains. The societies could then confer the filtration form for specific products to the relevant specialist to get country-specific information from.

- **Contact with the medical societies was difficult to establish.**
- **Clinical experts can provide insights into the current-standard-of-care, medical need in (specific) patient population(s), likely place in therapy of the new product, and estimation of patient volume in each treatment line.**

[ee] An effective IL-1 blocker exists but is only approved for Rheumatoid Arthritis (RA) and not for juvenile idiopathic arthritis. Nobody initiates these trials because there is no commercial interest (only 30-40 patients in Belgium)

6.1.6 Estimation of potential high financial impact

The goal was to make a rough estimate of the financial risks of the products in order to prioritize products. Parameters needed for the assessment on potential financial impact where collected through web-based research and input form clinical experts. Because of their relevance for high financial impact, the parameters are discussed in more depth here.

To estimate **annual drug price per patient**, several approaches were used (Table 23): the company gave an estimation, real prices were identified or prices were based on current treatment (with or without a premium, based on investor's opinion).

The estimated **patient numbers** in the treatment group (number of patients eligible for using the product) were difficult to estimate. Incidence and prevalence data were readily available from various sources, including registries and the scientific literature. For some products, the patients being treated could be estimated through national payer's data of the current treatment. However, the number of patients eligible for first-line, second-line, or third-line therapy could only be estimated based on the information provided by the consulted experts. In addition, the consulted experts provided very useful information on the actual clinical needs (e.g. although a product was in development for several subpopulations or lines-of-treatments the consulted expert informed us that the medical need was only high for one small subgroup) and on the impact of the pricing strategy, in addition to the outcome of the clinical trials, on the final line-of-treatment of the product. More patients could be eligible for treatment by moving the product from second-line to a first-line treatment[ff], and this was classified as a potential volume risk.

The **uptake** of the drug also needed to be estimated. For the three products that were discussed with the medical societies, the estimations were based on clinical expert's opinion.

[ff] For this particular product, the cost risks were already present in the second-line patient population.

Table 23 – Financial estimations for selected products

	Annual total cost/patient	Annual macro cost	Volume risk	Patient population	Cost source	Comments	Probability of market access[ii]
Product 1	Amber	Red	Red	Literature extrapolation	Company	Subpopulation numbers not well-defined	Low-middle
Product 2	Green	Green	Red	Registry Belgium	Web; real prices[i]	Uptake 100% scenario taken	High
Product 3	Amber	Red	Amber	Expert, Riziv data	Price of reference product(s) (current treatment)	Patient numbers based on patients in current treatment	High
Product 4	Amber	Red	Red	Expert +literature	Based on premium on price current treatment[iii]	Subpopulation numbers not well-defined; uptake unclear	Low
Product 5	Red	Red	Red	Data Belgium + expert (uptake)	Based on current treatment[iv]	Subpopulation defined by experts; smaller then clinical trials because of absence medical need	High

For confidentiality reasons, the names of the products are not provided; [i] Price database could be checked; ii Probability of market access is based on expert' opinion or HSS analyst estimation based on latest clinical information about the product; [iii] Source: investor's website: in line with price of similar product in other indication; [iv] Source: Scrip-related website: in line with current treatment of bulk patient group

Based on the estimated uptake and annual drug price per patient, the **macro cost** of the selected products was calculated (Table 23). To get a feeling of how the uncertainty about uptake might influence the financial macro cost, different scenarios were applied going as low as 20% uptake up to 100% uptake. However, for all 5 products the estimations still surpassed the green light threshold (i.e. the amber or red light) for at least one cost parameter (Table 23).

The **volume-risk** parameter was also difficult to estimate, but was based on the possibility of extension to other subpopulations in the same therapeutic area, different lines-of-treatment (i.e. from second-line to first-line), extension to other indication(s) or possibility of off-label use. The volume risk could be based on patient numbers or on total annual cost.

- **Pricing strategies are often unknown until close to market launch; hence alternative sources for the expected price of product must be used.**
- **No country-specific prices were retrieved.**
- **Alternative sources for price such as investor's websites can be found; however, the data is difficult to validate.**
- **Although incidence and prevalence data can be found , there is often no data on the proportion of patients eligible for the new treatment or on the expected uptake. The estimates are therefore based on expert opinion.**
- **Estimation of price and size of patient population is possible but uncertain; therefore scenario analyses should be performed.**

6.2 Lessons learnt from the feasibility study

The feasibility exercise showed that the process was possible within the Belgian context and helped to optimize the process.

The database template developed in this study gave a good impression as to the format of a possible future database. However, further investment in database development should be made to enhance capabilities and user-friendliness. For example the database should be able to track changes and timing of changes automatically, include the possibility to include "pdf" reports, display data subsets and respond to complex queries, and linking possible related products. Possible integration of automatic scanning queries as described in paragraph 5.6.2 should be investigated[gg].

The exercise of gathering information about the selected products helped to identify possible improvements and learning points for the HS process. First, the data collection process helped to identify lack of clarity in the parameters or non-logical order of parameters. For example, "type-of-innovation" was explained better by adding examples such as: new compound, new combination, new indication, new formula, new route of administration, orphan drug. The logical order of parameters was adapted so that important information about the product such as "mechanism-of-action" and "comparator" were discussed before related items such as "similar products".

Secondly, the amount, depth and format of information described was scrutinized. For example, the detailed information about the clinical trials (including parameters such as inclusion and exclusion criteria, patient numbers, all primary and secondary endpoints, treatment arms and dosages, length of follow-up, adverse events) were considered too detailed. It was decided to move these parameters towards the end of the data entry as additional information. Instead the HS researchers concluded that a brief description of the most important conclusion(s) of the trials in the section "clinical trials" was needed.

For the short description, a direct citation of the (peer-reviewed) publication could be reported, rather than providing an interpretation of the results, in order to avoid possible biases or pre-assessments by the researchers. Publications by companies as well as expert opinions can be included.

It was a delicate exercise to display all the data in a concise but informative manner. Bullet formats were not always considered sufficient to confer the information on each parameter. As a consequence, the text easily became too extensive and needed editing. However, the HS researchers got more used to this when more products were included.

Thirdly, the information sources of the web-based query were subject to debate. First, consistently referencing the source while filing out the database entry required some discipline. Second, the sources' reliability was sometimes doubtful, mainly because the websites were unknown to the researchers. Often, it was tried to confirm the data through searching other websites. In relation to costs, some investor's websites or commercial news sites stated numbers; often without referencing a source however. As this was often the only source of information about cost, it was still included in the data collection form. Therefore, involving an investor into the process might help to assess the reputation of the website/source.

The limited participation of companies was anticipated from the experience of other HSSs. As learned from the international comparison, the building of mutual trust between the HSS and companies is a time-consuming process, needed to ensure maximize participation and sharing of data. Creating more awareness about the goal, process and actual application of HS in national decision making, for example through industry associations like pharma.be, might enhance participation. Completing the data collection form was time-consuming for the companies, while the amount of parameters with extra information was limited in this small feasibility study. The main added value

[gg] For example, one can explore if products in phase III found by automatic scanning of clinical trial database could be automatically compared to the database entries of the HSS database and a new data entry automatically created for products that were not present.

of company meetings was the better estimation of MA application filing, and de-listing of halted products, which are important for the HSS. Therefore, we advise to pilot company contacts on an international level (European headquarters), as no country-specific information could be given. However, we propose to work with a somehow shrunk "data collection form" which should include the only the "Stage of development, availability, and licensing and launch plans", "Costs", "Unpublished completed clinical trials" and "the potential or intended impact of the technology (speculative)" sections.

The limited reaction of the medical societies was somewhat less expected, but one might speculate to be due to the low awareness of the medical societies about (the importance and use of) HS. Communication on HS to medical associations or other specialists' consultation bodies could potentially enhance participation. Both the face-to-face meetings and teleconference meeting worked well for gathering information on country-specific parameters, possibly because it was a one-to-one contact. Insights obtained through these medical societies meetings were extremely valuable to gain insights into the specific indication and current standard–of-care and for estimation of clinical and financial impact of the selected products. During implementation of the HSS, medical associations should be asked to assign specific (fixed) contact persons for specific subdomains in the specialist field. Contact with those persons should be planned on a regular basis, which should facilitate logistics and participation. Including other country-specific, non-clinical expert(s) for example experts from RIZIV or the Ministry of Health at these meetings could help to obtain better estimations on financial impact.

Cost data and the financial estimations were able to give "ballpark" figures about cost impact in the Belgian context. As such, the signalling function of the HS exercise was validated, as the current process successfully confirmed products with a potential financial impact. Going beyond the HS activities, the refinement in discussion with Belgian payer (RIZIV) might be useful to decrease uncertainty of the financial estimations. A template for a three-scenario analysis (worst, base-case, and best from a cost perspective) could be useful to get an idea of the possible range of financial impact. For budgetary planning purposes, an approach such as used by Van Dyk and Geldof [4] can be used to forecast the uptake profile of the new product over several years[hh]. For the prioritized products, data on expected MA and price need to be continuously tracked.

Our feasibility study was limited by a small sample and the slow response rate of stakeholders. The small sample did not hinder to test data gathering and make improvements related to the reporting of the parameters. However, the small sample and the time constraint made it difficult to fully test the consultation with the companies and the medical societies. Moreover, it was not possible to evaluate the process in the BeNeLuxA collaboration as the collaboration was still being drafted during the last stages of this study.

As a conclusion, as other HSSs have experienced before, a new HSS needs to "learn-by-doing". That is why we recommend that the implementation of a new BeNeLuxA HSS should include a pilot phase and a subsequent evaluation and adaptation, as suggested in paragraph 5.13.3.

[hh] Basically, uptake profiles (in increase in Defined Daily Doses) of existing reimbursed products in the indication (available through RIZIV databases) are calculated and used to simulate the uptake of the new products.

7 GENERAL DISCUSSION AND CONCLUSION

This report describes a feasible methodology for a trans-national HSS. It is the first to describe a joint HSS following on an initiative of the ministers of health of four countries to collaborate on pharmaceutical policy. A joint HSS will minimize duplication of efforts and enhance exchange of information. The implementation of a joint HSS between several countries will allow national decision makers to prepare for the fast-changing pharmaceutical landscape and will allow the identification of areas for joint activities (early dialogues, price negotiations, post-marketing data collection, pharmaceutical policy development).

7.1 Benefits and prerequisites of a performant joint HSS

Our feasibility study and international comparison show that several prerequisites exist to obtain a successful joint HSS. Table 24 summarizes the prerequisites and benefits of the proposed HSS, with a central HS unit working together with national HS liaison experts.

Table 24 – Benefits and prerequisites of international collaboration on HS with a central HS unit and national HS experts

	Collaboration	Central HS unit with national HS experts
Benefits	• No duplication of efforts, hence more efficient use of resources	• Fair contribution of all countries
	• Identification of possible joint activities based on the HSS's output	• Investment in relationship building with national stakeholders
	• Enlarged expert network	• Operational feasibility
	• Increased (expert) knowledge base	• Single point of contact for stakeholders
	• Increased negotiating power	• Dedicated employees ensuring stable quality
	• Secured processing of inputs to the joint HSS and output from the joint HSS through the national horizon scanning expert	• Link with national stakeholders
Prerequisites	• Agreement on scope of joint HSS	• Sufficient resources for the central HS unit
	• Alignment of joint HSS outputs with national health policy	• Clear mandate of national horizon scanning expert
	• Integration of joint HSS outputs in national processes	• Investment in relationship building with companies and medical societies
	• Commitment of individual countries to support the HS agency	• Regular evaluation of organizational model
	• Regular Evaluation of the joint HSS	

7.2 Wider societal benefits of a joint HSS

The successful implementation of the proposed joint HSS will enable the pro-active decision making regarding the use and reimbursement of new pharmaceuticals to benefit individual patients and society as a whole. Pharmaceutical policy may be improved through HS in several ways. First, drug policy may become more demand-driven, e.g. by giving priority to those pharmaceutical products that meet an unmet medical need. Second, knowing what is coming allows better anticipation of future challenges in terms of reimbursement decisions. Pharmaceutical policy can be prepared to cope with these future challenges, either on a national level or on an international level. A dialogue can be started with the decision makers in different countries, with companies and other stakeholders to discuss potential challenges of sustainability. Moreover, a HS system can ensure timely access to new drugs, which directly benefits patients with serious diseases with high unmet medical needs.

7.3 Flexible step-wise implementation of a joint HSS

It should be noted that the proposal for the joint HSS as described in this report cannot be realized in one year's time. Nevertheless, very concrete steps can already be taken in the short run to start with an operational HSS that serves certain but not all needs. In the longer term, more countries may wish to step into the HSS or use its' output. This may create opportunities that are not feasible in the short run. By not focusing on the short term possible achievements, the proposal will not be short-lived. It should also be noted that the system will also learn by doing. Flexible application of the proposal is recommended, with continuous reflection on the efficiency and usefulness of the produced outputs for the health care decision makers.

APPENDICES

APPENDIX 1. COUNTRY DESCRIPTIONS

Appendix 1.1. Dutch horizon scanning system

Context

In 2012, the Ministry of Public Health, Welfare and Sports (VWS, further referred to as Ministry of Health) introduced a novel policy instrument to contain the increasing financial burden of expensive new pharmaceuticals on the healthcare budget[ii]. This instrument is called the 'financial arrangement' (FA) (*financieel arrangement*). Realizing that the Ministry needed a more systematic approach for selecting products eligible for entering financial arrangements, a HSS was developed within the Ministry.

FA purpose

The purpose of the FA instrument is to negotiate the price of certain drugs that are expected to have a big financial impact on the health care system. FAs are specifically meant to be applied in settings with financial risks and where healthcare providers and insurers are not sufficiently capable of containing the costs of a product. FAs can be applied to both inpatient (intramural) and outpatient (extramural) pharmaceuticals (see Box 4). A key characteristic of the FA negotiations is that the outcome is not made public. The producer of a product has to pay the ministry the difference between the list price (the price that hospitals pay to the manufacturer) and the price negotiated between the Ministry and the manufacturer. This policy instrument is part of a larger set of instruments that can be used to contain the financial risks for the basic benefit package, which include conditional admission[jj] and funding.[37] From 2012 until 2015, eleven FAs in the form of price/ volume arrangements have been made; seven of them for outpatient pharmaceuticals. Until April 1st 2016, 18 FA have been made.[38]

[ii] In 2012, 6 expensive inpatient drugs (add-on list (see Box1)) made up over 70% of the budget for these drugs expensive inpatient drugs.[36] The introduction of another product with such a budget impact is considered a risk to the sustainability of the healthcare system.

[jj] Since 2012, the minister can decide to temporarily (usually maximum 4 to exceptionally 7 years) admit the product to the basic package of reimbursed products under certain conditions, for example patients receiving the care should participate in a clinical trial to collect more data about the efficacy of the product.

FA process

A FA process consists of five phases, involves multiple stakeholders, and is directed by the Ministry of Health. These five phases are: 1) detection; 2) advice by the Dutch National Health Care Institute (*Zorginstituut Nederland*) and selection; 3) negotiations; 4) reimbursement decision and transfer of information to the lower chamber of parliament; and 5) implementation.[39] The Dutch HSS was developed to support the first phase of the FA process.

Box 4 – The Dutch reimbursement system: inpatient versus outpatient pharmaceuticals

The Netherlands has separate regulatory processes for reimbursement for inpatient (intramural) or outpatient (extramural) pharmaceuticals. Pharmaceuticals prescribed outside the hospital are only reimbursed when they are enlisted within the 'pharmaceutical reimbursement system' (*geneesmiddelenvergoedingssysteem, GVS*). To be included on this list, the Dutch National Health Care Institute (*Zorginstituut Nederland*) determines if the product has added therapeutic value, if the costs are acceptable in relation to the health benefits (cost-effectiveness), and if the impact of reimbursing the product on the healthcare budget is manageable (budget impact). There is no such a-priori evaluation for products prescribed within the hospital. These products can be used as soon as they have been authorized by the European Medicines Agency (EMA). However, the mandate of the National Health Care Institute for the management of the basic benefit package does include the inpatient pharmaceuticals, meaning that the National Health Care Institute can indicate that a product should not be part of the basic benefit package, amongst others as a result of its poor cost-effectiveness or high budget impact if there is an appraisal.

By default, pharmaceuticals used within the hospital are reimbursed automatically within the price agreed upon by a hospital and an insurer for a diagnosis-treatment combination (*diagnose-behandelcombinatie*, *DBC*). Certain expensive pharmaceuticals, however, can be charged separately from the DBC. These products are listed on the “Add-On” list. Inclusion of new products on this list is determined by the Dutch Healthcare Authority (*Nederlandse Zorgautoriteit*, *NZA*) after a joint request from a hospital and a health insurer. Most of the inpatient pharmaceuticals targeted for a FA by Ministry of Health end up as “Add-on” pharmaceuticals.

Since mid-2015, the Ministry of Health has made it possible for selected new inpatient drugs from being reimbursed automatically (see textbox above for more information on the Dutch reimbursement system for pharmaceuticals). Rather, they are put in a 'lock' (*pakketsluis*) which means that the product is actively excluded from reimbursement before they enter the market (a negative list). After an appraisal process and possible negotiations, a decision can be made to include the drug in the basic benefit package. In the FA process described above, the lock is placed between steps 1 (identification) and 2 (advise by the National Health Care Institute). The lock creates more time for both diligent decision-making on the application of a FA and for the preparation of negotiations by ensuring that the product is not incorporated until the National Health Care Institute has assessed the pharmacotherapeutic and pharmacoeconomic dossiers as filed by the pharmaceutical company. The lock placement does not always have to result in a negotiation. In 2015, only one product (Nivolumab for lung cancer) was placed in the lock. In April 2016, the Minister of Health announced that she planned to add another four products[kk] to the lock.[3] To date (October 17nd 2016), three has effectively been placed in the lock (Ibrutinib for chronic lymphatic leukemia; Pembrolizumab and Nivolumab for lung cancer) while the legal procedure is still ongoing for one other product.[ll]

[kk] Planned products to be put in the lock: Ibrutinib for chronic lymphatic leukemia; Palbociclib for metastatic breast cancer; Pembrolizumab and Atezolizumab for lung cancer.

[ll] Interview with Evelien Klein-Lankhorst, Dutch Horizon Scanning System, (2016)

FA time horizon

The purpose of the lock is to explicitly exclude products from the basic benefit package when they become available on the Dutch market. Thus, the decision and announcement by the Ministry of Health that an inpatient product is placed in the lock has to be done before EMA market authorization. In general, this will be done in the post-opinion phase of the EMA process, i.e. between the (positive) opinion of the Committee on Human Medicinal Products (CHMP), and the final commission decision on market authorization[mm]. In contrast, the timing for outpatient pharmaceuticals is less critical, as these products are not by default part of the basic benefit package. An assessment of the financial risk is also part of the process for new products to be incorporated on the list of reimbursed outpatient pharmaceuticals (GVS). If such a risk is identified, and a FA is selected as the instrument to mitigate this risk, the product can be kept off the list until the FA process has been completed.

FA organization

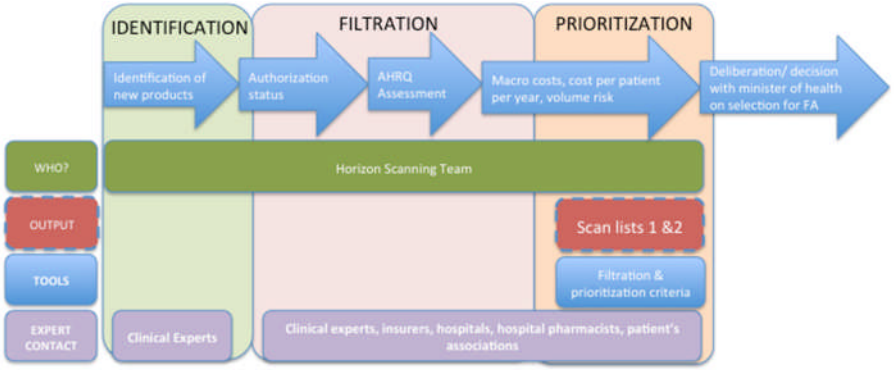
The Office of Financial Arrangements (*Buro Financiële Arrangementen Geneesmiddelen*) at the Ministry of Health was set up in 2014 to start professionalizing the process of FAs. The main tasks of this office are to perform negotiations between the Ministry of Health and pharmaceutical companies, draft contracts between parties, and arrange the financial structures, processes, and implementation of the FA agreement (phase 3 to 5 of the FA process). The office has a staff of 7 FTE. The same office is also responsible for the horizon scanning activities.

Purpose of the horizon scanning activity

The purpose of the horizon activities is to provide timely advice to the Minister of Health on the eligibility of new pharmaceuticals for a FA and to collate data about the products to inform the FA negotiation process. An overview of the Dutch HSS is presented in Figure 9.

[mm] In the standard (non-accelerated) EMA procedure, the duration of the post-opinion phase is 67 days (between 210 and 277 days after initial dossier submission).

Figure 9 – Schematic overview of the Dutch HSS



Methodology of the Dutch horizon scanning system

Scope and Customer of the Dutch HSS

The Dutch HSS focuses on all patented pharmaceuticals, including both inpatient and outpatient drugs, but excluding vaccines and biosimilars. In the output of the HSS of May 2016, 28 of out 52 products (53.8%) were outpatient and 24 (46.2%) were inpatient.[ll] The customer of the system is the Office of Financial Arrangements at the Ministry of Health, who uses the output of the HSS for the selection of products for the lock procedure and financial arrangements, as well as to gather information to support negotiations. Therefore, the group that scans is also the customer of the output.

Time horizon

All new pharmaceuticals expected to be introduced on the Dutch market within two years, are included in the HSS database.[nn] Output from the horizon scanning activities should thus be available before the market authorization decision of a product. Hence, identification and information collection usually starts shortly after finished Phase III studies.

Identification of new and emerging technologies

The Dutch HSS does not scan actively through a broad range of sources, but relies on the output of other agencies. More specifically, the Dutch HSS uses the biannually 'Potential High Impact Report' from AHRQ (US) as main source. It additionally scans the annual "Prescribing Outlook – New Medicines" report from UK-based UKMi to secure the identification of products that are possibly missed by the US system (for example first launched on the European market), and the new products that are filed at EMA ("Medicines under evaluation"). In rare occasions a product or new indication is first identified during stakeholder meetings. However, the AHRQ report is very inclusive and most missed products will show up in the next AHRQ report (personal communication). Furthermore, the HSS team gets e-mail notifications of a number of newsletters from both scientific journals (e.g. New England Journal of Medicine, Journal of the American Medical Association), and professional literature (e.g. Fierce pharma[oo], Scrip[pp]), but these are not scanned continuously. The Dutch identification process is perceived as highly inclusive by the HSS staff; however, this has not been evaluated yet.

Filtration of the identified technologies

The filtration process of the Dutch HSS consists of 3 steps. First, products that have received a risk classification ("high"/ "moderately high" and "lower end of the high impact potential") in the AHRQ report are collected in a list called 'List 1' (products with a potential financial risk), and those that did not receive a risk classification are listed in the so-called 'List 2' (products without potential financial risk). Products on List 2 receive no further scrutiny.

Secondly, products on List 1 are filtered by removing all products that have already accessed the Dutch health care market[qq]. For the remaining products on List 1 a database is constructed in Microsoft Excel and information is collected on relevant parameters. The parameters are divided in 4 subgroups (Table 25):

- Product and disease characteristics: information is mainly obtained from the AHRQ report, sometimes complemented with information from scientific journals
- Risk identification: these are mostly country-specific parameters and the information is collected through interaction with medical societies.
- Assessment and market access: authorization dates estimated by Horizon Staff; during every scanning round, the timeline for all products on list 1 is updated, as it can change (for example due to a fast track or stop clock period at the EMA)
- Other: information from other countries or other comments are included

[nn] Interview with Evelien Klein-Lankhorst, Dutch Horizon Scanning System, (2016)

[oo] http://www.fiercepharma.com

[pp] https://scrip.pharmamedtechbi.com

[qq] As products remain on the AHRQ list for a period of 2 years, many products on the list have already been launched on the market and are therefore not a candidate for negotiations anymore.

Table 25 – Overview of parameters collected in the Dutch horizon scanning database

Product and disease characteristics	Risk identification	Assessment and market access	Other
• Source and date of scan • Product and compound name • Therapeutic area • Clinical indication • Producer • Type/ class of product (i.e. biologic, antibody, small molecule) • Mode of administration • Mono or combination therapy • Landscape (future indications, ongoing trials, competitor products) • Reported outcomes (effectiveness) • Comparators • Approved indication • Estimated costs • Special FDA status • Medical need • Expert opinion on product potential • AHRQ impact category	• Involved professional association • Treatment costs • Competitor products (current and future) • Epidemiology (prevalence, incidence, patient volume) • Patient volume (expected, expert assessment, off-label risk, future expansion)	• FDA status • Data of FDA approval • EMA status • Date of (expected) EMA approval • National Health Care Institute status • Expected National Health Care Institute advice • National Health Care Institute notification • In- or out-of-hospital use	• Information from other countries

The third filtration step involves a classification of the financial risk of all products on list 1 on three cost criteria, namely:

- Annual macro costs: the estimated total annual costs for the product in the Netherlands. This is based on available data pertaining to patient volumes and the estimated price of the product.
- Cost per patient per year: this is based on available data on the estimated duration of the treatment (i.e. number of dosages needed) and the available product prices in the Netherlands and abroad.
- Volume risk: the risk that the estimated volume of patients will increase, for example due to expansion of the indication, or potential off-label use.

For each of the criteria, threshold values are defined for the financial risk (Table 26). Accordingly, each product gets a green-, amber- or red-light notification on each of the criteria. Products that score a green light on all three criteria are considered not to pose a financial risk, and are also put on list 2. Products that score at least one amber light on one of the criteria are

deemed potentially risky, and consequently form the list of products that are potential candidates for a financial arrangement (list 1).

Table 26 – Thresholds on financial risk criteria for filtration and prioritization

	Annual macro costs	Cost per patient per year	Volume risk (multiplication)
'Green light' (low risk)	€ 0 - € 10 million	€ 0 – € 15 000	1 (volume stays the same)
'Amber light' (intermediate risk)	€ 10 - € 40 million	€ 15 000 – € 50 000	1 – 2 (no change to doubling)
'Red light' (high risk)	> € 40 million	> € 50 000	>2 (at least doubles)

Sources for country-specific information

Information on country-specific parameters such as prevalence, incidence and patient volume (and potential volume risk for example through expansion of indications) is obtained through regular meetings with representatives of medical societies. With haematologists and oncologists, these meetings are held every three to four months, as a major part of the relevant new pharmaceuticals are developed in these medical specialities. Meetings with other medical societies are organized on an *ad-hoc* basis. Price information is difficult to obtain. Sometimes the AHRQ report includes (US) prices. Otherwise, list prices or insurance data from countries where the product is already on the market can be used when available (for example through the Euripid database[rr]). Alternatively the price of a new product is estimated based on the price of similar products already on the market (sometimes referred to as "reference" product). If, on rare occasions, this information is obtained from the producer, it is confidential and is therefore not included in the scan list.

The Dutch system is planning to start with seven working groups in seven disease areas that will meet 3 to 4 times a year. These working groups include specialists, patients' associations, health insurers, hospitals and hospital pharmacists (three times a year) additional information can be obtained. However, the primary goal of these meetings is to disseminate and discuss the information gathered by the HSS and to obtain timely feedback from the stakeholders.

Lastly, the HSS team has recently started to look into the possibility of involving investors in the HSS process as they might have developed alternative methodologies or have additional expertise to estimate prices, volumes, and indications and potential impact of the drug.

Outcome of the filtration process

During the latest scanning round published in December 2015, a total of 52 products were included on the scan lists.[40] List 1 (products with a potential financial risk), contained 14 inpatient and 14 outpatient pharmaceuticals. List 2 (products without potential financial risk) contained 24 products of which 10 inpatient and 14 outpatient pharmaceuticals. These data show that about 54% of the identified products are deemed to pose a financial risk.

Prioritization

Although all products on list 1 pose a potential financial risk for the Dutch healthcare system, it is not possible to select all products for a FA.[ss] Therefore, prioritization needs to be done. The scoring of products on the financial risk criteria (Table 26) serves as a prioritization system. Products scoring in the high-risk category (i.e. red light) are considered a priority for a

[rr] Euripid is an European web-based database for medicine prices supported by the EU which provides up-to-date information to the relevant authorities on the prices of and subsidies given to medicines.

[ss] Interview with Evelien Klein-Lankhorst, Dutch Horizon Scanning System (2016)

FA. However, not all red-light pharmaceuticals might be eligible for a FA, as other, less explicit criteria are taken into consideration such as the existence of well-developing decentralized price negotiations, expected cost-effectiveness, the advice given by the National Health Care Institute, the market share of the product and the perceived success rate of a FA. FA eligibility of products is discussed in monthly meetings between the HSS team and the Dutch National Health Care Institute. The HSS staff makes the final recommendation to the minister about a FA. The recommended FA status and justification are noted in the database.

Output of the HSS

All information gathered on the identified products is collected in a Microsoft Excel database, which is used internally by the Ministry of Health.

Peer review

There is no formal peer reviewing process. Rather, participating stakeholders are invited to comment on the (missing) information and risk assessment of products in the HSS during the meetings with medical societies, the meetings with the National Health Care Institute, and other meetings with the insurers, patients' associations, hospitals and hospital pharmacists.

Dissemination of output to users

The access to the HSS output is very limited. Until recently, the output of the HSS was only shared with the Ministry of Health and with the National Health Care Institute. However, interest from other parties in the field has increased. For external stakeholders, a summary of the scan lists will be published twice annually. These published lists include information on the name of the product (compound and brand name), therapeutic area, indication(s), expected EMA approval date, estimated patient volume, and estimated treatment cost per patient per year.[40tt] There is an intention to create a publically available website for the dissemination of the scan lists in the future. However, neither the results of the prioritization, nor the database itself is shared outside the HSS.

In addition, the information gathered by the HSS is presented in regular meetings with the National Health Care Institute (monthly), and medical societies, patients' associations, hospitals, and health insurers. These meetings are always a two-way exchange of information; the HSS team disseminates information on what they see as high risk products to the stakeholders, who can counter or amend this information with their own views and information.

Updating information

The updating of information on products included in list 1 of the HSS database is conducted continuously when information or evidence becomes available. Information on expanding indications is also screened through *clinicaltrials.gov*, when a new trial is registered for a different target population. Once a decision is made on whether a product is selected for a FA or not, there is no systematic updating of information, because the purpose of the HSS has then been fulfilled.

Evaluation of HSS methods and system

In 2015, an evaluation of the FA pilot process was conducted.[39] The goal of this evaluation was to determine how stakeholders viewed the FA process. The report provided four areas where improvements in the HSS could be realized. First, different independent scanning efforts, both within the Netherlands and internationally, should be integrated at the European level in order to improve the effectiveness and efficiency of the HSS. Second, stakeholders indicated that they would like to have more transparency into the results of the HSS. Thirdly, the team involved in making the inventory of new products should be made separate from the team preparing estimations

tt The scan lists are sent to: Bond van Generieke Geneesmiddelenindustrie Nederland (Bogin), College ter Beoordeling van Geneesmiddelen (CBG), Federatie Medisch Specialisten (FMS), Inspectie voor de Gezondheidszorg (IGZ), KNMP, KWF Kankerbestrijding, Nederlandse Federatie van Universitair Medische Centra (NFU), Nederlandse Vereniging van Ziekenhuisapothekers (NVZa), Nederlandse Vereniging van Ziekenhuizen (NVZ), Nederlandse Zorgautoriteit (NZa), Nefarma, Patiëntenfederatie NPCF, Verpleegkundigen en Verzorgenden Nederland (V&VN), Zelfstandige Klinieken Nederland (ZKN), Zorginstituut Nederland, Zorgverzekeraars Nederland (ZN)

on cost and volume risk. Finally, clear guidelines about contact with companies should be developed (cfr. EuroScan guidelines). No formal evaluation or assessment of the performance of the HSS was performed nor planned.

Resource requirements

The required activities for operation of the Dutch HSS are:

- A monthly meeting lasting 3 hours with 5 participants
- A monthly meeting with the National Health Care Institute with 5-7 people for 3 hours
- When the scan list is updated (twice a year), 3 staff members work 50% for 3 months
- Updating the database and project management requires one day per week by one person.
- Communicating with specialists and attending working groups: 21 – 28 meetings per year with a groups of approximately 12 people, each meeting one person from the HSS present.

Hence, the current HSS use about 1 FTE, but for obtaining a decently filled and maintained database at least 2 FTE are estimated to be needed for its current purpose.

Follow up after the HSS

After the HSS process, a technical expert meeting (involving four to five clinical experts (specialists) in the specific field) is organized for products that are selected through the HSS for a FA. During such a meeting, more detailed estimations of the potential patient population(s) and possible substitution effects for other pharmaceuticals are discussed. The information obtained during these meetings is used by both the National Health Care Institute and the HSS staff to further assess the drug and estimate more precisely the budget impact. This information is used by the National Health Care Institute for the assessment and by the HSS staff for preparing possible negotiations. Before negotiations start, the National Health Care Institute appraises the drug and advices the minister on reimbursement of the drug and inclusion in the basic benefits package. If this advice is positive and includes the advice to negotiate, the minister can decide on starting the negotiations. The HSS staff separately from the National Health Care Institute will advise the minister on this matter.

Future of the Dutch HSS

The Ministry of Health acknowledges the benefit of providing the HSS information to other stakeholders (i.e. medical societies, healthcare providers, pharmacies, and insurers) in order to prepare for upcoming new pharmaceuticals. To that end, the Ministry announced the initiation of the development of a new process of horizon scanning, named "Horizonscan+".[40] The objective of "Horizonscan+" is somewhat broader than that of the current HSS. It aims to timely alert and inform all stakeholders about new pharmaceuticals entering the market and about the possible effects of these products. As such, it can enable parties to have an early dialogue about potential future (clinical, budgetary or organizational) problems related to products on the HS. This will help ensure stakeholders can better organize procurement, make agreements on the use of new pharmaceuticals, prepare the care organization and financing of these products in a timely manner, and improve the bargaining power of hospitals and insurers. At the time of writing, little information is available about the plans for the organization of "Horizonscan+", as the concept is being developed.

The Ministry of Health was planning to publish a policy letter in the summer of 2016; however at the time of writing there was no publication available. It is likely that the Ministry of Health will not be the central organizer of the system. A suggested design is to set up seven disease-area working groups that will perform the HSS processes. These working groups will select the products, appropriate for their disease area, from a provided database. The database could be the AHRQ database on which the AHRQ High Impact Report is based, possibly adapted to include new parameters that are relevant to the Dutch system. The working groups would complement the database with country-specific data (e.g. estimation or modelling data on patient populations, substitution, budget impact, cost per patient, volume risk). Filtration and prioritization will then be performed in regular meetings of these working groups. The National Health Care Institute will coordinate

these meetings with a specialist as chair and a hospital pharmacist as secretary. As such, the Ministry of Health will only be involved as an observer and customer of the output of those meetings.

The Dutch system is a pragmatic, "light" HSS:

- **Its goal is to identify products with a potential high budgetary impact suitable for FA.**
- **It requires limited resources as it uses the output of other HSS and produces no formal assessment report.**

Appendix 1.2. Association of Local Authorities and Regions (SKL) – Sweden

History and organization

Horizon scanning of new drugs started in Sweden in 2007 in the County Council of Stockholm, by adapting the methodology of the UK-based Horizon Scanning Research & Intelligence Centre (NIHR HSRIC).[uu] The four big counties in Sweden (Fyrlänsgruppen: Stockholm County Council, Region Skåne, Region Västra Götaland, and Östergötland County Council) began working together for horizon scanning in 2009.[41] The Swedish Association of Local Authorities and Regions (SKL) created the Swedish Council for Novel Therapies (NT Council) in 2010 and then began collaborating on horizon scanning with the four counties. In 2015, the Horizon Scanning System (HSS) of SKL was incorporated in a bigger framework called "the Collaboration Model" (*Samverkansmodellen*) in order to improve the horizon scanning, introduction and monitoring of new drugs in Sweden. All counties in Sweden fund the framework. The model consists of a "managed introduction" framework, of which horizon scanning is the first step. Products selected through the horizon scanning system (HSS) can enter the next steps of the process: development of an introduction and follow-up protocol, health economic assessment, reconciliation step, price negotiation, recommendations, follow-up and monitoring (Figure 10). Not all steps are always recommended and the output of the HSS is used to decide which steps need to be addressed for a prioritized pharmaceutical.

[uu] Interview with Anna Bergkvist from the Swedish Association of Local Authorities and Regions, Region Skåne (May 3rd 2016)

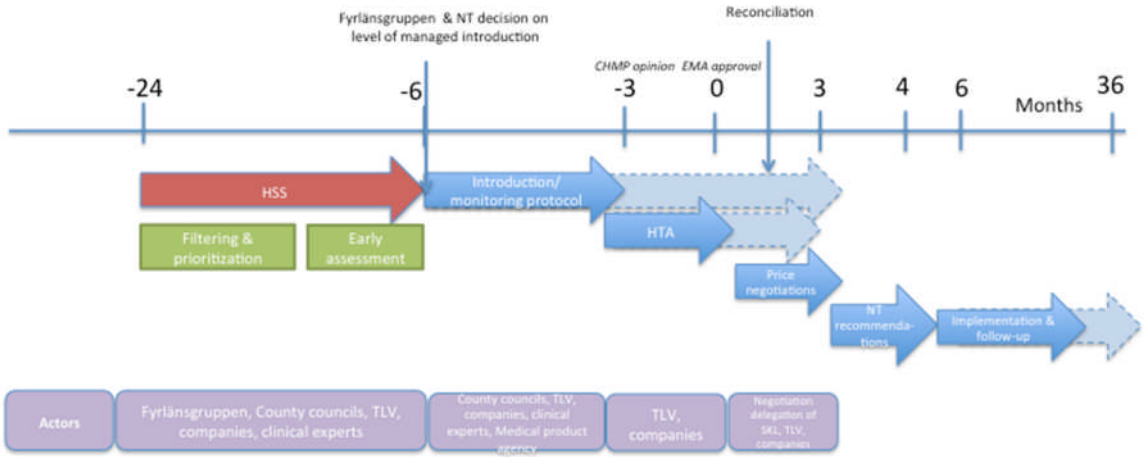
The HSS organization (Fyrlänsgruppen or HSS working group) consists of five persons (one from each county and a coordinating person), who all work part-time on the horizon scanning. The tasks (coordination, identification, company contact, report writing) are divided and assigned to different team members. Regular physical meetings of all team members are scheduled on a quarterly basis in addition to teleconferences taking place twice a month.[vv]

Other Nordic countries are deliberating with Sweden for possible collaboration. Norway is already doing some horizon scanning activities, Denmark is about to start, and Iceland and Finland are not conducting any activities at all.

Purpose of the system

The purpose of the HSS system is to enable the county councils to take decisions regarding the introduction of new and expensive medical products (1) faster, (2) more coordinated and (3) based on objective criteria.[41] Final output of the HSS is a detailed report, summarising the available evidence and/ or estimation about a product delivered to the NT Council approximately six months before expected approval.[16] It includes a recommendation to the counties about an appropriate level of managed introduction for the specific pharmaceutical.[vv] The horizon scanning focuses on both outpatient and in-patient drugs, but only inpatient drugs can be directly selected to enter the Collaboration Model. Outpatient drugs may enter the Collaboration Model when the outpatient reimbursement procedure at the Swedish Health Technology Assessment (HTA) agency (Dental and Pharmaceutical Benefits Agency (TLV)) was unsuccessful. For both kind of drugs, the NT Council can decide to perform price negotiations with the pharmaceutical company.

Figure 10 – Overview of the actors and steps in the Collaboration Model



[vv] Interview with Anna Bergkvist from the Swedish Association of Local Authorities and Regions, Region Skåne (May 3rd 2016)

Adapted from report "National Process For The Orderly Implementation: Final Report Of National Drug Strategy, Subproject 6.1." [42]

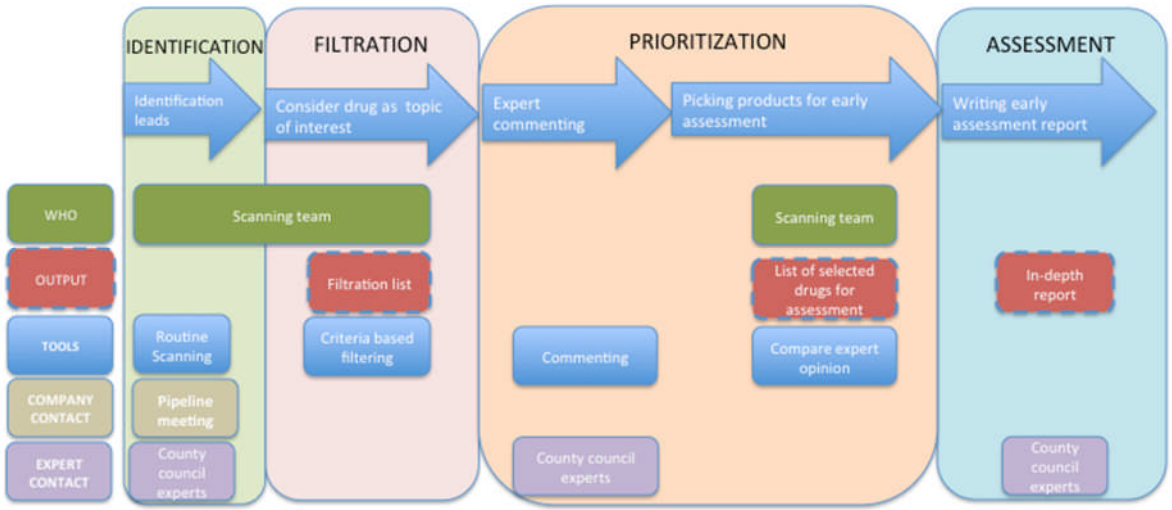
Process

A schematic overview of the Swedish HSS is presented in Figure 11.

Identification and monitoring

Drugs are identified at least 1-2 years before market authorization, preferably when the drug still is in phase II or III of development. Information on new drugs is retrieved from several organizations and authorities (e.g. NIHR HSRIC and the European Medicines Agency (EMA)), publications (e.g. PharmaOnline, and First World), clinical experts, and the pharmaceutical industry (through pipeline hearings and company websites).[8] The various information sources are divided among the workgroup participants and are scanned on a daily basis. Information gathered during the identification is stored in an Access database.

Figure 11 – Overview of the Swedish HSS



Since 2009, the HSS workgroup organizes pipeline meetings with the largest pharmaceutical companies in the Swedish market. Products of the upcoming 2 years are discussed in 45-minutes-appointments. The companies themselves highlight the most important products.

The following data are gathered once a new drug is identified: Anatomical Therapeutic Chemical (ATC)-code, substance name, company, indication, and mechanism of action, development status within the EU, estimated time of approval and estimated time of launch.[ww] Drugs are categorized in different categories, e.g. new substance, new indication, new combination, or new formula.

Filtration

Drugs with a possible market authorization within the next 1.5 years that meet at least one of the criteria in Table 27 are considered a drug of interest. Filtration is carried out by a member of the HSS staff.

[ww] Interview with Anna Bergkvist from the Swedish Association of Local Authorities and Regions, Region Skåne (May 3rd 2016)

Table 27 − Criteria to be considered as a topic of interest (minimum of 1)

Criteria description	
Large patient population	Potential impact on treatment guidelines/recommendations
Significant morbidity associated with the condition	Potential safety issues
Potential for clinical benefits	Potentially high media/patient interest
Innovative way to treat the disease	Too fast or too slow introduction can be expected after approval
Potential cost implications	Potentially legally, ethically or politically interesting
Can lead to reorganization of health care system	

Other criteria that are taken into account are:[16]

- Belonging to an evolving class of drugs
- Relevance to Swedish conditions
- Development in late Phase II or Phase III, or already submitted to the regulatory authorities for approval.

Drugs that are filtered or drugs for which filtration criteria are uncertain, are discussed with the clinical experts in the county councils.

Prioritization

Clinical experts in the four major countries are approached to share their opinion about the identified drug. The working group compares expert opinions on the drugs and then a decision is made whether an early assessment report is written or not. The clinical experts belong to the counties´ existing expert networks (so-called 'therapy-groups' (groups of oncologists, haematologists, etc.)). The filtration and prioritization process is performed every 3 months.

Assessment

It takes about 3-6 months to complete an early assessment report (in-depth report). These reports are written by the clinical pharmacologists and/or county experts, as they have the highest expertise on the subject. The opinions of the other experts are included as well. The report also includes a short assessment of the drug. Topics included in the report are displayed below in Table 28.[8, 43, 44]

Table 28 − Topics discussed in the detailed report

Topics	
Description of the drug	Other completed and ongoing studies with current substance
Estimated time to approval	Other drugs in the pipeline for the same indication
Clinical need and patient population	Estimated cost of therapy (annual treatment costs per patient)
Who will prescribe the drug	Clinical, service and financial impact
Current treatment alternatives	Possibility to monitor utilization post-launch
Clinical effect	Other markets
Clinical observations/safety	Possible sales arguments

Output

Quarterly report

After every filtration and prioritization round, the results are summarized in a newsletter, which is structured according to the drug groups. The early assessment reports, as well as the newsletters, are communicated with the SKL and other counties on a continuous basis and published online (http://www.janusinfo.se/Nationellt-inforande-av-nya-lakemedel/Nationellt-inforande-av-nya-lakemedel/Horizon-scanning/).[16]

Early assessment reports

About 20 early assessment reports are written on an annual basis.[xx] Based on the output of the early assessment report, the NT Council of SKL decides which level of "managed introduction" is recommended. Three levels of managed introduction exist:[16]

- Highest level of national introduction: All steps in the Collaboration Model are performed. A protocol for national introduction and follow-up is produced by Fyrlänsgruppen in collaboration with clinical experts. The protocol includes the recommendation made by the NT Council based on the early assessment, the health economic information (by TLV), the drug's place in therapy, a plan for follow-up, etc. and is delivered close to market entry.[xx] Companies can be involved in each step of the collaboration protocol.
- National managed introduction including health economic evaluation, recommendation on use and sometimes follow-up. The NT Group will issue a recommendation on a restricted use of the drug.[xx]
- No national introduction: The drug can be implemented at the local level, according to each county council's or region's ordinary routines.

For all three levels, joint price negotiations can be deemed appropriate.[xx] Although the NT Council makes mere recommendations, the counties usually follow them.

Expert contact

Expert input is used in the prioritization and the assessment phase. The experts are selected from the SKL network and are often part of so-called counties' 'therapy-groups' (groups of oncologist, haematologists etc.), which

[xx] Interview with Anna Bergkvist from the Swedish Association of Local Authorities and Regions, Region Skåne (May 3rd 2016)

are involved in strategic work regarding drugs.[yy] The experts take part in the writing of the reports, as well as in the development of recommendations for managed introduction.

Key points of the Swedish HSS

- **Selection for managed introduction, including -but not limited to- price negotiation, is the goal of the Swedish HSS.**
- **There is a intense collaboration between counties.**
- **Drugs are categorized in different categories, e.g. new substance, new indication, new combination, or new formula.**
- **SKL uses pipeline meetings with companies to identify products.**
- **Clinical experts are involved in all HSS activities, including the assessment.**

[yy] Interview with Anna Bergkvist from the Swedish Association of Local Authorities and Regions, Region Skåne (May 3rd 2016)

Appendix 1.3. Agency for Healthcare Research and Quality (AHRQ) – United States

History and organization

The AHRQ´s HSS started in December 2010,[13] funded under the American Recovery and Reinvestment Act of 2009 of which about 9.5 million dollar was used to set up HSS activities.[45] Funding of the Patient-Centered Outcomes Research Institute (PCORI) Trust is used to continue operating and refining the Horizon Scanning System.[31] AHRQ had set a 5-year contract with the Emerging Care Research Institute (ECRI) to execute the horizon scanning, which recently ended. The AHRQ is currently considering their next steps regarding a continuation of the project. The November 2015 Status Update report is the last published output from this HSS and it is currently unknown whether new scans will be performed. Medical librarians and a team of horizon scanning analysts staff the HSS centre.

Purpose of the system

The purpose of the AHRQ´s HSS is to conduct horizon scanning of emerging health care technologies and innovations to better inform investments in patient-centred outcomes research at AHRQ through the Effective Health Care Program.[13] An inventory is created with the technologies and innovations with the highest potential for impact on (1) clinical care, (2) the health care system, (3) patient outcomes, (4) costs, or (5) a paradigm shift.[13] The aim of the HSS is to identify emerging products that are within 3 years of potential diffusion into clinical practice.[13] The HSS focuses on the identification of pharmaceuticals and biotechnological products, but other health technologies and interventions are identified as well. Currently, 83% of all topics are pharmaceuticals or biotechnological products. Information is made publicly available. Beside the Effective Health Care Program from AHRQ, the output of the HSS is used by hospitals and health care facilities, as well as by third-party payers (e.g. insurers and government).

Process

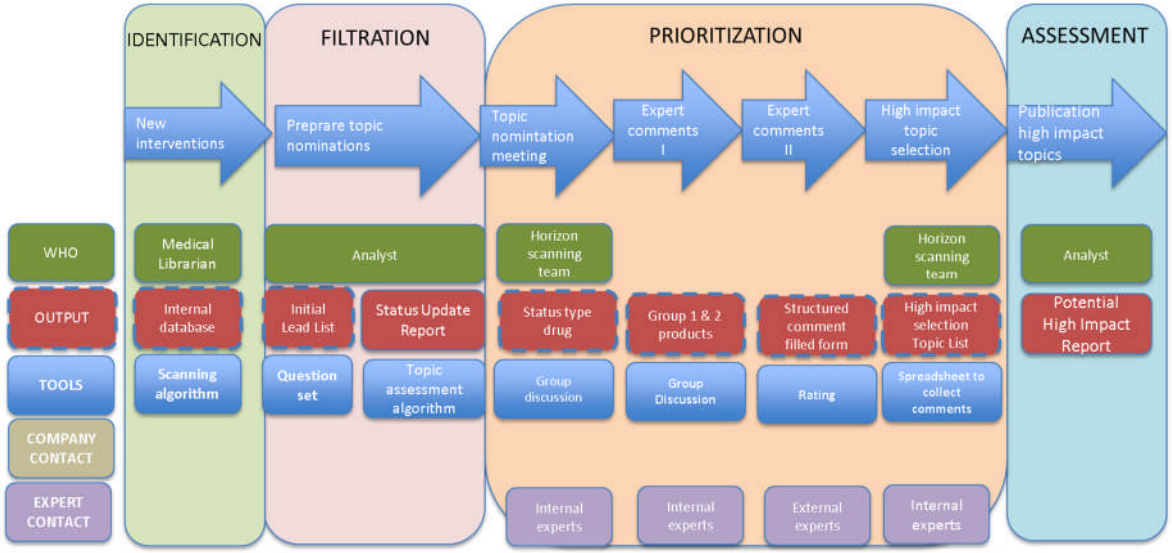
A schematic overview of the US HSS is presented in Figure 12.

Identification and monitoring

A total of 15 priority areas are defined by AHRQ, including one cross cutting area: 1. Arthritis and non-traumatic joint disease; 2. Cancer; 3. Cardiovascular disease; 4. Dementia; 5. Depression and other mental health disorders; 6. Developmental delays, attention-deficit hyperactivity disorder, and autism; 7. Diabetes mellitus; 8. Functional limitations and disability; 9. Infectious Disease; 10. Obesity; 11. Peptic ulcer disease and dyspepsia; 12. Pregnancy, including preterm birth; 13. Pulmonary disease/asthma; 14. Substance abuse, 15. Cross cutting area. Only drugs that fit in these areas are identified.

A detailed list of sources scanned for the identification of biological, drugs and off-label use can be found in 0. Every source is assigned to a medical librarian, who scans the sources regularly as determined in a schedule without employing a search strategy. When possible, email alerts notify the team when a new issue or content is available.[13] Items of interest are tagged with the priority area name and possible subcategories. Items of interest are also referred to as *leads*.

Figure 12 − Overview of the US HSS



Filtration

Sets of questions have been developed for those who analyse the sources to determine if an identified product is representing an intervention which is novel, innovative, relevant, or addresses a potentially important unmet need. The evaluation of the AHRQ´s system showed that the assessment of the potential impact was reliable and useful.[31] The following set of questions is used:

- Is this a new molecular entity (drug), biological, or device being developed for potential diffusion into the U.S. health care system AND in late Phase (3 or 4) clinical development or in Phase 2 clinical development with orphan, breakthrough, or fast-track status designation by FDA?

  If so, select.

  (Rationale: New molecular entities may be a signal of a new class of interventions intended to address a potentially important unmet need. New devices subject to a premarket application pathway may signal a new device addressing a potentially important unmet need.) Consider the following when answering this question:

- Is it subject to approval under FDA's Investigational New Drug, Biologics Licensing, combination-product application, or Investigational Device Exemption Premarket Approval processes? If so, select.

- Is it a generic drug? If so, do not select, because these are the "me-too" of existing drugs.

- Is it subject to 510(k) clearance or De Novo pathway? If so, select only if it appears to represent some sort of relevant innovation to address a potentially important unmet need.

- Is this a late-phase human clinical trial of either an apparent novel intervention or a novel way to use an existing intervention, and is it capable of diffusing into the U.S. healthcare system within 3 years? If so, select. (Note: Animal and in vitro studies are excluded.) (Rationale: Clinical trials may signal a new research question, or unmet need, being studied. Clinical trials also examine interventions that are not subject to regulatory pathways, such as surgical procedures.) The additional questions below help to determine if this is the case and also inform the stage of development and expected time to adoption.

- Has a trial been initiated or terminated?

- Are late-phase results being reported?

- Does this appear to be a different/off-label use of an available drug or biological? If so, select. (Rationale: Off-label use may signal an attempt by the clinical community to address an unmet need that is not being pursued by developers or innovators.)

- Is this a professional medical society meeting announcement? If so, should we monitor the meeting annually for new developments? (Rationale: New research about interventions in development to address unmet needs is typically presented at professional society meetings. Meeting abstracts and poster presentations presented in these venues may not appear in the peer-reviewed literature and can be a rich source of leads.)

- Is this a product launch? (Rationale: Such announcements can signal diffusion of an intervention intended to address a potentially important unmet need. Select if it appears to address a potentially important unmet need.) Do not select if the unmet need is a small, incremental development (e.g. next-generation).

- Is this a regulatory announcement? This includes manufacturers' announcements of intentions to file for regulatory approval/clearance as well as notices from regulatory agencies and advisory panels. (Rationale: These announcements may identify novel or relevant interventions that potentially address an unmet need.) Select if it appears to address an unmet need.

- Is this a different delivery mode for an existing drug or device? (Rationale: Changes in formulation (e.g., from injection administered by a clinician to an oral pill) or dosing regimens (e.g., from daily dosing to once-a-month dosing) are sometimes intended to address potentially important unmet needs, such as a need to improve patient adherence or access to a therapy.) If so, select.

- Is this being called an innovation AND is it in late phase development? If a developer refers to the intervention as an innovation, scanners may select it for further follow-up by an analyst to determine if it is truly innovative and addresses a potentially important unmet need.
- Is this an award for an innovative product, procedure, or process?

The product is uploaded to the *Initial Leads Lists* when the lead is still of interest after answering the set of questions.[13] Items on the *Initial Leads Lists* are assigned to the horizon scanning analyst who classifies the leads to a topic class.[13] The steps listed in Table 29 are used to create a list of *topics* (products of interests).

Table 29 – Steps for assessing and sorting leads to identify possible topics

Step	Description
1	Sort lead by AHRQ Priority Area, Subcategory, and Topic Class
2	Sort lead into "Topics Classes" (e.g. technology, service, care innovation, new use of existing intervention)
3	Tag lead with one or more identifiers (e.g. product name, manufacturer name, or program name) to enable grouping and sorting of related leads
4	Provide a brief description for each lead in a "Notes" field of the Initial Leads List (e.g. expected or potential impacts to the health care system, reasons for inclusion/exclusion, technology mechanism of action, competing technologies, etc.)
5	Choose status of the lead: • New – The lead was recently uploaded and has not yet been reviewed by an analyst. • Reviewed – The lead has been reviewed by an analyst, but no formal action has been taken at this point. • Linked – The lead has been reviewed by an analyst and linked to one or more topics. • Discarded – The analyst has determined that the lead is irrelevant to the HSS for any of several reasons (e.g. the lead is out-of-date, pertains to animals, is a duplicate, or does not meet criteria upon their further evaluation). The analyst provides a brief rationale for discarding the lead. • Archived – The lead had previously been saved or assigned, but is no longer relevant for any of several reasons. The analyst provides a brief rationale for archiving the lead (e.g., the lead is out-of-date, superseded by another lead).
6	Attach various tags to further classify the lead (e.g. lead source, manufacturer name(s), product/intervention name(s), clinical condition, mechanism of action)

Topics are then described according to the criteria in Table 30.

Table 30 – Description outline for potential topics

Description
Topic name/title
AHRQ priority area
Topic class
Potential/proposed patient population
Intervention description
Phase of development and confirmation that it is being developed for potential diffusion into the health care system
Potential comparators
Potential outcomes

Table 31 – Criteria for a topic entering into the prioritization phase

Step	Description of criteria
1	Is the intervention addressing an unmet need?
2	Is the intervention in late-phase development for the health care system? Or, can the intervention be adopted or diffused without going through a regulatory process (e.g. off-label use)?
3	Is the intervention novel, relevant, or innovative for addressing the need?
4	Would adoption or implementation of this intervention potentially shift/change/disrupt current care?

Prioritization

In deciding whether to nominate a topic for prioritization, analysts rely on a set of criteria and questions (Table 31) as well as their store of knowledge on a given type of intervention. The analysts present their case in a topic nomination meeting. The topic nomination meeting is attended by the librarians, the ECRI horizon scanning analysts, the content team leader, the project manager, and other invited staff and clinical experts. In the meeting, the analysts present the "proposed topics" from their assigned priority areas to the team and invited experts, followed by a discussion. The aspects discussed during these meetings are listed below:[30]

- Brief description of why the topic seems important in general
- Brief description of the unmet need the product addresses
- Description of how the product proposes to meet this unmet need and whether it seems novel or innovative
- Stage of development and confirmation of development for the US market
- Potential outcomes and areas of impact
- Potential comparators (existing and in development)

Meetings are scheduled once a month or more often if needed.[13] The decision to prioritize a product is based on a majority vote. If a question cannot be resolved during the meeting the product is marked as 'follow-up.'

In that case, results of additional research are communicated later to the team electronically, which votes again on the prioritization of the product.[13]

Two status types are used for prioritized drugs. 'Track only' is used in late-phase trials without published data and will result in continual identification of leads and material through daily scanning. The 'advance to target' status will result in in-depth searches by the librarians, which the analysts use to develop more detailed profiles.[13] Drugs need some preliminary late-phase efficacy and safety data to receive the 'advance to target' status.[13] The prioritized drugs are bundled together in the Status Update Report. The report is prepared five times a year. It provides a snapshot of the system and is publically available on the Effective Health Care website (https://effectivehealthcare.ahrq.gov/).

New 'advance to target' topics are added to the Horizon Scanning Production Queue. The topic is assigned to the analyst covering that priority area. The analyst reviews and selects the most relevant material to complete a template for the in-depth profile (Table 32).[30]

Table 32 – Template for in-depth profile of a new topic

Topics
Topic title
Potential importance of this topic
Disease/condition description
Intervention name and description
Related names for intervention
Potential competing and complementary technologies/services for the disease/condition
Potential care setting(s)
Ongoing trials and evidence development
Manufacturers or developers, and development status
Anticipated costs per patient
Potential clinical provider and training/credentialing issues
Potential staffing and infrastructure implications
Potential patient and clinical staff safety issues
Coverage, coding, and payment status
Indexing/linkages
References

Subsequently, the potential for impact of the topic is gathered through an expert comment process.

Experts are selected from a database of 150 external and internal clinical experts, based on their expertise. Experts are asked to score the potential impact of a topic by completing a "Horizon Scanning Structured Comment Form",[2] which consists of questionnaire covering 8 parameters.

Answers can be on a Likert-scale. A 4-point rating system is assigned to the Likert scale and points are added in order to get a final score for a topic per expert (Table 33). A written rationale by the expert for the scoring is required for each parameter.

Table 33 – Parameters and scoring points assessed in the Horizon Scanning Structured Comment Form

Parameters	1	2	3	4
Potential importance of the unmet need it intends to address	Not important	Small importance	Moderate importance	Very important
Potential to improve patient health	None	Small	Moderate	Large
Potential to affect health disparities	None	Small	Moderate	Large
Potential to disrupt the healthcare delivery system	No disruption	Small disruption	Moderate disruption	Large disruption
Potential for acceptance/adoption by patients	No acceptance	Low acceptance	Moderate Acceptance	Wide Acceptance
Potential for acceptance/adoption by clinicians	No acceptance	Low acceptance	Moderate Acceptance	Wide Acceptance
Potential impact on healthcare costs	None	Small Impact	Moderate Impact	Large Impact
Overall potential to fulfil the unmet need	None	Small	Moderate	Large

The expert comment process involves two phases:

- *Internal Expert Comment and Triage*: performed by 4-5 ECRI Institute experts, who place the topic in one of two groups: Group 1 consists of topics that, based on comments and ratings, have a potential for high-impact whereas Group 2 consists of topics that need further discussion. When there is consensus that the topic belongs to Group 1, it is sent out for external review. When the topic is classified in Group 2, it is placed in the 'passive' or the 'archive' track. 'Passive' track topics are still monitored, in contrary to 'archive' track topics.
- *External Expert Comment*: performed by 2-3 external experts, from either the expert database or newly solicited, selected for this phase. Experts are asked to declare any intellectual or financial conflict of interest in a topic.

Topics are eligible for consideration as "Potential High-impact Interventions" when 5 experts (including 1 external) have rated the product.[13] The expert comment and rating process gives insight into which interventions have the potential for a high-impact on health care utilization, patient outcomes, costs, disparities and access, infrastructure, and systems of care delivery.[13] For every eligible topic, ECRI calculates the mean and median expert score (Table 33). Comments can overrule values, which are only used as a preliminary signal of potential impact.[13] The designation as potential high-

impact is relative to the range of other interventions assessed within that priority area.[2] This approach prevents the focus being on only the one or two priority areas with the highest potential impact products.

The Horizon Scanning team and internal experts meet 6 weeks before the report is published to make a decision on the high-impact rating (no high-impact potential; lower end of the high-impact potential range, moderate high-impact potential and high-impact potential). Analysts make recommendations based on the information provided (literature and expert data) and the team uses a majority vote to determine if the topic is included in the report.[13]

Box 5 – Topic monitoring and updating

Often new information becomes available during the filtration and prioritization phase. When this happens, the information is entered into the Initial Leads List, which is linked to the Identified Topics List. Topics that need a new in-depth target topic profile are added to the production queue. The queue is prioritized in four steps from the lowest (1) to the highest (4) priority:[30]

- New topics with low potential for high-impact;
- New topics with a higher impact;
- Previous, active, topics currently being updated that were previously included in a high-impact report and for which expert comments will be older than 12 months immediately prior to the next scheduled High-impact report;
- Previous, active, target topics being updated that were previously considered for, or included in, a high-impact report and for which new information exists that could change experts' perspectives.

If information complements existing topics, an assigned analyst reviews the information and determines if the topic needs an upgrade (e.g. move to in-depth target profile) or can be relegated (e.g. archive or track only). If no information is found in the previous 9 months for topics with an in-depth profile, an active update search is performed to determine if the topic still has a potential high-impact.[30]

Active topics are (re)sent for expert comment if new information that could affect the expert rating or opinion becomes available, or when original comments are older than 12 months. Whether or not to archive a topic is discussed in a biweekly team meeting. Archived topics are relevant for a long-term context because they allow future end-users to draw conclusions about previous developments and the likelihood of success for a similar technology.[30] When archived, items are published as such in the upcoming Status Update.

Assessment

The final output of the HSS is the Potential High-Impact report. The interventions that are expected to have the greatest potential for high-impact are bundled in this bi-annual 15-chapter report.[2] AHRQ requested a maximum of 20 topics identified in each of the 14 priority areas.[13] Finally, the topic is classified into one of the three tiers, indicating degrees of potential high-impact.

Output

Since the start of the HSS in 2010, a total of 22 500 leads were uploaded and reviewed. In 5 years, 2 400 topics have been identified and tracked (10.6% of the leads). The system has two major output reports: the Status Update report and the Potential High-impact report.[13, 30]

Status update report

The Status Update report is published five times a year.[13] The three sections of the report are the (1) currently tracked topics; (2) new topics added since issuing the prior report; and (3) topics archived since the prior report.[13] Every section contains a table for each priority area. The report can be found online (http://www.effectivehealthcare.ahrq.gov/).

Potential High-impact report

The Potential High-impact report is generated twice a year for each priority area. The report is a one to three page description of information gathered on the product. A table for each priority area shows what the estimated high-impact potential is. The report can be found online on http://www.effectivehealthcare.ahrq.gov/.

Box 6 – Rapid costs analysis pilot protocol[13]

To illustrate the known or potential costs of identified and tracked moderate or high-impact topics, the AHRQ requested some exploratory and simple costs analyses. This pilot was performed with the topics included in the December 2013 and June 2014 reports. The cost estimation was based on: the prevalence of the disease, projected adoption, costs of an intervention costs of a similar intervention, and costs of an alternative intervention (for sources see Table 34). The medical librarians used topic-specific searches for each intervention, while the analysts made a literature-based decision on which comparators were taken into account. For pharmaceuticals that are not on the market yet, price estimates were used based on similar products entering the market in the preceding 2-3 years. When information on the (expected) uptake was missing, the perspective was optimistic with a degree of scepticism. The effectiveness was not taken into account. The cost estimation was based on a 1-year horizon. In addition, downstream costs were not taken into account.

Table 34 – Sources searched for cost data in the Rapid Costs Analysis pilot

Source
Embase.com
Lexis-Nexis
Pharma and MedTech Business Intelligence (Grey Sheet, Pink Sheet, In Vivo, Start-up, MedTech Insight)
GoodRX
Health Technology Assessment Information Service ECRI Database (information on clinical, safety, cost, and reimbursement for health care interventions)
Cochrane (cost studies)
The Wall Street Journal
Healthcare Cost and Utilization Project (HCUP) from AHRQ
Google
NICE (if no US information found)

Key points of the US HSS

- **The US system has a transparant and systematic methodology**
- **The US methodology is resource-intensive.**
- **The US system has a wide scope selecting pharmaceuticals that address unmet medical needs, are innovative or can change health care delivery. Cost is not a main prioritization criterion.**
- **Dividing the drugs into priority areas makes it easier to compare the potential impact between products. This helps to enhance the inclusiveness of a variety of priority areas, instead of only 1 or 2 areas that have a large number of potential high-impact products.**
- **The US system uses explicit methods with help of questionnaires to guide identification, filtration and prioritization processes, which enhance transparency and reproducibility.**
- **The final output of the HSS (Potential High-impact report) consists of a short description of the technology. This allows the team to prepare it on short notice (6 weeks).**
- **The prioritization process uses a quantitative scoring system.**
- **Expert opinion is used in the prioritization process by a scoring system in combination with potential commenting.**
- **The US system is exploring rapid cost analysis.**

Appendix 1.4. Italian Horizon Scanning Project (IHSP) - Italy

History and organization

The Italian Horizon Scanning Project (IHSP) was set up in 2006 and is coordinated by the Pharmaceutical Department of the Local Health Unit in Veneto.[21] The organization consists of three different teams: the Scientific Committee (IHSP-SC), the Database Team (IHSP-DT) and the Evaluation Team (IHSP-ET).[15] All these teams have their own responsibility and tasks (Table 35).

Table 35 – Italian HSS working teams

Type of team member	Number of members
Scientific Committee	
Representative of the Veneto Pharmaceutical Department	3
Medicine evaluation expert	10
Database Team	
Pharmacist	2 (1 part time, 1 full time)
IT expert	1 (part time – 1 day a week)
Administrative employee	1 (part time)
Evaluation team	
Clinician	50
Pharmacist	2 (1 full time, 1 part-time - 2.5 days a week)
Administrative employee	1 (part time)

Purpose of the system

The IHSP aims to collect, organize, and evaluate information on emerging medicines and medical devices with medicated coating.[15] The IHSP aims to identify emerging drugs 36 months before expected EMA authorization, in order to assess the degree of innovation and the potential impact on the National Health Service Italy (INHS) and Regional Health Service (SSR) of the Veneto region in advance.[21] Information on the clinical and economic impact gained in the horizon scanning can be used to improve planning and optimize the most appropriate use of resources (local, regional and national), as well as the decision if new drugs should be reimbursed or if they should be limited in prescription (on national level).[22]

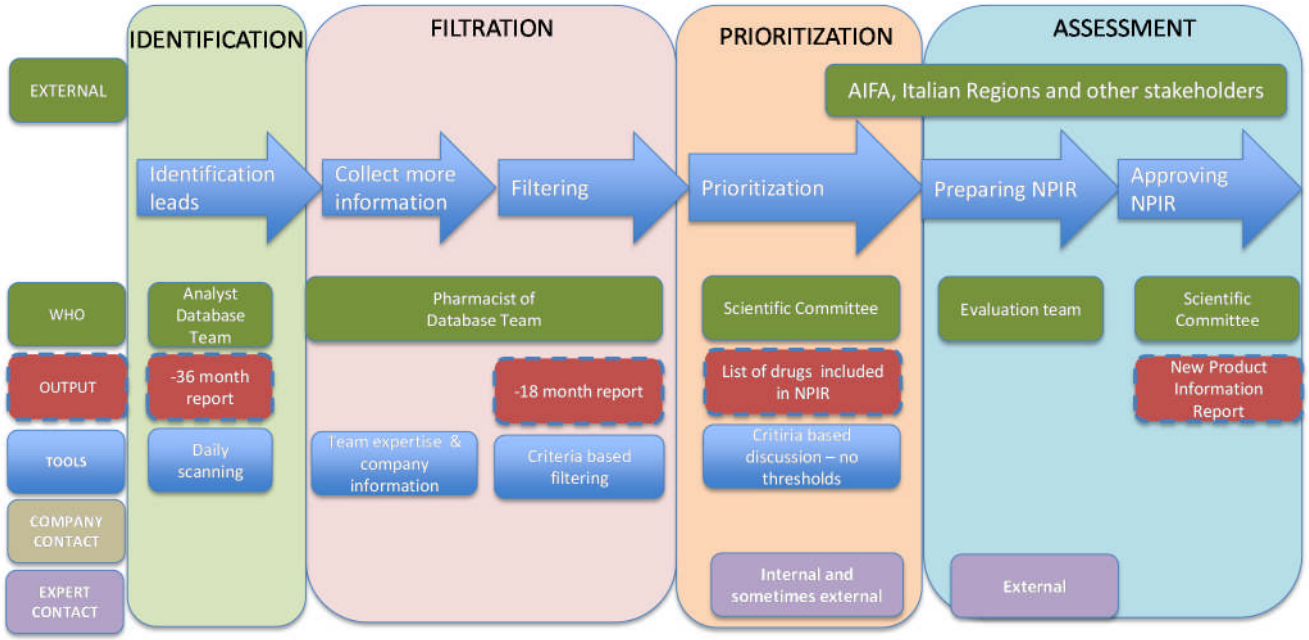
The main customers of the reports are: the Italian Medicines Agency (AIFA) (national authority responsible for drug regulation and reimbursement in Italy) and the Regional Health Services and Local Health Authority of Veneto. In Italy the decision whether or not a drug should be reimbursed is made at the national level, whereas the Regional Health Services are responsible for the local budget. They decide how to implement a new drug at local level in a structured way.[zz] Hence, the information from the HSS is also used to inform local decision makers.

Process

A schematic overview of the Italian HSS is presented in Figure 13.

[zz] Interview with Roberta Joppi, Mario Negri Laboratory of Drug Regulatory Policies, Italy, May 19th 2016

Figure 13 – Overview of the Italian HSS



Identification and monitoring

The IHSP-DT scans for new drugs in phase II/III of clinical development on a regular basis (daily/weekly), using the following types of sources:[12, 15, 22]

- Websites (e.g. pharmaceutical companies, financial analysis companies, international scientific societies, international regulatory authorities, health information websites).
- Medical-scientific literature
- Press releases and financial news of pharmaceutical companies
- Reports from the EuroScan network

The collected data are stored in a central database. The database is published online (http://horizon.cineca.it/), but its access is restricted to the IHSP teams or other selected customers.[15] Currently, one third of the drugs in the database are phase III products and two thirds of the drugs are cancer drugs.

The following data are collected when a new drug is identified:[21]

- Manufacturer or licensee company
- Trade name
- Specific therapeutic indication

- Stage of development
- Efficacy and safety from already completed trials.
- ATC group;
- route of administration;
- possible submission date of the Market Authorization Application;
- overview of all ongoing trials.

There is no contact with pharmaceutical companies in this, or in any other phase of the HSS. The IHSP-DT produces a list of identified drugs, which await commercialization within the next 36 months.[21] This list is known as the "36-month report".

Filtration[aaa]

The IHSP-DT's pharmacists perform a preliminary filtering based on (1) the anticipated market authorization date, (2) the available evidence and (3) the anticipated impact on the Italian health system. The impact on the system is not based on explicit criteria, but is a crude estimation by the pharmacist. In case of doubt, the product will be included. Emerging products are selected for the prioritisation process about 18 months before the estimated marketing authorisation date at EMA. Information on possible authorization dates is gathered through information released by the company, or financial documents which are produced quarterly. A report for each of the filtered drugs is produced and is available internally 18 months before the drugs will receive market authorization.[21] Each report includes the following items:

- drug/brand name /active substance; company
- ATC Group
- route of administration
- possible submission date of the Market Authorization Application
- proposed indication(s)
- summary of the available data on clinical efficacy and safety
- overview of all ongoing trials and completed studies not published
- possible price and economic impact (if available)
- alternative(s) already on the market
- possible competitors in development
- possible off-label use
- This report is also known as the "18-month report".

Prioritization

The IHSP-SC prioritizes the emerging drugs by assessing their clinical and economical value, along with their possible impact on the national / regional Health service according to the following pre-defined priority criteria:[15, 21, 22]

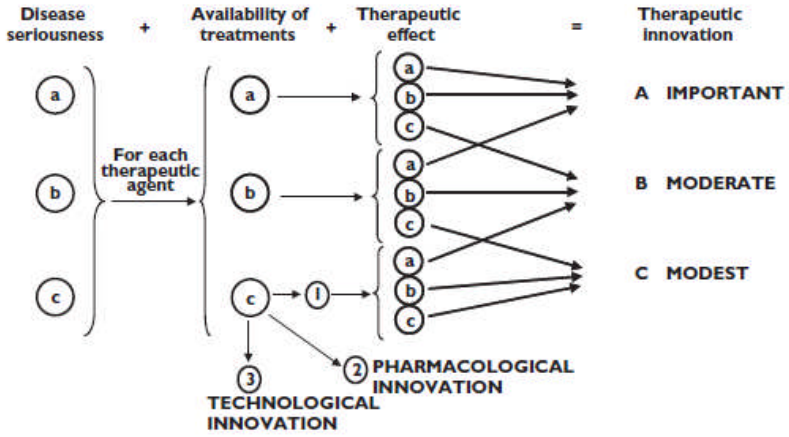
- Burden of disease
  - Epidemiology (rare – not rare)
  - Severity (severe – not severe)
  - Duration (acute – chronic)
  - Treatment (available – absent)
- Patient impact
  - Efficacy vs current treatments – e.g. mortality, morbidity, QoL (higher – equal or lower)
  - Safety vs current treatments (higher – equal or lower)
  - Compliance vs current treatments (higher – equal or lower)
- NHS pressures

[aaa] Interview with Roberta Joppi, Mario Negri Laboratory of Drug Regulatory Policies, Italy, May 19th 2016

- Social impact – e.g. media, patient associations, lobbies (yes – no)
- Service reorganization and/or staff training required (yes – no)
- Possible off-label use (yes - no)
- Economic impact on the NHS (high – low)
- Others
- Possible launch data (< 18 months - >18 months)
- Drug in development for other indication of interest (yes – no)
- Other drugs in development for the same indication (yes – no)

- possible marketing authorization date
- possible price and INHS sustainability
- possible innovation grade, therapeutic and economic impact. Innovation grade is determined based on a method described by Motola et al. [46, 47] (Figure 14).

Figure 14 – Algorithm to assign an innovation score



Disease seriousness: a = drugs for serious diseases; b =drugs for risk factors for serious diseases; c = drugs for non-serious diseases. Availability of treatments: a = drugs for diseases without recognized standard treatment; b = drugs for diseases where subsets of patients are less responsive to marketed drugs and/or other medical interventions, c = drugs for diseases responsive to marketed drugs or other medical interventions: C1 = more effective or safer than existing drugs; C 2 = mere pharmacological innovation, i.e. drugs with better kinetics or new mechanism of action; C 3 = mere technological innovation, i.e. a new chemical or biotechnological product with therapeutic role similar to already existing ones).Therapeutic effect: a = major benefit on clinical end-points (e.g. increased survival rate and/or quality of life) or validated surrogate end-points; b = partial benefit on the disease (on clinical or validated surrogate end-points) or limited evidence of a major benefit (inconsistent results); c = minor or temporary benefit on some aspects of the disease (e.g. only partial symptomatic relief of a serious disease).[47]

Prioritization is performed by consensus by the ISHP-SC without scoring the above listed prioritization criteria, noting the reasons for prioritization. The reasons for prioritization between 2008 and 2012 for each of the 44 prioritized products were:[21]

- high epidemiological and / or economic impact (13),
- the limited availability or the complete lack of treatments in that specific therapeutic area (13),
- high uncertainty of the possible place in therapy of the emerging drug (8),
- the possible better efficacy and/or safety profile or possible better compliance of the new medicine versus the available therapies (10).

For the prioritized products, the IHSP-ET (i.e. the pharmacist of the IHSP-DT along with experts from the IHSP-SC and/or other experts specifically

appointed by the IHSP-SC) produce the “12-month report”, which is also known as the New Product Information Report (NPIR).[bbb]

[bbb] Interview with Roberta Joppi, Mario Negri Laboratory of Drug Regulatory Policies, Italy, May 19th 2016

Assessment

To produce the NPIR a template is utilized including the following information:

- active substance
- brand name; company
- ATC Group; dosage
- route of administration
- development state
- clinical need and burden of disease
- overview on the pharmacokinetics and pharmacodynamics of the selected drug
- summary of efficacy/safety data from available clinical trials
- critical evidence assessment
- existing comparators and treatments
- possible place in therapy
- ongoing trial(s) for the same or other indication(s)
- social / economic impact (if price available)
- literature search strategy
- references.

Impact calculations can be performed based on information from patient databases (see Box 5).

It usually takes 1 to 2 months to complete the NPIR and after completion the report is approved by the IHSP-SC.

Box 7 – Calculation of impact: Target population calculation

The target population is based on the inclusion/exclusion criteria of the pivotal registration study(ies) together with the analysis of the clinical features and pharmacological treatment of "real" patients identified using the administrative database "ARNO-CINECA".[48] This database contains health service usage data on 11 million people connected through the ARNO database. It is a good representation of the Italian population. It contains information on the general practitioner's prescriptions, hospital admissions and discharges, diagnosis tests and diagnostic examinations. This information is linked to other data flows (vital statistics, health and social indicators) to build comparable epidemiological and economic indicators.

Case study example *Prasugrel*

Based on the inclusion criteria described in the TRITONTIMI study, the number of patients that were subjected to an intervention procedure of percutaneous angioplasty (percutaneous coronary intervention, PCI) + stent were identified within the ARNO database. It had been considered that treatment with *prasugrel* has greater efficacy in patients with diabetes than in non-diabetics, therefore different assumptions on coverage of these patient groups were made. The duration of treatment was assumed to be equal of that of a currently used anti-platelet agent i.e. clopidogrel.

The results based on this cohort were extrapolated to the entire Italian population.

Output

36-month report

The 36-months report is published annually. A list of drugs which may obtain market authorization by the EMA within the next 36 months, are included in the report. The following items are included per drug:[15]

- medicine´s name
- licensee
- stage of development
- possible submission date of the marketing authorization dossier to EMA
- main proposed indication(s)
- ongoing studies

The report is composed by the IHSP-DT.[15] AIFA was provided with information, and since they directly funded till 2008 an independent research program, research areas were identified which were interesting to the Italian NHS but which are not met by the pharmaceutical companies.[22]

18-months report

For drugs which have preliminary phase III data, a report is made twice a year. The following items are included in the report:[15]

- general information (active ingredient(s), brand name, licensee, ATC code, administration route, strength, international authorisation state, possible launch date)
- proposed indication(s)
- burden of disease
- summary of the available data on clinical efficacy and safety
- possible price and economic impact (if available)
- possible marketing authorization date
- alternative(s) already on the market
- possible competitors in development
- possible off-label use.

The report is composed by the IHSP-DT.[15] The 18-months report shows results from the phase III completed trials, so that prioritisation can take place. This report is not specifically addressed to policy-makers, and is mainly utilized for internal purposes.[22]

New Product Information Report (NPIR) (12-months report)

The New Product Information Report contains information concerning the prioritized medicines possibly being authorized by the EMA within the next 12 months. The following items are added to the information already published in the 18-months report:[15]

- critically assessment of the available data on clinical efficacy and safety and the quality evaluation of the studies
- ongoing studies for the same or other indication(s)
- evaluation of the innovation grade
- possible place in therapy
- Italian NHS and financial impact
- clinical and patient impact
- discuss the case for mode of introduction such as need for registries to ensure the appropriateness of prescription and additional efficacy and safety data.[22]

The report is composed by the IHSP-ET.[15] The Italian customers (AIFA and Veneto Regional Health Service) require the confidentiality of the reports and also the IHSP-SC is reluctant to share the reports publically. There is an ongoing discussion about the possible publication of the new product information report after EMA authorization.

Expert contacts

External and internal clinical and non-clinical experts are involved in the prioritization and assessment phase. It depends on the topic if external experts are invited to the process. If so, the external experts are only involved in the assessment phase.

Key points of the Italian HSS

- **HSS output is also used to inform decision makers to manage entry of emerging drugs at the regional level.**
- **The Italian HSS focuses on the time period early in development pathway (36 months prior to expected market authorisation).**
- **The Italian HSS produces three reports (-36, -18 and -12 months before expected market authorization) with increasing amount of information about the product. The 18 month report is compiled when preliminary data about phase III trials are available.**
- **While the "-36 months report" is a short report with minimal information (basically on the ongoing phase III studies), the "-18 month report" contains a summary of the available evidence and "-12 month report" contains a critical assessment of the available information.**
- **The Italian HSS does not use company contacts as a source of information.**
- **Innovativeness of the pharmaceutical is one of the priority-setting criteria and is defined by an algorithm.**
- **The impact on the system is not weighted. However, the impact is discussed by the IHSP-SC during the prioritization meetings based on explicit criteria.**
- **Prioritization is done by consensus.**
- **Administrative databases are used to make impact predictions of new technologies.**
- **Reports are not publicly available.**

Appendix 1.5. Horizon Scanning Research & Intelligence Centre (NIHR HSRIC) – England/Wales

History and organization

The Horizon Scanning Research & Intelligence Centre (NIHR HSRIC, until 2012 known as the National Horizon Scanning Centre (NHSC)) has been performing horizon scanning activities since 1998. NIHR HSRIC became part of the National Institute for Health Research (NIHR) in 2006, and is commissioned on a 5-year term to perform national horizon scanning activities. The English HSS staff is divided into pharmaceutical, medtech research and review teams. Due to the scope of this project, the description of the NIHR HSRIC process is entirely based on the work done by the pharmaceutical team. The pharmaceutical team consists of three senior

analysts (equivalent to 2.3 full time positions), eight analysts specialized in horizon scanning[ccc] and a part-time medical advisor.

Purpose of the system[ccc]

The aim of NIHR HSRIC is to provide advance notice to the Department of Health in England and Wales, and the health service policy-making bodies of significant new, emerging technologies. The main customer of the NIHR HSRIC´s output is the National Institute for Health and Care Excellence (NICE).

The process starts up to three years prior to launch of a product in the NHS England (NHSE) (products in clinical phase II, phase III, and pre-launch) aiming to collect information 24-30 months before launch. NICE wants to receive a brief report on a new product at least 20 months before launch.

The identification process uses two principal approaches:

- Focused routine identification carried out by the pharmaceutical team´s analysts: an ongoing 'horizontal scan' designed to identify significant and urgent advances, regardless of clinical specialty;
- In-depth scanning and reviews carried out by research and review team analysts: 'vertical scans' which focus on areas with known multiple or complex developments, or in patient groups with significant or unmet needs. In-depth scanning reviews can be requested by national customers and collaborators or chosen by NIHR HSRIC itself. Health professionals, researchers and patients are welcome to propose technologies that may need attention via the NIHR HSRIC website 'suggest a topic' page.

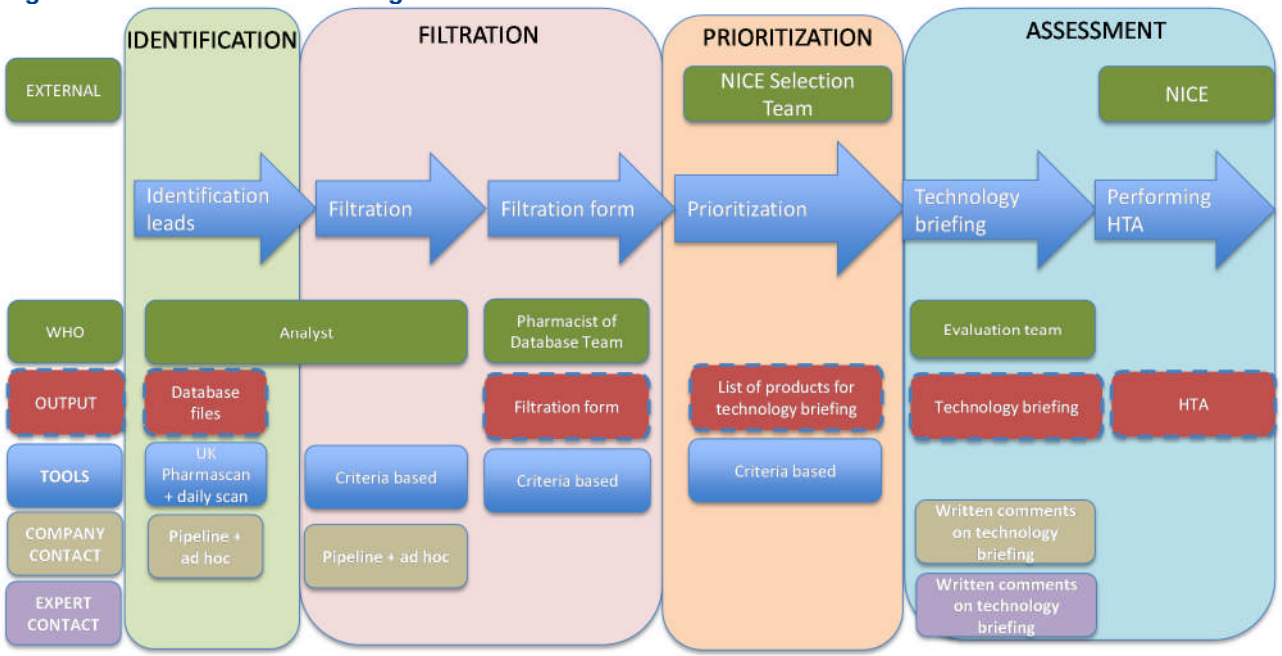
The main performance indicator of the HSS is the completeness, or inclusiveness, of the system. A lower specificity is not the main concern for NICE.

Process

A schematic overview of the English HSS is presented in Figure 15.

[ccc] Interview with representatives of the Horizon Scanning Research & Intelligence Centre (April 18th 2016)

Figure 15 – Overview of the English HSS



Identification and monitoring

The two main sources of information for NIHR HSRIC are the UK PharmaScan database and direct contact with pharmaceutical companies. The UK PharmaScan is a nationwide database, including information on all products that will be launched in the UK. In an ideal world, all pharmaceutical companies would proactively fill in UK PharmaScan as a drug enters phase III trials or is three years from launch, whichever is sooner. However, often companies need prompting for completion of the UK PharmaScan record and not all pharmaceutical companies are registered users. NIHR HSRIC ensures that all companies are aware of the need to complete UK PharmaScan, however, NIHR HSRIC will also accept information provided from the companies through other channels. The UK PharmaScan database is scanned every other day to identify new or updated products.

Box 8 – Company contacts

Regular contacts (Pipeline meetings)

NIHR HSRIC tries to set up annual meetings with the key pharmaceutical companies identified through the Scrip 100 list[ddd] and companies listed as having significant pipelines in the NIHR HSRIC database. The regular contacts with the industry have several advantages. Firstly, building a relationship with the people within a company helps to obtain key information. However, in case of human resource turnover at the pharmaceutical company, these meetings will help ensure that the responsible person is aware of the procedures of the NIHR HSRIC. These meetings will also create awareness of the necessity to collaborate with the NIHR HSRIC team to maximize timely reporting of technologies to NICE and the implied access to the NHS. Secondly, pipelines are reviewed during regular meetings based on the NIHR HSRIC database to see if pharmaceuticals are missing, discontinued or in need of an update.

Meetings can be organized as face-to-face meetings at NIHR HSRIC or by teleconference. A disadvantage is that this is a very resource intensive process.

Ad hoc contacts

NIHR HSRIC tries to gather as much information as possible from the *UK PharmaScan*. However, in some cases the identified drug is not entered in the database before the required timeline and companies need to be contacted directly by NIHR HSRIC. Sometimes companies are not willing to cooperate. NIHR HSRIC emphasizes the message that cooperation maximizes timely reporting of technologies to NICE needed to acquire UK market access. The information provided by the company is treated confidentially.

ddd Originally, the Scrip 100 was a ranking of the 100 biggest companies in the pharmaceutical industry by drug sales. That list has now grown to over 500 companies, but the numbers are still dominated by the top 150 companies. http://www.scrip100.com/scrip100.html)

Besides information from the company contacts and the *UK PharmaScan,* other sources are used as well:[eee]

- Scientific journals
- Trial registries
- Medical, general, and commercial media (e.g. Scrip, PharmaTimes, and Biospace)
- Commercial pharma R&D databases (e.g. Adis R&D Insight, PharmaProjects)
- Clinical experts
- Patients and patient organisation suggestions
- Other horizon scanning organisations/alert services (i.e. Medicines Awareness Daily Alert, New Drugs Online, Prescribing Outlook, UKMi).

Each member of the team scans their own dedicated sources. Analysts are not dedicated to a medical field. Scanning frequency depends on the source. When a new product is identified, it is added to the internal database. Because of the very early timeline of NIHR HSRIC (up to three years before launch), most of these sources provide limited information, therefore companies can be contacted to obtain the most accurate and up-to-date information.

Once an identified product is added to the database, the file will be completed with the following information:

- Technology summary
  - Technology name – including all synonyms
  - Indication – including subgroup, stage, and place in treatment
  - Description of technology
  - Specialty and ICD10 code
  - Primary and other companies
- Licensing and regulatory information
  - Information source and notes
  - Technology (sub)type
  - Trial status and notes
- Filtering information
  - Relationship to existing NICE guidance
  - UK licensing plans
  - Innovation
  - Need for medical input

Filtration

Filtration is performed to ensure that the products fall within the scope of the horizon scan. The criteria used for filtration are: appropriateness for the NHS and timeline to product licensing and launch. First biosimilars for an indication are included. HIV products, prophylactic vaccines (remit of other agencies), generics and subsequent biosimilars are excluded.

The medical advisor will recommend whether the drug is appropriate for the NHS.[eee] When a product does not pass the initial filtration, the topic is closed in the database and the product will not be monitored anymore. The list of closed topics is sent to NICE on a monthly basis. When a product passes the filtration process, it is set to 'continuous tracking' status and a review date is created based on the anticipated timeline and the available data. The products in the database are ranked according to the review date and possibly the proximity to launch. Since April 1st 2016, cancer drugs skip the

[eee] Interview with representatives of the Horizon Scanning Research & Intelligence Centre (April 18th 2016)

filtration and prioritized phases because a technology briefing is always required by NICE.

Once a product gets through the filtration phase and is within the timeframe, a filtration form will be completed. The filtration form is on average two pages long and includes the following information:

- Technology name and code(s)
- Drug class and pharmacological action
- Commercial developer
- Treatment schedule/administration route
- Other indications (for products that have an existing license for another indication)
- Patient group(s) and/or indication(s)
- Place in treatment pathway
- Size of eligible patient group
- Clinical trials and phase
- Current/planned guidance
- Licensing, launch, and marketing plans

The form is filled out by a horizon analyst, which is then validated by a medical advisor. Completion will usually take one to two hours if the company provides information and the analyst is familiar with the patient group. When the filtration form is completed and the anticipated launch date is within the specific time frame (20 months before for new drugs or 15 months before for new indications), it is sent to the NICE Topic Selection Team on a weekly basis (average of 3 forms per week). Forms are shared with other stakeholders as well, such as the Department of Health, NIHR HTA program, NHS England, Scottish Medicines Committee (SMC), All Wales Medicines Strategy Group (AWMSG) and the Department of Health of Northern Ireland.

Prioritization

Product prioritization for assessment is performed by the NICE Selection Team taking the following criteria into account:[fff]

- Impact
  - Significant health benefit
  - Significant impact on health-related policy
  - Significant impact on NHSE resources

[fff] Interview with representatives of the Horizon Scanning Research & Intelligence Centre (April 18th 2016)

- Variation
  - Evidence of significant variation in use
- Added value of national guidance
  - For example, significant controversy on the interpretation of evidence

NICE has seven weeks to determine whether or not it requests a technology briefing for input into the scoping of a full HTA/NICE appraisal.[ggg] The process of topic selection is a closed process (for public and NIHR HSRIC). Sometimes patients and patient's associations appeal against the decision; in these cases NICE follows a procedure that may finally result in a different decision. When products are not suitable for a separate assessment, they are assessed with similar products by the Medicine Prescribing Program (MPP) or the NICE guideline group (e.g. diabetes drugs).

Assessment

The final assessment of the horizon scan is reported in a technology briefing. For all pharmaceutical briefings a standardized and thorough internet search is completed to identify up-to-date information on the patient group, current treatment options, and ongoing or completed clinical trials. Parameters in the technology briefing are:[49-51]

- Target group
- Technology
  - Description
  - Innovation and/or advantages
  - Developers
  - Availability, launch or marketing
- Patient group
  - Background
  - NHS or Government priority area
  - Clinical need and burden of disease
- Patient pathway
  - Relevant guidance
  - Current treatment options
- Efficacy and safety
- Estimated costs and impact
  - Cost
  - Impact – speculative

The time needed to complete a technology briefing varies form a few days to up to two weeks, depending on the therapeutic area. The medical advisor will review drafts of the briefing. Once a draft is finished, it is sent to the pharmaceutical company and one to two experts[hhh]. Experts comment on the clinical setting, the relevant patient group, and how the new products compare to current treatments and services. The company has the opportunity to provide feedback, may be asked specific questions (e.g. clarification on the patient group), or is asked to highlight confidential information. Technology briefings are published on a monthly basis on the HRSIC and EuroScan websites and shared with NICE and other interested parties without the confidential information enclosed. Once the technology briefing is finished and delivered to NICE, the status of the product is changed to "closed" and the monitoring stops. From then on, NICE is the responsible party to monitor the product and to evaluate the technology

[ggg] Interview with representatives of the Horizon Scanning Research & Intelligence Centre (April 18th 2016)

[hhh] About three to four experts are asked to provide feedback, of which one or two experts will finally participate.

briefing in order to advise the minister on a potential scope for the HTA appraisal.[iii]

If either the technology development is slowing down or new information suggests the topic is outside of NIHR HSRIC's timeframe before a briefing is submitted, the technology is monitored on a watchful waiting list, which is shared with NICE. If development ceases, the respective file is closed in the database and no actions are taken anymore.

Output

The output of the horizon scan comprise:

- An *SQL-based* database: filled with information on every identified drug. This database is updated on a daily basis by the horizon analysts.
- Closed topic list: a list with topics which did not pass the filtration shared with NICE on a monthly basis.
- Filtration forms: shared on a weekly basis with NICE and other stakeholders
- Watchful waiting list: products where development is slowing or new information suggests the topic is outside NIHR HSRIC's timeframe before a briefing is submitted - shared between NICE and NIHR HSRIC.
- Technology briefings: shared on a monthly basis.

About 1000 new technology entries, including drugs, were added in 2015.[iii] There has been an increasing trend in the number of filtration reports (Table 36), and the percentage of briefings requested has remained steady, which has increased the workload. This is mainly due to the higher sensitivity goals, leading to the incorporation of products even when no licensing information is available.

Table 36 – The English output

Financial year	Filtration forms sent to NICE	NICE Briefing requested
2015-16	301	225 (82%)
2014-15	191	147 (78%)
2013-14	130	99 (77%)

Expert contact

NIHR HSRIC keeps a database of relevant external experts. New experts are identified through sources such as specialistinfo.com or by the directory of NIHR Senior Investigators. In order to maintain a good working relationship with experts, NIHR HSRIC tries to limit the workload for each expert. Therefore, there is usually a 12-month gap between requests to review a product. There are typically three to four experts approached, of which usually one to two agree to participate in the comment process.

Key points of the English HSS

- **The English system is integral to the reimbursement process in England/Wales and provides information for the research planning by NICE.**
- **The English system aims at being as inclusive as possible and starts scanning at an early time point.**
- **The system is resource-intensive, because of its focus on inclusiveness and company contact.**
- **UK PharmaScan and company contacts are very important sources for the English HSS. The English system has regular and ad hoc contact with companies to obtain information about the**

[iii] Interview with representatives of the Horizon Scanning Research & Intelligence Centre (April 18th 2016)

products. Building relationships through company contact however is very time-consuming.

- **Clinical experts are involved to provide country-specific data on clinical setting, relevant patient group, and how the new products compare to current treatments and services.**

Appendix 1.6. UK Medicines Information (UKMi) – United Kingdom

History and organization

UKMi is an NHS pharmacy-based service responsible for providing information to healthcare professionals to support managed introduction of new medicines into the NHS, and assist organizations in developing medicine management policies.[52, 53] UKMi supports healthcare professionals in the primary and secondary care sector with guidance on use of medicines in individual patients.[52, 53] In addition, UKMi raises awareness of new products or indications with hospital managers and health care commissioners and providers.[jjj] The UKMi organization is a virtual network of medicines information centres. Several regional centres collaborate virtually to produce horizon scanning information resources such as the New Medicines pages of the SPS website (formerly the New Drugs Online database which was established in 2000) and the Prescribing Outlook series (first published in 2003).[jjj] The collaborative approach allows the data to be as robust and timely as possible; however, competing priorities and demands at each contributing centre could impact the national horizon scanning work.

The UKMi Horizon Scanning & Medicines Evaluation (UKMi HSME) working group is a subgroup of the UKMi Executive, and is composed of eight NHS employees who work at regional medicine information centres, most of them with a pharmacy background and experience in primary or secondary care[kkk]. Each of them is responsible for routinely scanning a specific set of resources.[ggg] The total workload is estimated to be about three Full Time Equivalents (FTE's) (this includes producing Prescribing Outlook), however, the time needed to complete the scanning is variable depending on relative experience of the individuals.

[jjj] Interview with Joan McEntee, & Helen Davis from the UKMi (May 6th 2016)

[kkk] In contrast to the English/Wales system (HRSIC) where all team members are academics.

The UKMi HSME working group has two meetings a year (one face-to-face, one teleconference) and minutes are published online (https://www.sps.nhs.uk/networks/ukmi-horizon-scanning-and-medicines-evaluation-working-group/). The group members liaise as needed with the lead administrator.

Purpose of the system

The output of the UK HSS is used to: [23]

- Anticipate organisational and financial pressures on NHS services[ggg]
- Manage budgets
- Plan services: Development/redesign
- Disinvest: A new treatment may mean that existing services are no longer required
- Manage entry (E.g. set-up of monitoring services)
- Identify drugs suitable for homecare: Used to facilitate discussions with commissioners

Information provided by UKMi is tailored to the needs of the NHS. UKMi works collaboratively with NIHR HSRIC, the Scottish Medicines Committee (SMC) and the All Wales Medicines Strategy Group (AWMSG).[jjj]

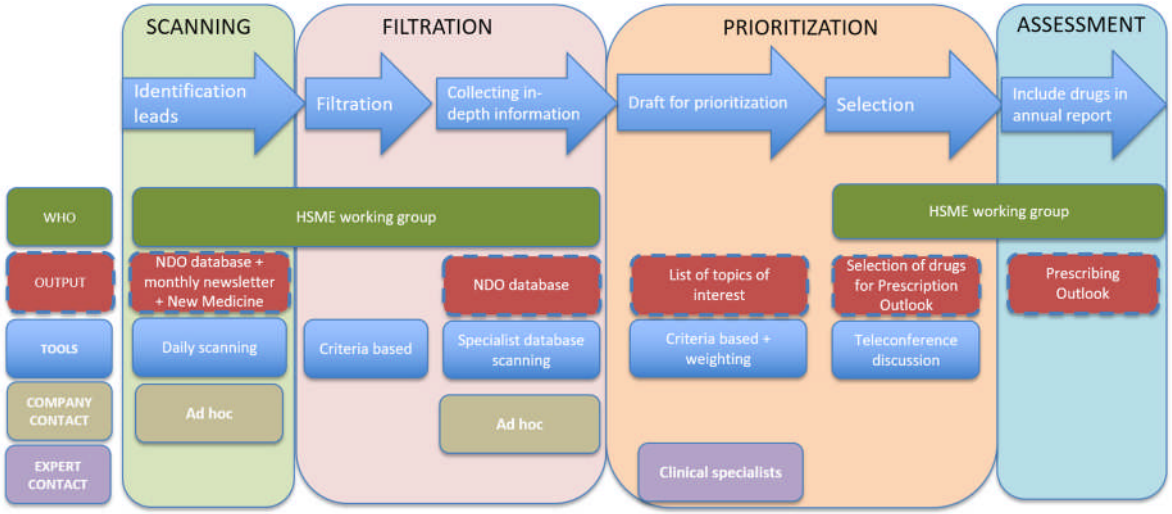
Process

A schematic overview of the UK HSS is presented in Figure 16.

Identification and monitoring

Data collection starts when a drug enters Phase III (or Phase II for orphan/fast-tracked drugs). Launch dates are predicted per quarter, however the Prescribing Outlook only includes the year of the estimation. The process of information gathering takes place daily and an internal Access database (NDO – New Drugs Online) has been developed to store, retrieve and assess this information.

Figure 16 – Overview of the UK HSS



Types of sources scanned are:[23, 24]

- Journals – specialist and general
- General media
- Specialist media for pharmaceutical press releases higlighting
- Conference presentations and top-line trial data
- Development news including regulatory news
- Biosimilar news
- Industry
- Company websites, especially pipelines
- Ad hoc meetings
- Licensing agencies (e.g. EMA, Medicines and Healthcare products Regulatory Agency (MHRA))
- Clinical specialists
- NICE
- Other horizon scanning organisations (e.g. NIHR HSRIC, SMC and AWMSG)
- UK PharmaScan and other specialist databases

There is a lot of variability in the detail of the outputs of UK PharmaScan, because technology records in the database are filled in by the companies themselves.[III]

Drugs are tracked in the NDO from the time they are in late phase II trials up until two years after launch. Selected information from NDO is also made available on the Specialist Pharmacy Service (SPS) website, most of it freely available but with some confidential information, such as anticipated launch dates, only accessible via password to registered NHS staff. Links to evidence-based evaluations, such as drug reviews (e.g. UKMi, NICE – Evidence Summaries, NIHR HSRIC), national guidelines (NICE, SMC, AWMSG), and licensing authorities' assessment reports are added to the database entry (commonly referred to as a 'monograph') once available.[III]

Sometimes drugs are detected at the point of launch. For most of these, new monographs are not created; the purpose of NDO is to plan ahead and if the drug is available it's already too late. If the drug offers a significant advantage over existing therapies a new monograph will be created, as the drug's launch can then be included in New Medicines Newsletter, which aims to inform NHS staff of recent significant medicines regulatory changes.[III]

The contents of a monograph in the NDO contains:[23]

- Name of the drug (generic, company, synonym)
- Indication and formulation
- Pharmacology and epidemiology
- Key trial data
- Stage in licensing process (UK, EU, US)
- Anticipated UK launch date
- Orphan status
- Links to independent evaluations e.g. NIHR HSRIC and the London New Drugs Group (LNDG)
- Information if a drug is already in NICE pipeline
- Implications

Cost data are not available until very near to launch. Products for new indications or for rare diseases, or drugs launched with companion devices or diagnostics, are sometimes missed by the system or data are not available.[ccc]

[III] Interview with Joan McEntee, & Helen Davis from the UKMi (May 6th 2016)

Filtration

Drugs are included in the database if they fulfil one of the following criteria:[mmm]

- Likely to reach the UK market, and
- Have positive clinical data, and
- In development Phase III or late Phase II trials if the product is being fast tracked (Product can be used even if they are not within the strict eligibility parameters for a specific clinical trial),
- Orphan drugs

Box 9 – Drugs not (yet) relevant for UK market

It is sometimes unclear if a company plans to market the drug in the UK. Drugs in early developments (Phase II) may have a fast-track or breakthrough status in another country, but are being developed by a small non-UK company which does not appear to have any office set in the European Union (currently a lot of small US companies are emerging). If the drug appears to be innovative it will be likely that the company will find a partner to support them in marketing the drug in the UK. In this situation, it is advised to create a monograph for such a drug.

Drugs with only little therapeutic advantage over existing therapies are usually not included in the database. A wait-and-watch strategy is used to observe further development of the drug and when it is filed.[mmm]

Filtering is done by all members of the UKMI HSME working group. UK Medicines Information, 2007 #36} Companies are not contacted on a routine basis, but meetings are organized, mostly on request of companies themselves. If necessary, companies are approached to request additional information, for example for cost data after the product is approved.

Prioritization

Drugs listed within NDO are prioritized annually for inclusion in Prescribing Outlook – New Medicines. First, NDO is used to create a list of drugs likely to be launched in the next three years.

The list is sent to members of the UKMI HSME working group and clinical specialists in primary and secondary care for scoring. A teleconference then takes place attended by UKMI HSME working group members and selected other UKMi staff to refine the list of drugs for including in Prescribing Outlook.[mmm] The following criteria are used to determine if the impact is high enough:[24]

- Expectation for improvement in disease management
- First in class or major new indication
- Limited alternatives
- High drug costs
- Large target population
- Expectation of significant effect on service implications
- Drug/disease area is considered a NHS priority
- Significant additional indications in advanced pipeline stage
- Drug is in EU licensing process
- Expectation for media interest

The relative weight given to these factors for deciding/estimating the expected impact of the drug, is made by the HSS team members. Opinions often vary and sometimes there are disagreements.[24] The relative weighting of these factors are not made public.

Assessment

Prioritized drugs are listed in an annual report called ”Prescribing Outlook - New Medicines”. The drugs are structured according to British National Formulary (BNF) chapter and authors of the report are assigned to the same

[mmm] Interview with Joan McEntee, & Helen Davis from the UKMi (May 6th 2016)

chapter each year, so that they gain more expertise in this specific area.[nnn]
Parameters reported are indicated in Table 37.[54]

[nnn] Interview with Joan McEntee, & Helen Davis from the UKMi (May 6th 2016)

Table 37 – Parameters in Prescribing Outlook

Parameter	Description
Generic name and formulation	
Pharmacology	• Therapeutic class • Administration details
Indication	The closer to launch, the more specific
Current status	• Phase II/III • Application submission • Recommendation for approval (EMA) • Licence • Launch • Promising innovative medicine designation • Breakthrough therapy • Fast-track • Priority review
UK-availability	• Estimation of date of availability
Reference product & company	• Only relevant for biosimilar drugs
Patient expiry of reference product	• Only relevant for biosimilar drugs
Population	• Prevalence • Incidence
Sector	• On which sector (primary or secondary care) will the drug have impact
Implications	• Patient options • Monitoring • Testing requirements • Service implications
Financial	• Cost implications • When patient access scheme may apply, this is indicated
Tariff	• Actual or anticipated tariff
CDF	• Listed in Cancer Drugs Fund – only for chemotherapy drugs
Efficacy	• Key studies

Safety	• Link to product information if drug is marketed • Adverse effect which may influence licensing requirements
Guidance	• NICE • NHS England • SMC • AWMSG
Reviews	Includes reviews made by[i]: • London Medicines Evaluation Network • Midlands Therapeutics Review & Advisory Committee • NICE Evidence Summaries • Horizon Scanning & Intelligence Centre • Regional Drug & Therapeutics Centre • Northern Treatment Advisory Group

[i] *provided review is not older than two years*

Output

New Medicines pages of the SPS website and New Medicines Newsletter

The New Medicines pages of the SPS website include products in development that are identified through horizon scanning. Most of the information on the pages is freely available, although some information is only available to NHS staff who register (e.g. confidential and commercially sensitive information such as anticipated launch dates and commissioning information).

The monthly New Medicines Newsletter highlights major updates, including changes in development stage and drugs recently added to the SPS website.[53] It is published at www.sps.nhs.uk.

Prescribing Outlook Series

The Prescribing Outlook series is a more in-depth output of the HSS, to assist NHS budget holders and those involved in planning potential impact of prescribing new drugs.[53] The Prescribing Outlook series consists of three parts:

- *New Medicines:* This part includes information on drugs and major new indications expected to be launched or approved over the next 18 to 24 months. It contains brief clinical and therapeutic data plus information on predicted launch date, potential target population and estimated impact on service delivery and cost.[54] Separate sections cover biosimilars, recently launched drugs (previous year), and anticipated patent expiry dates.
- *National Developments:* This part aims to provide advanced information to commissioners and providers about the impact on clinical practice and prescribing budgets of national guidance issued by NICE. It is intended to inform discussions between commissioners and providers and to highlight issues around implementing guidance. Drugs with patent(s) due to expire in the near future are highlighted. The report contains information on national targets that may have budgetary implications over the next 12 to 18 months. It aims at providing information to facilitate implementation of new drugs, to adjust national guidelines, and organization of care while providing an estimated total cost of implementation.[55]

- *Cost Calculator:* The cost calculator part is based on *New Medicines* and *National Developments.* It provides an Excel spreadsheet to calculate potential cost of prescribing changes in a *local population*, which can be used for budget setting processes. The main focus of the document is on drugs commissioned by Clinical Commissioning Groups. A budget holder can enter the regional specific population figures to calculate regional cost implications. Assumptions in the model are highly speculative, and crude estimates are used for drug uptake.[56]

All three parts are available in autumn of each year, to facilitate planning for the next financial year. [53]

List of medicines' evaluations

A list of new product evaluations from other agencies is produced every month. The list is freely available on https://www.sps.nhs.uk/articles/new-product-evaluations-a-resource-for-medicines-management-september-2016/.

Key points of the UK HSS

- **The UKMi system is mainly targeted at NHS commissioners, managers and health care providers.**
- **The HSS activities are a collaborative effort between different regional medicine information centres in the UK. Most staff have a pharmacy background.**
- **There is an annual HSS output providing information about products that are expected to become available within the next 12 to 24 months.**
- **The cost impact of the products is highlighted and budgetary templates are provided through the Cost Calculator tool.**

Appendix 1.7. Scottish Medicines Consortium (SMC) – Scotland

History and organization

The HSS started in 2003 when the Scottish Executive requested that the Scottish Medicines Consortium (SMC) would establish a horizon scanning system, to provide the Scottish Health Board with information regarding new medicines. This information would be used to support financial and service planning for their managed implementation in practice.

The horizon scanning team includes senior pharmacists, finance experts, health service researchers and an administrator.[10] The entire team consists of 30 members.

Purpose of the system

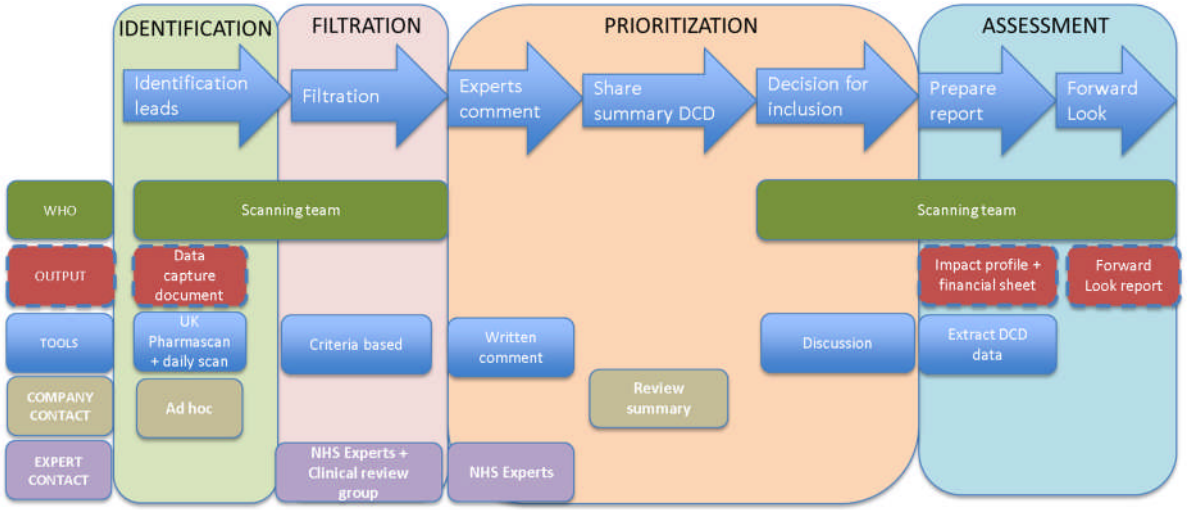
The current purpose of the HSS is to provide the financial planners with reliable information, in order to support resource planning for the managed introduction of new drugs. Horizon scanning encompasses new drugs, as well as existing drugs that are prescribed for new indications, licence extensions and new formulations of existing medicines. NHS boards are provided with information on potentially high-impact medicines that may come to the market within the next calendar year. To do this, the goal is to identify pipeline drugs 12 to 24 months before launch. [10 11]

Besides regular scanning activities, horizon scanning intelligence can be used to answer ad hoc enquiries from NHS Scotland. This can range from a simple enquiry about an expected launch date, to more complex requests about the provision of input to ten-year plans for service development for a specific clinical specialty.[10]

Process

A schematic overview of the Scottish HSS is presented in Figure 17.

Figure 17 – Overview of the Scottish HSS



Identification and monitoring

The horizon scanning team performs continuous identification of new drugs.[10] This is done by extracting pipeline updates from *UK PharmaScan*, or contacting companies who did not include their information to the *UK PharmaScan*.[10] Other types of sources scanned are:[10]

- Confidential NHS Publications
- Regulatory authorities
- Pharmaceutical and commercial analyst companies
- Other NHS organisations involved in horizon scanning: NIHR HSRIC and UKMi.

Information from this scan is captured in a data capture document (DCD). It includes calculations and assumptions regarding the potential impact. DCD's are only used internally. The scanning provides information about the following questions:[10]

- How does the new product differ from existing products?
- What is the likely indication for the new product?
- How many people in Scotland would be eligble for treatment?
- What proportion of them is likely to receive the new product?
- What is the incremental drug acquisition cost of the new product relative to existing products?
- Would the new medicine be associated with any major service implications?

Every year in March, a list is made with all new medicines expected in the following calendar year.[10]

Filtration

The filtration process is used to identify medicines with the potential for high budget and/or service impact.[10] The Horizon Scanning Steering Group, the Clinical Review Group, and NHS experts share their views on the potential impact by written comments.[10] An identified medicine is regarded as having a high-impact if:[10]

- It has a predicted net drug budget impact for NHS Scotland of >£500K per annum, or
- It may be associated with major service implications (e.g. care change from secondary care setting to primary care setting)

Box 10 – Contact with the industry

When a medicine in clinical development is identified and added to SMC's tracking list, the pharmaceutical company developing the drug is identified. If the SMC has not had any previous contact with the company, the Horizon Scanning Team will attempt to identify the most appropriate contact person within the company with responsibility for horizon scanning intelligence.[10] If the estimated drug impact is high enough, the company will be contacted by email to inform them that their new drug will be included in the report. Companies may also be contacted on an ad hoc basis to clarify or request additional information on particular products. In the request examples of type of information needed are given (Table 38). The SMC maintains a database of company contacts. Contact with the industry is perceived as time consuming.[10]

Table 38 – Type of information requested by the Scottish HSS

Information useful to SMC Horizon Scanning Team	Examples
Acquisition cost An indication of potential cost range or upper or lower levels of range	• Expected to cost between £5 000 to £10 000 per patient per annum • Expected to cost more than £80 000 per patient per annum • Expected to cost less than £500 per patient per annum
Cost relative to comparators An indication of potential cost relative to existing treatments	• Will be priced in the same range as other drugs in class • Likely to cost less than alternative treatments • Likely to cost 10% to 20% more than alternative treatments
Estimated uptake An indication of uptake range or upper or lower levels of range	• Likely to be given to at least 90% of eligible population • Likely to be given to less than 5% of eligible population • Likely to be given to between 40% to 60% of eligible population
Estimated uptake An indication of estimated uptake relative to existing treatments	• Likely to replace existing drugs within the same class, but no increased numbers of patients prescribed this class • Likely to be given to up to 10% of patients already receiving this class of drug • Likely to increase the proportion of the eligible population receiving drug therapy for this condition by up to 90%

Prioritization

The DCD is sent to the NHS clinical experts. Ideally, five to six experts from a variety of NHS Boards throughout Scotland are approached to comment on the gathered information. If there are not enough experts available (e.g. when reviewing a drug impacting a rare disease), additional experts are identified through the Scottish Area Drug and Therapeutics Committees. Experts are specifically asked to give feedback on the assumptions regarding the eligible population, uptake and place in therapy.[10] Expert comments are reviewed by one of the team members and incorporated into the DCDs. After this, summaries are prepared and shared with the companies for review. Company comments are reviewed by one of the team members, and, if considered appropriate, incorporated in the report. The team decides then, based on the information gathered in the filtration phase and the expert opinions, if a drug should be included in Forward Look. No hard thresholds or explicit criteria are used for this decision.

Assessment

After the decision whether or not to include the drug in the final report, information from the DCD is extracted into Impact Profiles (Table 39) and financial spreadsheets to be included into the Forward Look report.[10]

Table 39 – Example of an Impact profile

Drug C (Brand C) Intravenous Injection (Company)	
Indication	Treatment of adults with moderate to severe psoriasis unresponsive to standard therapies.
Regulatory information	Plan to file with EMA Q1 2016. Estimated UK launch Q4 2016.
Mode of action	First in class [Brief description of mode of action inserted]
Categorization	New medicine
Estimated eligible population	Derived through published literature. Derived through clinical expert consultation.
Clinical evidence	Positive phase III clinical results published.
Anticipated dosage regimen	The recommended dose is 30mg by intravenous injection once per month.
Established comparator(s)	Drug Y 100mg subcutaneously per week. Estimated cost £3,000 per annum (including VAT).
Comparator(s) in the clinical development pipeline	No.
Treatment duration	Continuous therapy.
Estimated drug acquisition cost	Reflects an SMC estimate. Drug C will be used as an alternative to existing therapy.
Service setting and anticipated impact	To be used in the secondary care setting. Non-significant service impact predicted.
Additional information	There is significant uncertainty surrounding the launch of this product. The predicted launch date may slip into the next financial year.

The report is distributed in confidence to key Health Board personnel (i.e. CEO's and, Directors of Medicine, Finance, Pharmacy and Public Health) through a secured website.[10]

Output

Forward Look annual report

The Forward Look report is produced since 2005 and is published on annual basis.[10] The report is split into two sections:

Impact profiles on drugs expected to be associated with moderate to high net drug budget impact and/or major service implications (Table 39)

- Tabulated information on all new drugs likely to be launched in the UK in the following calendar year

The SMC and Health Boards recognize that figures in the Forward Look report may represent a 'worst case scenario' given that some of the new drugs listed may not reach the UK market within the predicted time frame or not at all due to abortion of development or negative reimbursement appraisal from SMC.[10]

Financial spread sheets summarize the estimated incremental net drug budget impact of each significant new drug by geographical area and by individual NHS board. Spreadsheets are categorized in cancer and non-cancer drugs.[10] Spreadsheets include data on:

- Annual net cost of treatment per patient
- Estimated eligible population
- Estimated uptake figures in year 1 and steady state
- Estimated total costs of each new drug in year 1 and at steady state per area
- Service implications – to detect potential additional costs or available savings (e.g. medicine registration can be more/less complex)

The Forward Look financial spreadsheets have been developed to allow this ongoing, dynamic in-year adjustment by Health Boards.

Forward look quarterly updates

An update is produced four times a year to highlight significant developments or a change in information on drugs included in the main report. The first update of the year (January) shares information about all drugs, the other three updates only share information on high-impact drugs.

Expert contact

The SMC Horizon Scanning team works closely with expert clinicians practicing within the NHS Scotland. For rare conditions, only one or two (instead of five or six) relevant clinicians are available in the SMC expert panel. In these circumstances, additional efforts are made to identify further relevant clinical experts, for example via requests to Scottish Area Drug and Therapeutics Committees (ADTC) or identification of relevant clinicians practicing within the NHS in England, Wales or Northern Ireland.[10]

Key points from the Scottish HSS

- **The main input for the HSS is information from company contacts and the UK PharmaScan in addition to other HSS system outputs.**
- **Forward Look includes specific financial information to help in the financial planning for the upcoming calendar year.**

Appendix 1.8. All Wales Medicines Strategy Group (AWMSG) – Wales

History and organization

The All Wales Medicines Strategy Group (AWMSG) started in 2002 to inform the Welsh Government's Minister for Health and Social Services.[57]

The group's main functions are:[58]

- To advise the Welsh Government on future developments to assist in strategic planning
- To advise the Welsh Government on the development and implementation of a prescribing strategy
- To develop timely, independent and authoritative advice on new medicine.

Members of AWMSG include general practitioners, specialist physicians, pharmacists, nurses, representatives of the pharmaceutical industry, lay representatives, NHS managers, and health economists.[59]

For the purpose of horizon scanning, the AWMSG is supported by the All Wales Therapeutics and Toxicology Centre (AWTTC) since 2012.[57]

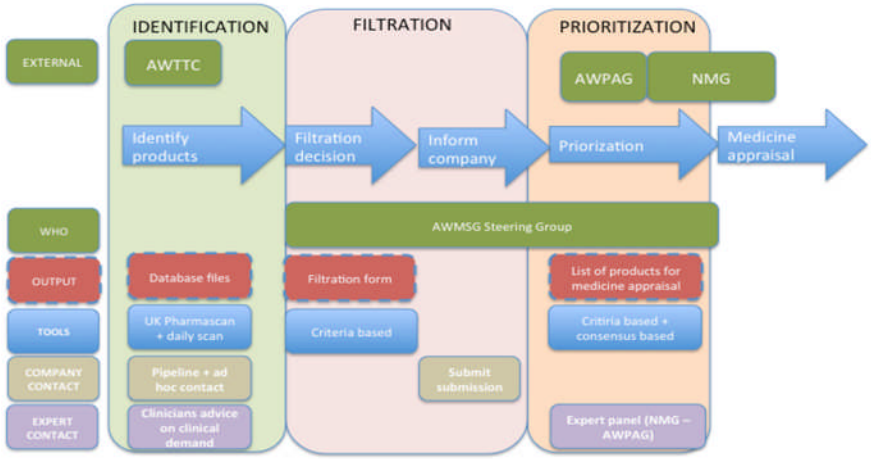
Purpose of the system[ooo]

The horizon scanning process gathers information on new medicines, which is an essential function to aid better planning and support earlier introduction of new medicines for use in NHS Wales. The HSS selects new drugs, which might be suitable for a medicine reimbursement appraisal process.[59] The information gathered in the HSS is at least 12 months before the drug is authorized in the UK. [57] HSS work by AWMSG is complementary to that of NICE: if drugs are mentioned in the NICE work program and a technology appraisal is expected within 12 months of market authorization the drug will not be considered by AWMSG.

Process

A schematic overview of the Welsh HSS is presented in Figure 18.

Figure 18 – Overview of the Welsh HSS



Identification

Normally, the initiation for the appraisal process currently lies with the applicant company through the completion of an initial submission form (Form A). Form A should be completed for all newly licensed medicines, each new indication and/or formulation. It should be submitted before marketing approval is obtained, and ideally within one month of receipt of positive opinion from the Committee for Medicinal Products for Human Use (CHMP). Form A provides the information required by the AWMSG Steering

[ooo] Personal Communication from Caron Jones, All Wales Therapeutics and Toxicology Centre (2016)

Committee to decide whether a medicine requires appraisal (when it is not on the NICE work program in the coming 12 months).

In addition, the AWTTC horizon scanning group actively screens a number of sources (e.g. UK PharmaScan, UKMi New Drugs Online, NICE Medicines Awareness Daily newsletters) to gain intelligence on new medicines. Once a new drug is identified, information is gathered through company contact by the "Therapeutically Development Assessment user group". This group facilitates interaction, regarding the identification and appraisal in a timely manner.

Clinicians can advise AWTTC on any clinical demand for certain medicines and specialist clinician groups are kept informed of the AWMSG work program.

Filtration

The initial submission form (Form A) is assessed by members of the AWMSG Steering Group team (Table 40). The team takes a number of factors into consideration when deciding whether or not the medicine meets the criteria for appraisal: the AWMSG exclusion criteria (i.e. medicines that would fall outside the remit of AWMSG would not be routinely captured in the internal database and subsequently would not be pursued, e.g. vaccines, generic medicines). The list of exclusion criteria can be found in Table 41.

Table 40 – Information included in the initial appraisal submission (Form A)

Category	Description
Product information	• Marketing authorization (MA) holder • Approved name of drug • Trade name • Formulations/strengths and route of administration • Full licensed indication • Indication covered in this submission • If license has been amended, details of changes • Authorizing body

	• MA application date, CHMP positive opinion date, anticipated MA date, date MA granted, (anticipated) UK launch date • Likelihood to be included under early access to medicines scheme
Exclusion criteria (NICE) if applicable	• Title of NICE Technology Assessment, NICE ID number, link to webpage • Anticipated publication date of final NICE advice, number of months anticipated from date of MA to publication of NICE final advice
Exclusion criteria (New formulation of an established medicine)	• Details of alternative formulations available • Price based on maximum dose per patient per year/treatment course • Difference in price between product in this submission and alternative
Exclusion criteria (equivalent generic is available)	• Name of equivalent generic or branded generic product • Price based on maximum dose per patient per year/treatment course • Difference in price between product in this submission and alternative
Cost and patient eligibility	• Consideration of submitting a Wales Patient Access Scheme[i] (simple or complex) or Department of Health Patient Access Scheme? • Price based on maximum dose per patient per year/treatment course based on list price + based on Patient Access Scheme price • Additional costs associated with use of new medicine per year/treatment course • Estimated number of patients in Wales eligible for this medicine
Limited submission details	• Estimated budget impact in NHS Wales and rationale • Proposed comparators (and price)
Comparator and place in therapy	• Company-proposed comparator treatment(s) • Expected place in therapy (e.g. first line)
End-of-life, orphan medicines and medicines for rare diseases	• Does the medicine have orphan or ultra-orphan status or has it been developed specifically for a rare disease? • Does the medicine meet the AWMSG policy on appraising life-extending, end-of-life treatments?

[i] *Wales Patient Access Scheme: Patient Access Schemes (PAS) are arrangements which may be used on an exceptional basis for the acquisition of medicines for the NHS in Wales and England. PAS propose a discount, rebate or other variation from the list price of a medicine that may be linked to the number, type or response of patients, and/or the collection of new evidence (outcomes). These schemes should aim to improve the cost effectiveness of a medicine and therefore allow the All Wales Medicine Strategy Group (AWMSG) to recommend treatments which it might otherwise have found not to be cost effective (http://www.awmsg.org/healthcare_wpas.html).*

Table 41 – Exclusion criteria for medicines' appraisal

Exclusion criteria	Description
1	Product was granted marketing authorization prior to 31 October 2002 for high cost medicines (i.e. those ≥ £2,000 per patient per year); 1 April 2007 for all cardiovascular, malignant disease and immunosuppressant medicines; 1 October 2010 for all other medicines.
2	NICE intends to publish final advice for the same product and indication(s) within 12 months from the date of marketing authorization.
3	Change is made to the market authorization holder, trade name or manufacturer, with no change to the licensed indication, formulation, route of administration, pharmacokinetics/pharmacodynamics, posology or cost.
4	Marketing authorization is solely for a new strength or strengths of an existing, available, generic or branded generic product, with no associated change to the licensed indication or route of administration.
5	Combination products that are comprised of medicines licensed prior to 1 October 2010, even if the individual components have not previously been appraised by NICE or AWMSG. (If any component of the combination product has been licensed after 1 October 2010, the medicine is unlikely to be excluded from appraisal.)
6	Product is a new formulation or combination of an established medicine which is either an oral formulation intended for patients unable to swallow tablets or capsules, or an alternative formulation of an established medicine which costs the same or less than the existing established medicine.
7	An equivalent generic or branded generic product is available and the new product costs the same or less.
8	Product does not have Prescription Only Medicine status.
9	Product is a vaccine considered by the Joint Committee on Vaccination and Immunization.
10	Product is used solely for the acute treatment of poisoning.
11	Product is a biosimilar medicine which costs the same or less than the reference product and where the reference product has either been recommended by AWMSG or NICE for the same indication(s), or the reference product was licensed and made available prior to October 2002.
12	Product is a medical device; i.e. it does not have a license as a medicine from the Medicines and Healthcare products Regulatory Agency (MHRA) or EMA.
13	Product is a diagnostic agent.
14	Product is a medical gas.
15	Product is classified as a blood product and does not have a medicinal license from the MHRA or EMA.
16	Product is a parenteral preparation for fluid and electrolyte imbalance.
17	Product is used as an intervention in surgical procedures/wound management.
18	Indication does not apply for the UK.

Prioritization[ppp]

If a medicine meets the criteria for filtration, the pharmaceutical companies are informed and are asked to submit either a full or limited submission. The prioritizing criteria may be applied if the number of appraisal submissions received exceeds the AWMSG meeting capacity, however this happens rarely.

AWMSG uses a consensus-based approach to prioritize drugs: an expert panel, consisting of NHS clinicians, professions allied to medicines, health economists, industry representatives, patient advocates and lay representatives, try to promote the best use of medicines for patients in Wales.[57] Experts´ advice is provided by two advisory subgroups: the New Medicines Group (NMG) and the All Wales Prescribing Advisory Group (AWPAG).[57]

Prioritization, when required, would include consideration of factors (in no particular order) such as clinical demand/patient demand (identified via clinical networks and patient organizations), whether there is a perceived unmet health need, service/resource impact, the type of submission and timeliness e.g. a re-submission, medicine which has been licensed for some time/new chemical entity/first in class. However, AWMSG had only to prioritize on very rare occasions.

Furthermore, the AWMSG team attends meetings of the All Wales Cancer Drugs Group (AWCDG), and the medical specialists representatives from the AWCDC and the cardiac network attend Steering Committee meetings to help prioritize potential appraisals.[60] The AWCDG acts as point of contact for clinical experts who contribute to new drug appraisals.[57]

Assessment

The AWMSG provides the committees with a confidential report detailing the products that are expected to be appraised during the following year.[59] After filtration /prioritization, the product enters the formal reimbursement appraisal process (full HTA) after which AWMSG formulates an advice. Positive AWMSG advice is binding for the NHS Wales, and health boards have a legal obligation to make funding available within three months of publication of ratified AWMSG advice.[61] The AWMSG conducted 163 appraisals between July 2003 and March 2013, of which 59% received a positive recommendation, 19% received a positive recommendation for 'optimized use', and 22% received a negative recommendation.[57]

Output

AWMSG disseminates a confidential report with details about the products that are expected to be appraised during the following year to the medicines and therapeutics advisory committees.

Key points from the Welsh HSS

- **Companies are obliged to fill out forms when a new drug is filed.**
- **No active identification, but identification through company request or scanning of other HSS databases in Great Britain.**
- **The Welsh HSS is embedded in the reimbursement process.**
- **It is complementary to the English system since it filters out products that are assessed in time by NICE.**
- **Information comes mostly from pharmaceutical companies through the initial submission form.**
- **Prioritization is rarely done.**

[ppp] Personal Communication from Caron Jones, All Wales Therapeutics and Toxicology Centre (2016)

APPENDIX 2. SCANNING AND SEARCHING RESOURCES FOR BIOLOGICALS, DRUGS AND OFF LABEL USE BY AHRQ

Resource name	Type	Biologicals	Drugs	Off-Label use
ACM TechNews	2,3,4,8			X
AdvaMed	2,3,4,5,8			X
Advances in Pharmacy ASHP Daily briefing	2,3		X	
AHA Ermerging Science Series	1	X	X	
AlphaGalileo	3	X	X	X
American laboratory	2,3,4,5,8	X		X
American Medical news	2,4,5			X
JAMA Internal Medicine	1,4,5,6,9	X	X	X
Aunt Minnie Insider	2,6,11			X
BioPhotonics	2,3,5,7,8	X		X
BizJournals	2,4,5,7	X	X	X
BMJ	1,2,4,5,6,7,9	X	X	X
Business Week	2,3,5,6	X	X	X
CADTH Health Technology Update & CADTH Issues in Emerging Technology	1,2,4,8	X	X	
CancerNetwork	1,2,6,8,9	X	X	X
Cardiology Today	1,2,4,8,9	X	X	X
Cardiovascular Update	1,2	X	X	X
Circulation	1,2,4,5,7,9	X	X	X
Clinica	2,4,6,8	X	X	X
Clinical care options	9,11	X	X	X
CMS Updates to Coverage	10	X	X	
CMS Updates to Coverage Pages	8,10	X	X	
Diabetes Technology & Therapeutics	1,4,5,7	X	X	X
Diagnostic Imaging	2,6,8,11			X

ECRI Institute Health Technology Forecast database	1,2,8,11	X	X	X
ECRI Institute Health Technology Trends	2,4,5,8	X	X	X
ECRI Institute Hotline Responses	1,4,8	X	X	X
EurekAlert!	3	X	X	X
European Radiology	1			X
F1000Posters	1	X	X	
FDA Advisory Committee alerts	12	X	X	
FDA Approval alerts	12	X	X	
FDA Drug Daily Bulletin	12		X	
FDA Orphan Drug Designation Database	12	X	X	
Fierce Markets Network	2,4,8,10	X	X	
Forbes	2,4,8	X	X	X
Fortune	2,4,8	X	X	X
The Gray Sheet	2,4,8			X
GenomeWeb	2,4,8	X		
Health Imaging & IT	2,4,11			X
Healthcare IT News	2,4,8,10			X
iHealthBeat	2,4			X
Imaging economics	2,3,4,8			X
In Vivo	2,4,8	X		X
International journal of Healthcare Technology and Management	1,11			X
JAMA	1,2,4,5	X	X	X
Journal of Clinical Psychiatry	1,2		X	X
Journal of Health Services Research and Policy	1,4	X	X	X
Journal of Medical Devices	1,2			X
Journal of Pediatrics	1	X	X	X
Kaiser Family Foundation publications	1,2,4,5	X	X	
LabMedicine	2	X		

Lancet	1,4,5	X	X	X
Managed Care	2,4,10	X	X	
MDLinx	1,2,11	X	X	X
MedGadget	2,3,4,6,8			X
Medical Device Daily	2,9,10			X
MedicalPhysicsWeb	2,4,5,6,8			X
Medpage Today (includes conference coverage)	2,4,5,6,9,11	X	X	X
Medscape	1,2,9,11	X	X	X
MIT Technology Review	2,4,5,6,7,8	X		X
Neurology	1,4,5	X	X	X
Neurosurgery	1,2			X
New England Journal of Medicine	1,2,4,5,7,9	X	X	X
NHS HTA publication update				X
Obesity	1,2,4,5		X	X
Oncology	1,2,4,5	X	X	X
Orthopedics	1,2,4,5	X	X	X
OrthoSuperSite.com	1,2,4,6,7,8,9	X	X	X
Pain Research and Management	1		X	X
Pharmacy & Therapeutics	1,2,8,10		X	
Pink Sheet	2,4,8		X	X
PLoS Medicine	1,2,4,6	X	X	X
PlosCurrents	1,4,5	X	X	
Psychiatric News	2,4,5,7		X	
Psychiatric Times	1,2,4,5,6,11		X	
Radiotherapy and Oncology	1,5	X		X
Start-up	2,8		X	X
TEC Assessments	1	X	X	
Telemedicine and e-Health	1,2,8			X

The New York Times	2,3,4,5,9	X	X	X
Theheart.org	2,3,4,5,9	X	X	X
Therapeutics Daily	2,8	X	X	X
UroToday	1,2	X	X	
Wall Street Journal	2,4,5,6,7	X	X	X

1. Original research and scientific reviews, 2. News, 3. Press Releases, 4. Commentary, 5. Editorial, 6. Blogs, 7. Letters, 8. Product information, 9. Education/CME, 10. Coverage Decisions, 11. Conference reports, 12. Regulatory

APPENDIX 3. DATABASES SEARCHED BY AHRQ

Resource	Biologics	Drugs	Off-label use
Embase	X	X	
EuroScan	X	X	
Healthcare News, current (Lexis-Nexis)	X	X	
PRNewwire	X	X	
PsycINFO	X	X	
PubMed/Medline	X	X	

APPENDIX 4. ADAPTED LIST OF SOURCES FOR IDENTIFICATION (AHRQ)

	Resource name	Price	Type of resource
1	FDA Approval alerts	Free	Alerts
2	CADTH Health Technology Update & CADTH Issues in Emerging Technology	Free	HSS output
3	Advances in Pharmacy ASHP Daily briefing	Free	Daily news
4	Cardiology Today	Free	Daily news
5	Clinical care options	Free	Daily news
6	EurekAlert!	Free	Daily news
7	GenomeWeb	Free	Daily news
8	M3 medical	Free	Daily news
9	Medpage Today (includes conference coverage)	Free	Daily news
10	Medscape	Free	Daily news
11	Pink Sheet	Free	Daily news
12	PlosCurrents	Free	Daily news
13	Psychiatric News	Free	Daily news
14	Psychiatric Times	Free	Daily news
15	UroToday	Free	Daily news
16	CancerNetwork	Free	Daily news
17	Fierce Markets Network	Free	Daily news
18	F1000Posters	Free	Database
19	FDA Orphan Drug Designation Database	Free	Database
20	NHS HTA publication update	Free	HTA report
21	ECRI HTA information services	Subscription	HTA services and alerts
22	Circulation	Subscription can be requested	Journal
23	Diabetes Technology & Therapeutics	$1,041	Journal
24	In Vivo	Free	Journal
25	Journal of Clinical Psychiatry	Online $136	Journal

26	Journal of Pediatrics	$277	Journal
27	Neurology	Price can be requested	Journal
28	New England Journal of Medicine	€188	Journal
29	Oncology	€ 3.571	Journal
30	Pain Research and Management	$295	Journal
31	PLoS Medicine	Free	Journal
32	Radiotherapy and Oncology	$517	Journal
33	JAMA Internal Medicine	subscription fee	Journal
34	BMJ	€168	Journal
35	JAMA	$3,973	Journal
36	Lancet	€ 212	Journal
37	Pharmacy & Therapeutics	Free	Journal
38	Cardiovascular Update (Mayo)	Free	Quarterly Newsletter
39	FDA Drug Daily Bulletin	Free	Daily news
40	EMA Human Medicines update	Free	Monthly newsletter
41	EMA What's new?	Free	Daily news
42	EMA's applications for centralised marketing authorisation (medicines under evaluations, positive opinion, negative opinions, re-evaluation, withdrawal)	Free	Database
43	EMA's Extensions of indication	Free	Database
44	EMA's Orphan designations	Free	Database
45	Adis database	Subscription	Database drugs in development
46	SCRIP	Subscription	Pharma Intelligence
47	Pharmaprojects	Subscription	Database drugs in development
48	Mednous	Subscription 360 euro	Monthly newsletter- investment focused

APPENDIX 5. EXAMPLE FOR AUTOMATION OF IDENTIFICATION PROCESSES

An automated search can make the HSS more efficient for several reasons. First, a system like DISQOVER could significantly improve, accelerate and simplify the identification process of new pharmaceuticals. Indeed, the system aggregates multiple relevant (public) data sources, diminishing the time spent on checking several websites/newsletters independently. In addition, private or licensed sources can be aggregated and linked to public sources in a private DISQOVER installation, resulting in data that is combined, compiled and enriched, making it more valuable.

Secondly, it could streamline the data collection process for each product by linking additional data sources about clinical evidence, pricing, … Even more, filters (for example pricing of clinical evidence) can be easily configured in DISQOVER and defined specifically for the purpose of the project, which might help to look fast for data (for example clinical stage) about a specific product in a range of data sources.

Thirdly, it can enhance the transparency and reproducibility of the searches: every search is stored and shareable with others. In addition, it will always have the most recent information, since new items that match the search are automatically added.

APPENDIX 6. QUESTIONNAIRE FOR IDENTIFICATION AID (ADAPTED FROM AHRQ)

Sets of questions are developed for those who analyse the sources to determine if an identified product is representing an intervention which is novel, innovative, relevant, or addresses a potentially important unmet need (adapted from AHRQ). The following set of questions is used:

- Is this a new molecular entity (drug) or Advanced Therapy Medicinal Products (ATMP or biological) developed for potential diffusion into EU AND in late Phase (3 or 4) clinical development or in Phase 2 clinical development with orphan or fast-track status designation by FDA/EMA?
- If so, select.
- (Rationale: New molecular entities may be a signal of a new class of interventions intended to address a potentially important unmet need.) Consider the following when answering this question:
- Is it subject to EMA/FDA approval?
- Is it not a generic drug or vaccine? If it is a generic product or a vaccine, do not select, because generic products and vaccines are outside remit

- Is this a late-phase human clinical trial of either an apparent novel intervention or a novel way to use an existing intervention, and is it capable of diffusing into the U.S. healthcare system within 3 years? If so, select. (Note: Animal and in vitro studies are excluded.) (Rationale: Clinical trials may signal a new research question, or unmet need, being studied. Clinical trials also examine interventions that are not subject to regulatory pathways, such as surgical procedures.) The additional questions below help to determine if this is the case and also inform the stage of development and expected time to adoption.
  - Has a trial been initiated or terminated?
  - Are late-phase results being reported?
- Does this appear to be a different/off-label use of an available drug, biologic, or device? If so, select. (Rationale: Off-label use may signal an attempt by the clinical community to address an unmet need that is not being pursued by developers or innovators.)
- Is this a different delivery mode for an existing drug or device? (Rationale: Changes in formulation (e.g., from injection administered by a clinician to an oral pill) or dosing regimens (e.g., from daily dosing to once-a-month dosing) are sometimes intended to address potentially important unmet needs, such as a need to improve patient adherence or access to a therapy.) If so, select.

  Is this being called an innovation AND is it in late phase development? If a developer refers to the intervention as an innovation, scanners may select it for further follow-up by an analyst to determine if it is truly innovative and addresses a potentially important unmet need.

APPENDIX 7. EXAMPLE OF A DATA COLLECTION FORM (SOURCE: NIHR HSRIC)

Pharmaceutical information proforma

The NIHR Horizon Scanning Research & Intelligence Centre (NIHR HSRIC) is funded by the National Institute for Health Research to provide advanced notice of health technologies and interventions that are likely to have a significant impact on patients and/or the NHS in the next 2 to 3 years. For more information on our methods and processes see www.hsric.nihr.ac.uk

- Please fill in as much information as possible in as many relevant boxes as possible. For some early developments we understand that there will be little information.
- Please use a **different proforma for each major patient group** for which the product is in late-stage clinical trials i.e. phase III, late phase II trials, or is later in the licensing or approval process.
- Please mark in the last column any rows with **commercially confidential or sensitive information** giving more details in the associated text box.

Date:		Name:	
Organization:		Position in company:	
Telephone:		Email:	
Address:			

Technology description	Confidential information
Generic name.	
Brand name(s), synonyms and/or code names.	
Patient group and/or indication including stage of disease and targeted patient sub-groups. e.g. advanced or metastatic disease in women with HER-2 positive breast cancer	
Place in the treatment pathway - e.g. first-line, second-line.	
Brief description of the product, including therapeutic or pharmacological action.	
Is it a new class of drug?	
Intended use of the product - e.g. prevention; treatment.	
Route of administration e.g. oral, subcutaneous, intravenous (short or infusion)?	
Treatment schedule and /or combination - e.g. once a day, twice a day, days 1-5 in a 28 day cycle.	
Is the new product planned to be additional to current therapy or used as a substitute?	
Is the product already available for a different patient group?	
Who are the commercial developers and/or distributors?	

Stage of development, availability, and licensing and launch plans	Confidential information
Does the product have an EMA or MHRA marketing authorization in a different patient group/s?	
When do you anticipate submitting a marketing authorization application (MAA)?	
When do you anticipate receiving a marketing authorization (MA)?	
Is your product a designated orphan drug in the EU or USA?	
Is your product available, licensed or launched in the USA, Canada or Australia? If not do you have licensing plans for these countries?	

Current alternatives	Confidential information
What are the current treatment or management options for the patient group?	
What advantages does the new product have over current options? e.g. innovation, new route of administration, fewer adverse effects, shorter length of stay, fewer infections etc.	
Is there any evidence of a variation in access to current alternatives?	

Costs	Confidential information
What is the cost per treatment or per unit of administration and/or estimated cost over a specified time period?	
Are there additional costs related to your product? e.g. intravenous administration, days in hospital, monitoring tests	
What is the cost of current treatment or other management options for this patient group?	

Clinical need, burden of disease	
What is the burden of disease in England and Wales (or the UK)? e.g. number of patients and sub-groups; and related mortality, morbidity, service use and quality of life. Please give references to any key epidemiological studies.	
Estimated potential uptake of the technology amongst the relevant patient group or healthcare professionals.	
Are there likely to be any barriers to diffusion of the technology in the NHS in England and Wales?	

Research evidence
Published clinical trials. Please list references, and attach copies of relevant publications and abstracts from publications or conferences that are not readily available on the Internet.
Unpublished completed clinical trials. Please give details of the following, and/or attach copies of protocols, press releases and abstracts • trial number/name • location • trial funders, sponsors • study design • inclusion and exclusion criteria • treatment arms • length of follow-up • primary and secondary endpoints • numbers of patients in trial • start date • date of full patient accrual • date of interim analysis • expected date of final analysis or publication • results
Ongoing clinical trials. **Please give details of the following, attaching copies of protocols, press releases and abstracts** • trial number/name • location • trial funders, sponsors • study design • inclusion and exclusion criteria

- treatment arms
- length of follow up
- primary and secondary endpoints
- planned patient numbers
- start date
- anticipated date of full patient accrual
- expected date of interim analysis
- expected date of final analysis or publication

What is the potential or intended impact of the technology (speculative)?

Copy this symbol ☑ to the relevant boxes

Patients

□ Reduced morbidity	□ Reduced mortality or increased survival	□ Improved quality of life for patients or carers
□ Other, please specify:		

Services

□ Increased use e.g. length of stay, out-patient visits	□ Service re-organization required	□ Staff or training needs
□ Decreased use e.g. shorter length of stay, reduced referrals	□ Services – other, please specify	

Costs

□ Increased unit cost compared to alternative	□ Increased - more patients coming for treatment	□ Increased - capital investment needed
□ New costs, please specify:	□ Savings, please specify:	□ Other, please specify:

APPENDIX 8. PARAMETERS TO INCLUDE IN THE DATABASE

General	Regulatory affairs & market entry	Technology description	Innovativeness	Burden of disease	Dosage
Product name (brand + INN)	Development stage at identification	(novel) Indication	Level of innovation (new, add-on, substitute,..)[1]	Incidence (per country)	Dosage per treatment
Therapeutic area[2]	Current development stage	Type of innovation[3]	What advantages does the new product have over current options?	Prevalence (per country)	Frequency of treatment
Lead source	Orphan drug status (US or EU or both)	Approved indication(s) (+date)		Description of possible existing pharmaceutical gap[4]	Length of treatment[5]
Lead status	Fast track status (US or accelerated approval EU) / other status (IM in the UK or ATU in France)	Possible future off-label use		% percentage of patients currently treated in relation to the prevalence / incidence	Total dosage per patient
Last record edit date	Expected CHMP opinion date	Type of medicine[6]		Volume of patients per treatment line, e.g. x in first, y in second, z in third and so on	
Developer + Licenser	Expected market authorization date (FDA & EMA)	Mechanism of action			
	Expected market launch date/quarter (Per country)	Route of administration			
	Likeliness to be further developed	Combination therapy			
		Expected place in therapy			
		Comparator(s)			

[1]Type of innovation: new compound, new combination, new indication, new formula, new route of administration, orphan drug);
[2] Classification of drug in therapeutic areas (see list in xxx) to facilitate data collection;
[3] new, add-on, substitute, more effective or safer than existing drugs; mere pharmacological innovation, i.e. drugs with better kinetics or new mechanism of action; mere technological innovation, i.e. a new chemical or biotechnological product with therapeutic role similar to already existing ones;
[4] Pharmaceutical gap means drugs for diseases without recognized standard treatment, the delivery mechanism or formulation is not appropriate for the target patient group, subsets of patients are less responsive to marketed drugs; or when an effective medicine either does not exist or is not sufficiently effective;
[5] Average treatment time is preferred, if not available median treatment time or if that not available median time to progression;
[6]Type of medicine: biological, antibody, small molecule, biosimilar, combination

Clinical	Landscape	Country specific	Trials
Expected impact on QOL (expert, company, literature)	Other similar products: current Standard of Care or other treatment alternatives	Unmet medical need (+ area)	Trial references: • finalized trials • published trials • ongoing trials • planned trials
Expected impact on life expectancy (expert, company, literature)	Competitors in development	Relevant guidelines	Short description of available results of clinical trials
Expected impact on inconvenience (expert, company, literature)	Variation in access of current alternatives	Inpatient/outpatient status	
Expected impact on safety (expert, company, literature)		Expected reimbursement appraisal/HTA (yes/no and when possible expected date)	
		Patients in treatment group	
		Potential off-label use	
		Annual uptake (for example first 3 years)	
		Barriers for entering market	

[1] *if infusion, assumption about weight to be included, e.g. average patient of 80 kg*

APPENDIX 9. DATA COLLECTION FORM

Pharmaceutical information collection form

This form is used to collect relevant product information from the manufacturers for the horizon scanning (HS) exercise.

The goal of the horizon scanning exercise is to provide key Belgian policy-makers and research funders with advance notice of health technologies and interventions that are likely to have a significant impact on the Belgian health care system within the coming 2 to 4 years. Information held by the horizon scanning group (HS group) is used to provide advice to designated national policy-makers responsible for planning or supporting their introduction into the health care system. For more information on the project see https://kce.fgov.be/nl/study-program/studie-2015-57-hsr-methodologie-voor-horizon-scanning.

The current form is a test form based on the "Pharmaceutical information proforma" from the English Horizon scanning system (National Institute for Health Research: Horizon Scanning Research & Intelligence Centre (NIHR HSRIC)). According to the experiences in the test phase, the form might be adapted. *The information provided by the companies in this form will thus not be used by any policy-maker.*

- Please fill in as much information as possible in as many relevant boxes as possible. For some early developments we understand that there will be little information.
- Please use a **different proforma for each major patient group** for which the product is in late-stage clinical trials i.e. phase III, late phase II trials, or is later in the licensing or approval process.
- Please mark in the last column any rows with **commercially confidential or sensitive information** giving more details in the associated text box.

Date:		Name:	
Organization:		Position in company:	
Telephone:		Email:	
Address:			

Technology description	Description	Confidential information
Generic name.		
Brand name(s), synonyms and/or code names.		
Patient group and/or indication including stage of disease and targeted patient sub-groups. e.g. advanced or metastatic disease in women with HER-2 positive breast cancer		
Place in the treatment pathway - e.g. first-line, second-line.		
Brief description of the product, including therapeutic or pharmacological action.		

Is it a new class of drug?	
Intended use of the product - e.g. prevention; treatment.	
Route of administration e.g. oral, subcutaneous, intravenous (short or infusion)?	
Treatment schedule and /or combination - e.g. once a day, twice a day, days 1-5 in a 28 day cycle.	
Is the new product planned to be additional to current therapy or used as a substitute?	
Is the product already available for a different patient group?	
Who are the commercial developers and/or distributors?	

Stage of development, availability, and licensing and launch plans	Description	Confidential information
What is the current stage of development? Pre-clinical, phase I, II, III, others?		
Does the product have an EMA or MHRA marketing authorization in a different patient group/s?		
When do you anticipate submitting a marketing authorization application (MAA)?		
When do you anticipate receiving a a CHMP opinion or marketing authorisation (MA)?		
Is your product a designated orphan drug in the EU or USA?		
Does your product has any other fast track status or particular regulatory status in the EU or USA?		
Is your product available, licensed or launched in the USA, Canada or Australia? If not do you have licensing plans for these countries?		

Current alternatives	Description	Confidential information
What are the current treatment or management options for the patient group?		
What advantages does the new product have over current options? e.g. innovation, new route of administration, fewer adverse effects, shorter length of stay, fewer infections etc.		
Is there any evidence of a variation in access to current alternatives?		

Costs	Description	Confidential information
What is the cost per treatment or per unit of administration and/or estimated cost over a specified time period.		
Are there additional costs related to your product? e.g. intravenous administration, days in hospital, monitoring tests		
What is the cost of current treatment or other management options for this patient group?		

Clinical need, burden of disease	Description	Confidential information
What is the burden of disease in Belgium? e.g. number of patients and sub-groups; and related mortality, morbidity, service use and quality of life. Please give references to any key epidemiological studies.		
Estimated potential uptake of the technology amongst the relevant patient group or healthcare professionals.		
Are there likely to be any barriers to diffusion of the technology in Belgium?		

Research evidence	Description	Confidential information
Published clinical trials. **Please list references, and attach copies of relevant publications and abstracts from publications or conferences that are not readily available on the Internet.**		
Unpublished completed clinical trials. **Please give details of the following, and/or attach copies of protocols, press releases and abstracts** • trial number/name • location • trial funders, sponsors • study design • inclusion and exclusion criteria • treatment arms • length of follow-up • primary and secondary endpoints • numbers of patients in trial • start date • date of full patient accrual • date of interim analysis • expected date of final analysis or publication • results		
Ongoing clinical trials. **Please give details of the following, attaching copies of protocols, press releases and abstracts** • trial number/name • location • trial funders, sponsors • study design • inclusion and exclusion criteria • treatment arms		

- length of follow up
- primary and secondary endpoints
- planned patient numbers
- start date
- anticipated date of full patient accrual
- expected date of interim analysis
- expected date of final analysis or publication

What is the potential or intended impact of the technology (speculative)?

Copy this symbol ☑ to the relevant boxes

Clinical Impact

□ Reduced morbidity	□ Reduced mortality or increased survival	□ Improved quality of life for patients or carers
□ Other, please specify:		

Services impact

□ Increased use e.g. length of stay, out-patient visits	□ Service re-organization required	□ Staff or training needs
□ Decreased use e.g. shorter length of stay, reduced referrals	□ Services – other, please specify	

Costs impact

□ Increased unit cost compared to alternative	□ Increased - more patients coming for treatment	□ Increased - capital investment needed
□ New costs, please specify:	□ Savings, please specify:	□ Other, please specify:

Please return to the HS group member who requested this information, or email to XXX or phone: XXX

APPENDIX 10. COMPARISON OF DATA COLLECTED BY COMPANY

The parameters included in the data collection form can be found in the first column. The second column consists of a code if:

- S: the information provided by the company is **similar to** the information gathered through a literature scan
- N: the information provided by the company is **new** compared to the information gathered through a literature scan
- D: the information provided by the company is **different** compared to the information gathered through a literature scan
- A: the information provided by the company is **additional** to the information gathered through a literature scan
- M: the information provided by the company is **missing** compared to the information which was gathered through a literature scan

Different information

- Place in therapy: for one of the two products, the database included only 'second line', the company mentioned that it will apply for approval for both first and second line. The other product had 'more than three lines in the database', and more than two lines in the data collection form completed by the company.

Additional information

- Additional information was given by the companies during the meetings for the parameters related to effectiveness (related to performed, but unpublished trials).
- More details on (planned) EMA submission dates can only be obtained from the company, unless the submission was already done or the information was available from their website.

Lack of information

- Information missing was the costs per unit for the new treatment.

New information

- The data collection form of only one product included very specific data on the uptake of the product.
- Annual product cost estimates were given for one of the two products only, but needed to be treated confidentially.

Technology description	Product 1	Product 2
Generic name (Brand name(s), synonyms and/or code names.)	A	S
Patient group and/or indication including stage of disease and targeted patient sub-groups.	A	S
Place in the treatment pathway	D	D
Brief description of the product, including therapeutic or pharmacological action.	A	S
New class of drug	S	S
Intended use of the product	S	S
Route of administration	S	S
Treatment schedule and /or combination	S	N
Additional to current therapy or substitute?	A	N
Already available for a different patient group	S	S
Commercial developers and/or distributors	S	S

Stage of development, availability, and licensing and launch plans	Product 1	Product 2
Current stage of development	S	S
EMA or MHRA marketing authorization in a different patient group	S	S
Date of marketing authorization application (MAA)	D	S
Date of CHMP opinion or marketing authorisation (MA)	S	S
Orphan drug in the EU or USA	S	S
Fast track/other status	S	S
Is your product available, licensed or launched in the USA, Canada or Australia? If not do you have licensing plans for these countries?	S	S

Current alternatives	Product 1	Product 2
Current treatment	D	A
Advantages over competition	A	A
Variation in access	N	N

Costs	Product 1	Product 2
Cost per treatment or per unit of administration and/or estimated cost over a specified time period.	M	N
Additional costs	S	S
Costs of current treatment	N	N

Clinical need, burden of disease	Product 1	Product 2
Burden of disease in Belgium	N	D
Potential uptake of the technology	S	N
Barriers to diffusion of the technology in Belgium?	S	N

Research evidence	Product 1	Product 2
Published clinical trials. **Please list references, and attach copies of relevant publications and abstracts from publications or conferences that are not readily available on the Internet.**	M	A
Unpublished completed clinical trials. **Please give details of the following, and/or attach copies of protocols, press releases and abstracts** • trial number/name • location • trial funders, sponsors	M	A

• study design • inclusion and exclusion criteria • treatment arms • length of follow-up • primary and secondary endpoints • numbers of patients in trial • start date • date of full patient accrual • date of interim analysis • expected date of final analysis or publication • results		
Ongoing clinical trials. **Please give details of the following, attaching copies of protocols, press releases and abstracts** • trial number/name • location • trial funders, sponsors • study design • inclusion and exclusion criteria • treatment arms • length of follow up • primary and secondary endpoints • planned patient numbers • start date • anticipated date of full patient accrual • expected date of interim analysis • expected date of final analysis or publication	M	A

APPENDIX 11. EVALUATION FORMS

Appendix 11.1. Stakeholder's evaluation form

Thank you for participating in the feasibility exercise for the KCE study for a methodology for a horizon scanning system (https://kce.fgov.be/nl/study-program/studie-2015-57-hsr-methodologie-voor-horizon-scanning). The data collection form was selected to aggregate information about new and emerging pharmaceuticals. As part of the process, we contacted you to get information about a new and emerging pharmaceuticals.

The experiences and input of the stakeholders are highly valued. This evaluation form is made to collect your views on the process and the data collection. We kindly ask you to fill out the form in order to help to optimize the methodology for horizon scanning. The information provided will be only used in an anonymous manner. Thank you for your cooperation!

Date:		Name:	
Organization:		Position in company:	
Telephone:		Email:	
Address:			

Description of the drug

The information on a drug identified by the HSS is collected in the filtration form.

1. Was all necessary information provided? If no, please elaborate.

Criteria

2. Would you exclude one or more of the criteria mentioned in the data collection form? If yes, please elaborate which you would exclude.

3. Do you have additional criteria that should be covered in the data collection form?

4. Which data is most likely to differ between the countries?

Process

5. What is your opinion about the stakeholder meeting and data collection?

6. How could the process of horizon scanning be optimized in the context of an international collaboration between the Netherlands/ Belgium/ Austria and Luxemburg?

7. Do you think company offices on a European level could have a role in the (country-specific) data collection or should national subsidiaries be directly contacted?

8. Additional Comments :

Please return to the HS group member who requested this information, or email to XXX or phone: XXX

Appendix 11.2. Experts input evaluation form

Thank you for participating in the feasibility study for the KCE study for a methodology for a horizon scanning system (https://kce.fgov.be/nl/study-program/studie-2015-57-hsr-methodologie-voor-horizon-scanning). The collection form was selected to aggregate information about new and emerging pharmaceuticals. As part of the process we contacted you to get information about a new and emerging pharmaceuticals.

The experiences and input of the stakeholders are valued highly. This evaluation form is made to collect your view on the process and the data collection.

Please fill in the general information below – and answer the questions on the next page. Thank you for your cooperation!

Date:		Name:	
Organization:		Position in company:	
Telephone:		Email:	
Address:			

Description of the drug

The available information on a drug identified by the HSS is shortly described in the collection form.

1. Was all necessary information provided? If no, please elaborate.

Criteria

2. Would you exclude one or more of the criteria mentioned in the data collection form? If yes, please elaborate which you would exclude.

3. Do you have additional criteria that should be covered in the data collection form?

4. Which data is most likely to differ between the countries?

Process

5. What is your opinion about the stakeholder meeting and data collection?

6. What is your view on the international collaboration between the Netherlands/ Belgium/ Austria and Luxemburg on horizon scanning and possibly price negotiations?

7. Do you think international medical societies could have a role in the country-specific data collection or should national medical societies be directly contacted?

8. Additional Comments :

Please return to the HS group member who requested this information, or email to XXX or phone: XXXX

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