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EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

Horizon Scanning, Topic Identification, Selection and Prioritisation for European cooperation on HTA

- Draft recommendations

Developed by Work Package 4 Joint production of Health technology assessments WP4
Lead Partner: NIPHNO

VERSION LOG

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NIPHNO= Norwegian Institute of Public Health, QA template = Question & Answer template (see Appendix 1) *This document; **Planned

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Aims

This report has been prepared by the European network on Health Technology Assessment (EUnetHTA) Joint Action 3 (JA3) work package 4 (WP4) to provide:

- draft recommendations for a horizon scanning system (HSS) to serve European joint and collaborative HTA activities beyond 2020
- a work flow for topic identification, selection and prioritisation (TISP) to support activities within EUnetHTA JA3 WP4
- recommendations for a pilot of the WP4 TISP

The pilot is scheduled for September to December 2018. Experiences from the TISP pilot will be used to refine the EUnetHTA JA3 WP4 TISP workflow and inform the final recommendations on HSS beyond 2020.

The task is part of EUnetHTA JA3 WP4 deliverables coordinated by the WP4 lead partner the Norwegian Institute of Public Health (NIPHNO).

Content

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Acronyms – Abbreviations

AGENAS The national Agency for regional health services (Agenzia nazionale per i servizi sanitari regionali), Italy
AISBL An international non-for profit organisation (a specific type of legal entity: L'Association Internationale Sans But Lucratif)
AIFA, Italian Medicines Agency, Italy
Avalia-t, Galician Agency for HTA Spain
AQuAS, Agència de Qualitat i Avaluació Sanitàries de Catalunya (the Catalan Agency for Health Information, Assessment and Quality), Spain
CADTH, Canadian Agency for Drugs and Technologies in Health, Canada
CE Conformité Européenne (European Conformity)
DPA/MEH, Directorate for Pharmaceutical Affairs Ministry of Health, Malta
ECPM, Switzerland
EOF, National Organization for Medicines, Greece
EA Early Awareness
EC European Commission
ED Early Dialogue
EKAPTY NKUA, National and Kapodistrian University of Athens, Greece
EMA European Medicines Agency
EU European Union
EUDAMED European Database on Medical Devices
EUnetHTA European Network for Health Technology Assessment European Network for Health Technology Assessment
EuroScan The International Information Network on new or emerging, appropriate use and re-assessment needed Health Technologies (EuroScan International Network)
FDA Food and Drug Administration (USA)
GOG, Gesundheit Österreich GmbH/Geschäftsbereich, Austria
HIQA, Ireland HAS National Authority for Health, France (Haute Autorité de Santé)
HSS Horizon Scanning System
HTA Health Technology Assessment
HTAi HTA international
HTAi IG DEA HTAi Interest Group on Disinvestment and Early Awareness
HTAi PF HTAi Policy Forum
INFARMED, National Authority of Medicines and Health Products Portugal
IVD In-Vitro-Diagnostic
JAZMP, Public Agency of the Republic of Slovenia for Medicinal Products and Medical Devices Slovenia
NIPHB, Institutu National De Sanatate Publica (INSP) Romania
NOMA, Norwegian Medicines Agency
JA Joint Assessment
JA3 Joint Action 3
KCE Belgian Health Care Knowledge Centre
LBI-HTA Ludwig Boltzmann Institute for Health Technology Assessment
MAH Marketing Authorisation Holder (pMAH prospective MAH)pMAH prospective MAH)
MD Medical Device
MoH Ministry of Health
NET New and Emerging Technologies
NHS National Health Service (England)
NICE National Institute for Health and Care Excellence (England)
NIHR National Institute for Health Research
NIHR HSRIC Horizon Scanning Research & Intelligence Centre (England)

NIHR-IO NHIR Innovation Observatory (England)
NIPHNO The Norwegian Institute of Public Health
NSPHMPDB, National School of Public Health Management and Professional Development Bucharest, Romania
OT Other Technologies
Osteba, Basque Office for Health Technology Assessment- Ministry for Health, Spain
P Pharmaceuticals
PICO Population/Intervention/Comparator/Outcomes
PLEG Post Launch Evidence Generation
POP Planned and Ongoing Projects
QA Question Answer
REA Relative effectiveness assessment
RER, Regione Emilia-Romagna Italy
SFOPH/SNHTA, Swiss Network for HTA Switzerland
SOP Standard Operating Procedure
SPS Specialist Pharmacy Service
TISP Topic Identification, Selection and Prioritisation
UBB Babeș-Bolyai University, Romania
UCSC Università Cattolica del Sacro Cuore, Italy
WG Working Group
WP Work Package
ZIN National Health Care Institute (Zorginstituut Nederland)

Glossary

Joint assessments: EUnetHTA Joint Assessments (JA) are health technology assessments jointly produced by at least four EUnetHTA partners in different European countries. EUnetHTA processes, guidelines and the HTA Core Model® are used for the production of assessments that are subject to extensive review procedures in order to ensure high quality. JAs are centrally coordinated by the WP4 Co-Leads and comprise a broad stakeholder involvement, including the use of a EUnetHTA submission file in addition to a scoping (e-)meeting with industry (1).

Collaborative assessments: EUnetHTA Collaborative Assessments (CA) are primarily produced in non-pharmaceutical technologies. They only differ from the EUnetHTA JAs with regard to coordination, i.e. the project management is performed in a decentralised manner by WP4 Co-Lead and WP4 Activity Centre Department Leads. In CAs, the use of submission file and scoping (e-) meeting with industry are optional. CAs should facilitate timelines that are aligned with national work programs and should contribute to the sustainability of assessment production after 2020 due to decentralised coordination (1).

Developer: Used in this document for industry, manufacturer or any other parties developing a technology. This may include both commercial and non-commercial developers. Commercial developers holding regulatory approval are also named marketing authorisation holder (MAH) or prospective marketing authorisation holder (pMAH) in this document.

Disruptive innovation/technology: An innovation that improves a product or service in ways that the market does not expect, typically first by designing for a different set of consumers in a new market and later by lowering prices in the existing market (2).

Emerging technology: A health technology that has not yet been adopted within the health care system. Pharmaceuticals are in the Phase II or III clinical trial, or pre-launch stage; medical devices are in the pre-marketing stage (2).

Health technology: An intervention developed to prevent, diagnose or treat medical conditions; promote health; provide rehabilitation; or organize health care delivery. The intervention can be a test, device, medicine, vaccine, procedure, program or system (3).

Horizon Scanning: The systematic identification of health technologies that are new, emerging or becoming obsolete and that have the potential to effect health, health services and/or society. Related terms include early awareness and alert system (3).

Innovative health technology: A common definition of what constitutes an 'innovative health technology' is currently lacking. From a public health perspective, the level of innovativeness of a health technology is primarily defined by the benefits it generates for patients. These can be in the therapeutic, clinical or quality of life domains, but also in the socioeconomic domain(2).

New technology: A health technology that is in the launch, early post-marketing, or early diffusion stages(3).

Obsolete technology: A health technology that is no longer the standard of care or whose clinical benefit, safety or cost-effectiveness has been superseded by available alternative technologies (3).

Prioritisation: The assignment of an order of priority based on explicit or implicit criteria for selection of health technologies for assessment (2). Application of specific criteria to the selected/filtered

technologies with the purpose of retaining for assessment the technologies with greater impact and according to the system's/network's capacity for assessment (4).

Selection/filtration: Application of a set of pre-defined criteria to the identifies technologies, in order to retain the technologies relevant to the pre-determined technology scope and time frame[1] (Adaptation from EuroScan toolkit(4), time frame added).

Stakeholder: Stakeholder may refer to an accountant, group, organization, member, or system that affects or can be affected by an organization's actions (Wikipedia). In this case, we consider stakeholders to include regulators, patients and consumers, payers, healthcare professionals (experts and as well as other healthcare professional) and developers (industry, researchers and any other commercial or non-commercial developers of health technology) as well as those holding or applying for market authorisation, or those that in other ways have rights connected to the use of the technology or will be impacted by the use of the technology. Stakeholders could both be individuals or represented by organisations.

Unmet need: A common definition of what constitutes an unmet need is currently lacking (2). In the HTAi Policy Forum (HTAiPF) background paper on Horizon Scanning (2) references for the following have been provided: Unmet need can be defined as a condition whose treatment or diagnosis is not adequately addressed by an available therapy or diagnostic. Addressing unmet need has been defined as: If it (the intervention) has an effect on a serious outcome of the disease or condition that is not known to be influenced by available therapy; has a benefit for patients who are unable to tolerate the available therapy or whose disease has failed to respond to available therapies; provides effectiveness similar to available therapies, while avoiding serious harm that can occur with available therapies.

Transformative technology: We have found no clear definition of transformative technology, but the expression is often used in connection with horizon scanning. We have in the context of this report defined a transformative technology as: a technology that may have large impact on patient health status or health care systems, and transform the way care is provided.

Relative effectiveness assessment (REA): Relative effectiveness assessment can be defined as the extent to which an intervention does more good than harm, compared to one or more intervention alternatives for achieving the desired results when provided under the usual circumstances of health care practice(5).

Executive summary

The aim of this document is to provide draft recommendations for a horizon scanning system (HSS) to serve the European HTA network beyond 2020, and to provide a workflow for topic identification selection and prioritisation (TISP) for EUnetHTA JA3 WP4 activities. A question answer (QA) approach adapted from the EuroScan Toolkit was used to provide 13 recommendations, most importantly we (the working group) recommend:

- to establish a cooperative HSS following standard operational procedures (SOPs) and a coordinating secretariat to act at the central level of the system. Cooperation with existing HSS, HS initiatives and scientific networks should be explored to avoid duplication of work
- that the purpose of the HSS should be to support planning, timeliness and relevance of the HTA network's activities in a technology lifecycle perspective
- that the target of the HSS should be those planning and prioritising HTA activities at any level of the network, including individual HTA agencies and stakeholders
- to at least start with pharmaceuticals (medicinal products), medical devices (MDs) and in vitro diagnostics (IVDs), with possibilities of further extension to any potential high impact (innovative), transformative or disruptive technologies as well as obsolete technologies with the focus being on patient needs
- to deliver minimal data-sets for monitoring, and filtration of identified technologies according to pre specified selection criteria and more comprehensive datasets for planning and prioritisation according to pre specified prioritisation criteria

Furthermore, the working group recommends to perform a TISP pilot restricted to pharmaceuticals, MDs and IVDs and EUnetHTA JA3 WP4 activities (mainly early rapid REA). The purpose of the pilot should be to explore:

- cooperation with existing HSS and networks
- WP4 partners' ability to share information from national TISP processes
- stakeholder involvement
- the use of selection and prioritisation criteria

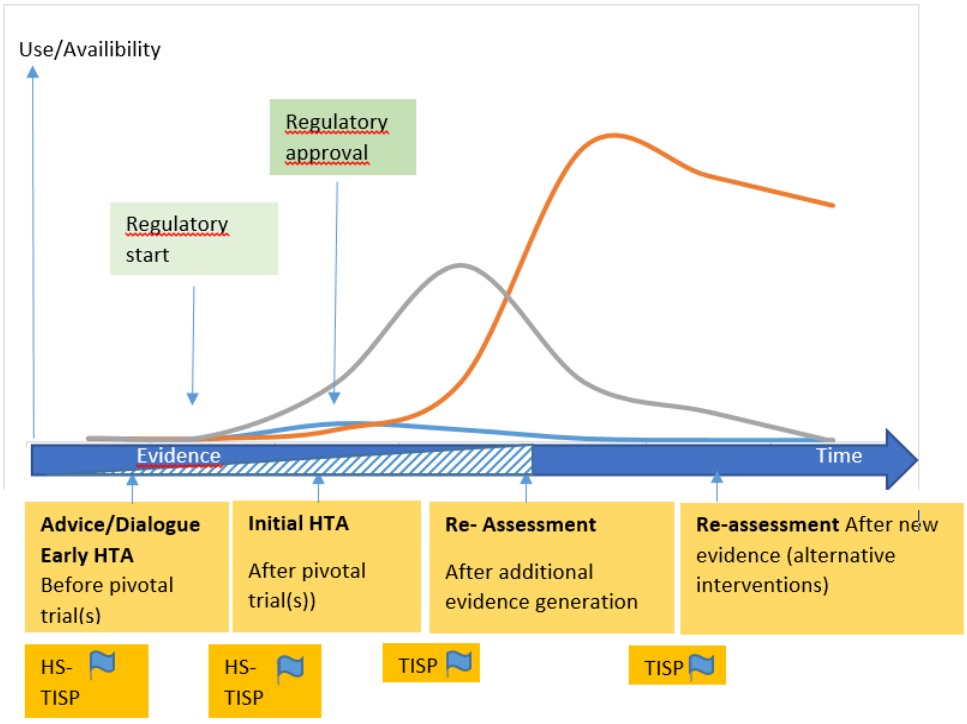
Experiences from the pilot will further guide EUnetHTA WP4 TISP procedures, and will be used to inform the final recommendations planned to be available by July 2019.

Introduction

Horizon Scanning

Horizon scanning (HS) needs to be defined depending on its purpose. According to the Health Technology Assessment (HTA) Glossary (3) HS is: "The systematic identification of health technologies that are new, emerging or becoming obsolete and that have the potential to effect health, health services and/or society». This definition has been adapted from the EuroScan International Network (4) and opens for a broad purpose with regard to cooperation on HS to support HTA as well as HTA related activities in a technology life cycle perspective (figure 1). The main use of HS systems (HSS) in relevance to HTA has been topic identification, selection[2], and prioritisation[3] (TISP) for the purpose of assessing new technologies. These assessments have typically been used to inform reimbursement decisions and clinical guidelines. In this context, HSS are also referred to as Early Warning Systems (EWS), Early Awareness Systems (EAS) or Alert Systems (AS) (2;4;6;7).

Figure 1 *Time points for Horizon Scanning (HS) and Topic Identification, Selection and Prioritization (TISP) to serve Health Technology Assessment (HTA) related activities in a technology lifecycle perspective*



HTA= Health technology assessment, HS= Horizon Scanning, TISP= Topic Identification, Selection and Prioritisation

Existing HSS typically aim at increasing timeliness and relevance of the activities they support. The systems share similarities in that they go through processes of TISP. However, they will differ in

[2] Selection or filtration is the process used to ensure that the identified technology is within in the scope of the HSS. Identified technologies that are not within the scope of the HSS will not be part of the selected data-set.
[3] Prioritisation is the process used to prioritise between technologies that are within the scope of a HTA activity.

terms of size, resources, operational level, mandate, customers, and organisational embedding. Therefore there are, and will be substantial differences in methodology, timeframe, output and criteria for prioritisation. The most obvious difference is that HSS serve different customers or target groups and therefore need to prioritise and select different technologies (2;6). The activity to be supported by a HSS may also vary, and as technology adoption is a major driver of health expenditure growth, engaging in cooperative HS and HTA activities has recently been promoted as means to directly support procurement processes not only re-imbursement decisions (2;5;7-9). In addition, early dialogue (ED) with developers, planning and post launch evidence generation (PLEG) as described in the EUnetHTA JA3 work plan (10) and identification of obsolete technologies (11-13) as well as the monitoring of incorporated technologies (14) could benefit from an HSS.

Proposed European Regulation on HTA

On the 31th of January 2018 the European Commission (EC) published a proposed regulation on HTA (15). The proposed regulation provides the basis for a permanent and sustainable cooperation (on HTA) at the EU level, beyond 2020. Four main pillars of HTA activities are covered by the proposal:

- joint clinical assessments
- joint scientific consultations whereby developers can seek advice from HTA authorities
- early identification of promising emerging health technologies
- continuing voluntary cooperation in areas not covered by joint clinical assessments

According to the proposal, individual EU countries will continue to be responsible for assessing non-clinical (e.g. economic, social, ethical) aspects of health technologies, and making decisions on pricing and reimbursement.

In the proposal, joint clinical assessments are limited to:

- *medicinal products undergoing the central marketing authorisation procedure, new active substances and existing products for which the marketing authorisation is extended to a new therapeutic indication (line extensions)*
- *certain classes of medical devices (MDs, class IIb and III) and in vitro diagnostic medical devices (IVDs, class D) for which the relevant expert panels established in accordance with Regulations (EU) 2017/745 and 2017/746 have given their opinions or views and which have been selected by a Coordination Group based on the following criteria:*
    - *unmet medical need*
    - *potential impact on patients, public health, or healthcare systems (e.g. burden of disease, budget impact, transformative technology)*
    - *significant cross-border dimension*
    - *Union-wide added value (e.g. relevance to a large number of Member States)*
    - *the resources available to it*

HS is mentioned in the proposal in connection with identification of emerging technologies and it is stated that input from cooperative HS will help develop annual work programmes, and facilitate the prioritisation of technologies that are to be retained for joint activities. However, there are no clear recommendations on how a HSS may be built up, sized or maintained. The recommendations for a HSS in this document are for an HSS integrated with the EU proposal for joint assessment as well as continued voluntary collaboration in areas not covered by the joint assessments. The draft recommendations provided in this document cover the TISP process to be performed before the joint assessment, but do not cover any aspects of assessments.

EunetHTA JA3

To support cooperation between HTA bodies, the European Union (EU) has invested in scientific and technical cooperation by supporting the voluntary EUnetHTA network through one project (2006-2009) and three Joint Actions, of which the third, EUnetHTA Joint Action 3 (JA3) runs until 2020. Participants (partners) of JA3 are non-for-profit agencies that produce or contribute to the production of HTA from all EU Member States, as well as Switzerland and Norway (10).

EUnetHTA JA3 aims to define and implement a sustainable network on HTA cooperation in Europe. Specific objectives are:

- to increase production of high-quality joint and collaborative work on HTA (WP4)
- to increase uptake and implementation of joint work at the national, regional, and local level (WP7)
- to support life cycle approach to improve evidence generation (WP5)

Currently, there is no HSS in place within EUnetHTA . Activities are initiated in slightly different ways:

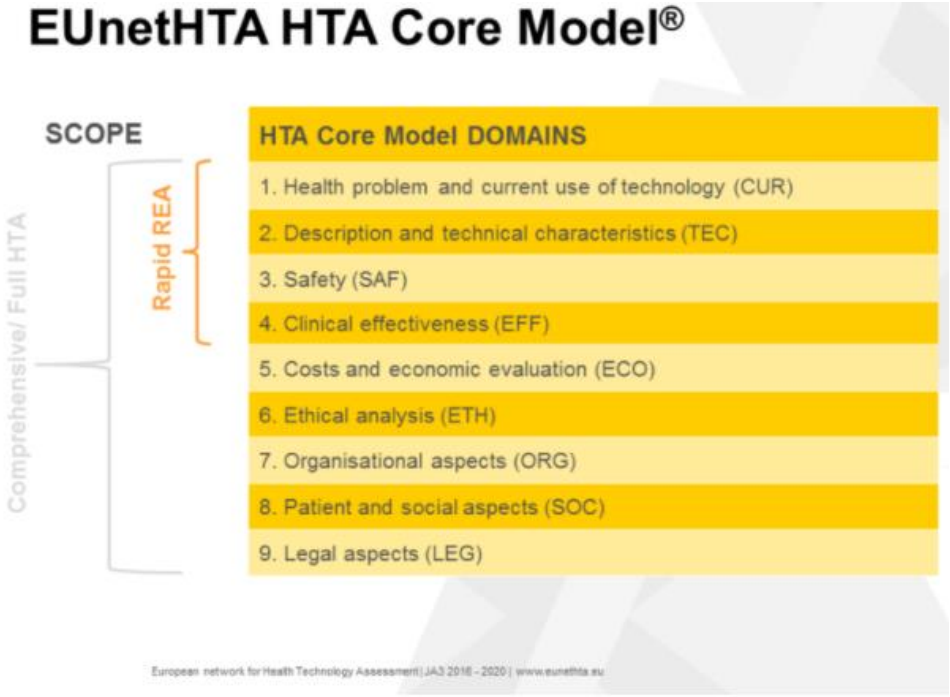
Assessments within EUnetHTA JA3 WP4

Assessments are coordinated by EUnetHTA JA3 WP4 and performed by WP4 partners as:

- joint assessments (pharmaceuticals, MDs and IVDs)
- collaborative assessments (OTs including, but not restricted to MDs and IVDs)

Most assessments are based on the HTA Core model (figure 2), focusing mainly on the first four domains (rapid REA).

Figure 2 *EUnetHTA Core Model*



From www.eunethta.eu

Initiation and coordination of assessments of **pharmaceuticals** is the responsibility of WP4 Co-lead partner Zorginstituut Nederland (ZIN). Developers and EUnetHTA partners are encouraged to submit

documentation and suggest topics. At the time of establishment of the TISP working group (November 2017), only if, and when documentation was submitted by a developer, there was a call for collaboration amongst EUnetHTA WP4 partners. Recently (June 2018), a more pro-active approach is explored using public available information from existing HSS to inform EUnetHTA WP4 partners as to reveal interest. Based on a letter of interest from EUnetHTA WP4 partners to engage in a HTA process, developers will be contacted and asked to provide a letter of intent to submit documentation.

Initiation and coordination of assessments of **other technologies** (technologies that are not pharmaceuticals, OTs) is the responsibility of WP4 Co-lead partner LBI-HTA. Currently, topics concerning assessment of OTs are identified in three ways:

- A WP4 partner selects a topic and approaches the WP4 Co-Lead for OT. The proposing partner is volunteering as author. The WP4 Co-Lead sends out a call for collaboration to WP4 partners who are asked if the topic is relevant for them and if, for which role (co-author, dedicated reviewer) they could volunteer. If there is no interest, the assessment will not be performed.
- Topics are suggested by stakeholders (restricted to manufacturers and/or patient organisations), and a call for collaboration is prepared by the WP4 Co-Lead asking for author, co-author and reviewers. If there is no interest, the assessment will not be performed.
- A partner identifies a relevant project in the POP database and contacts the other party to enquire about possible collaboration. If the partner agrees on a collaboration and on their role (co-author or dedicated reviewer), a call amongst WP4 partners can be put out for the remaining roles (co-author or dedicated reviewer).

The majority of OTs prioritised for assessment by JA3 WP4 have so far been identified by the first route.

Early dialogue (ED) within EUnetHTA JA3 WP5A

The initiation of ED within EUnetHTA WP5A is led by the French HTA agency Haute Authorité de Sante (HAS). Developers submit an application to the EUnetHTA WP5A ED secretariat.

For **pharmaceuticals** the EUnetHTA ED secretariat asks the EUnetHTA ED Working Party to select eligible topics based on information provided by the applicant. The following selection criteria are applied:

- potential for added value
- unmet need, high disease burden (life-threatening/chronic disabling disease)
- new mode of action

For **MD/IVD** the EUnetHTA ED secretariat evaluates the validity of the request (i.e. pivotal trial and not feasibility trial) based on documents provided by the applicant. ED is restricted to MD classified as class IIb and III, digital devices, and IVD with following criteria:

- unmet medical need
- potential impact on patients, public health, or healthcare systems

An ED for MD/IVD can only take place before the pivotal clinical trial has begun. The request will be considered eligible if the criteria are met, and if at least three WP5A partners are interested and have

available resources to participate in the ED. So far no ED on MD/IVD has been completed (two are planned).

Initiation of post launch evidence generation (PLEG) within WP5B

The initiation of PLEG within EUnetHTA WP5B is led by the French HTA agency Haute Authorité de Sante (HAS):

- A WP5B partner selects a topic for PLEG and approaches the WP5B lead to propose a call for collaboration.
- The WP5B lead sends out a call to WP5B partners who are asked if the topic is, or will be relevant for them and if the partners could volunteer to participate.

National horizon scanning systems to inform HTA and reimbursement in Europe

EUnetHTA WP7 (national implementation and impact) has gathered data from 59 European HTA agencies in 31 countries about their existing HTA and reimbursement processes including information about how topics were selected and prioritised for HTA (16). Twenty nine countries (94%) reported to have HTA procedures for pharmaceuticals and 22 (71%) reported to have HTA procedures for non-pharmaceutical health technologies. Of these countries, nine (England, Scotland, Ireland, Norway, Sweden, Estonia, France, Netherlands, Italy) for pharmaceuticals and nine (Scotland, Ireland, Norway, Sweden, Estonia, France, Belgium, Italy and Spain) for non-pharmaceuticals, reported using HS procedures to support topic identification. Some other countries reported to develop or consider developing such procedures.

Not all countries who use HS use it for all types of topics, in some instances this may only be for certain topic types e.g. inpatient products, reviews or multiple technology assessments. Where HS is not used, in most cases either industry submits an application for assessment or topics are requested by a decision maker, e.g. ministry of health (MoH) or payer.

Organisations involved in the topic selection procedure include industry, HTA agencies, MoHs and payers. For non-pharmaceutical health technologies, providers, medical and clinical societies and regional authorities also have a role in topic selection/prioritisation. In approximately 50% of the countries, the HTA agency does not have a role in topic selection/prioritisation because they carry out work on any topics requested from them either by decision makers or through industry submission.

For pharmaceuticals, 15 out of 29 countries (52%) have topic selection or prioritisation criteria. For non-pharmaceutical health technologies, the corresponding figures are 15 out of 22 countries (68%). Topic selection criteria are similar for pharmaceutical and non-pharmaceutical health technologies and most frequently based on:

- economic or resource impact
- potential health benefits
- severity or burden of disease
- population size
- importance to policy and/or healthcare

Output from European HSS vary, with some systems producing publicly available information, some producing partly available information and some producing information only available for a specific audience. Publicly available information ranges from early awareness reports, and two to three page alerts to short listings.

How information from national HSS may be used to inform EUnetHTA activities or activities of a permanent HTA network is outside the scope of the present document, but will be explored in the EUnetHTA pilot.

HS networks and collaborative initiatives

Based on prior knowledge of publications (2;4;7;9;12) and inspection of selected websites we have identified a limited number of non-commercial and/or publicly funded networks and collaborative initiatives on HS:

EuroScan

The International Information Network on new or emerging, appropriate use and re-assessment needed Health Technologies (EuroScan International Network) is a non-for-profit collaborative, member driven network and scientific association (17). EuroScan has been in place since 1999 and has contributed widely to develop and share HS related methods and information. Voluntarily produced information on health technologies has been shared through a web-site and a database available for EuroScan members. In 2017 the EuroScan secretariat was moved from Birmingham University in England, to Rheinishe Fachhochschule in Cologne, Germany. Based on this process there have been several changes in the association, including the establishment of a formal legal entity for a scientific association based under German law. Currently (June 2018), the EuroScan web-page is not updated on a regular basis and the future type of output to be available is not clear, but according to personal communication it will include voluntarily shared information and an online scientific journal. EuroScan has a memorandum of understanding with the International association of HTA Agencies (INAHTA), World Health Organisation (WHO), Health Technology Assessment international (HTAi), HTAsiaLink, and the HTA Network of the Americas (RedETSA) and is positive to a collaboration with EUnetHTA (information on the website). Some EUnetHTA agencies are EuroScan members.

HTAi IG DEA

HTAi has an interest group on disinvestment and early awareness (HTAi IG DEA) with approximately 300 individual members (7;18). HTAi IG DEA aims to be a key international centre for sharing knowledge and expertise, both in methods for prioritising and assessing obsolete or low-added value technologies and in the practical application of disinvestment for health systems. Current activities include the development of a toolkit for disinvestment and a survey on disinvestment candidates. The HTAi DEA collaborates closely with EuroScan.

BeNeLuxA/IHSI

A collaboration has been initiated on ministry level in Belgium, Netherlands, Luxemburg and Austria (the BeNeLuxA collaboration) to strengthen collaboration on procurement of medicines (7;19). As an extension of this collaboration, an initiative to develop collaborative HS to inform TISP for joint HTA for the BeNeLuxA region was established. In 2017 this initiative was further extended by inviting more countries to participate. The new initiative, now referred to as the International Horizon Scanning Initiative (IHSI), is based on countries (European and non-European) at MoH level who are invited to participate in establishing an international not-for-profit association (AISBL) that through an open tender process plans to purchase HS services on behalf of its members. As of May 2018 the AISBL has not yet been established, but a tender process is planned for 2019. Contact between EUnetHTA and the IHSI initiative has been made.

The Nordic Pharmaceutical Forum

The Nordic Pharmaceutical Forum, an informal Nordic collaboration between medicinal regulatory agencies and procurement agencies focused on pharmaceuticals, has started an initiative to share HS

information and methods (9). Currently, this is restricted to exchange of national experiences (Input from author).

Cross-regional collaborations within the same country

Both in Spain and Italy collaborative HS activities are cross-regional with task sharing. The Spanish collaboration on HS is focused on non-pharmaceuticals with several HTA agencies sharing tasks on proactive identification and assessment. Output of the Spanish system is a list of identified topics and short alerts used in the topic selection process. The system intends to inform both re-imbursement on the regional level and decisions for the national benefit basket (7). The Italian regional network for HTA (RIHTA) has been recently integrated within a National HTA Programme targeting non-drug technologies. Topic identification is performed at regional as well as central level while prioritisation is done by a national steering committee. Lists of technologies in need of assessment and list of new or emerging technologies are produced. From those lists, topics are prioritised for assessment at national level [input from author].

Outside Europe

The Canadian HTA agency CADTH provides HS output on both pharmaceuticals and other technologies(20;21). The Australian Institute for Safety Compensation and Recovery Research ISCRR (22)has developed its HS activity in partnership with CADTH.

How and if information derived through or from these networks and initiatives may be used to inform EUnetHTA activities or activities of a permanent HTA network is outside the scope of the present document, but will be explored in the EUnetHTA pilot.

Methods

This document was prepared based on a collaborative approach involving 31 EUnetHTA WP4 partners and a stakeholder consultation process. In June 2017, WP4 Lead partner NIPHNO recruited members of the working group based on a call for collaboration amongst members of WP4 and the EUnetHTA executive board. A coordinating team from NIPHNO was set up. Two members of the NIPHNO coordinating team and seven members from the responding agencies have acted as authors. Representatives from the remaining responding agencies have acted as reviewers.

The coordinating team collected background papers based on prior knowledge and inspection of the following web pages: the HTAi IG DEA web site (18), the EUnetHTA web site (23), the BeNeLuxA initiative web site(19), the EuroScan web site (17), Horizon scanning related web sites of the Canadian HTA agency CADHT (21) and NHS, UK horizon scanning websites(24;25) and the Dutch horizon scanning website(26). In addition, a non-exhaustive search for recently (2016 and later) published scientific literature on HSS and HS restricted to PubMed, NHS evidence, Epistemonikos and Google were used. Searches were performed in December 2017 and repeated in June 2018.

The NIPHNO coordinating team met with a subset of authors in November 2017 in Vienna focusing on non-pharmaceuticals (other-technologies (OT)), and with another subset of authors in Oslo focusing mainly on pharmaceuticals (P). The authors agreed to use a question-answer (QA) based approach to provide draft recommendations. Questions (Appendix 1) were derived from The EuroScan toolkit for Horizon scanning (4) and modified it to suit the aims of the activity. Most importantly, no question regarding early assessment was included as this was not considered to be within the scope of the report. Input (answers to the questions), was received from the authors and edited by the coordinating team.

A crude draft reflecting the results of the QA approach was prepared based on the background papers and the answers from authors. Reviewers were asked to provide additional input to the crude draft. A teleconference with authors was held and NIPHNO provided a second draft that was shared with authors. Based on input to the second draft, NIPHNO translated the manuscript (third draft) into a traditional report format (Executive summary, Aims, Background, Methods, Results and Discussion) and shared this (draft version 3) with the authors. After incorporation of feedback including restructuring of the recommendations (see Appendix 1), a fourth version (the current version) was submitted to the whole working group (authors and reviewers). After incorporating input from reviewers a draft for consultation (draft version 5) will be prepared by NIPHNO.

Consultation will be performed by contacting the EUnetHTA Executive board, EUnetHTA partners and a selected number of stakeholders by mail and invite them to provide comments to the draft. An overview of consulted stakeholders and their input will be provided. Finally, NIPHNO will send the report for a last short consultation amongst the working group (authors and reviewers). No objections will be considered as agreement to the recommendations. Objections with clear alternative formulations will be discussed in a TC amongst authors. The final draft recommendations and the recommendations for the pilot will be published on the EUnetHTA website. The pilot will be performed during the autumn 2018 and final recommendations are planned to be delivered by July 2019.

Results 1. Draft recommendations for a horizon scanning system

Based on the QA process (Appendix 1), 13 draft recommendations for a cooperative HSS to serve European joint and collaborative HTA activities beyond 2020 have been prepared.

1. The purpose of the HSS

The main purpose of a HSS to serve the European HTA network beyond 2020, is to support planning, timeliness and relevance of joint and collaborative HTA activities and to reduce unnecessary duplication of work. In addition, a cooperative HSS should support and promote the implementation of structured national HSS or TISP processes for HTA activities. Those planning and prioritising HTA activities at any level of the network, as well as individual HTA agencies and stakeholders should be considered the main target group and audience for the HSS. HTA activities to be supported should reflect technology lifecycle and do include:

- early dialogue with developers
- initial assessment (assessment close to market entry)
- planning additional evidence generation
- reassessment

2. Organisation of the HSS

Cooperation involving all network members or member states supporting the HSS should reflect the process of establishment, ownership, governance and funding of the HSS. A coordinating secretariat should act at the central level of the system. To ensure high quality and reliability, identification, selection and preparation of outcomes should be performed by a professional HS unit. Collaboration with, and learning from existing HSS, new HS initiatives such as the IHSI initiative (19) and scientific networks such as EuroScan(17) should be explored to avoid duplication of work.

3. Technology scope of the HSS

The technology scope of the HSS should at least be pharmaceuticals, medical devices and IVDs considered for joint activities as outlined by the EU proposal for a regulation in HTA (15), that is:

- *all medicinal products undergoing the central marketing authorisation (MA) procedure, new active substances and existing products for which the marketing authorisation is extended to a new therapeutic indication (line extensions) class IIb and III medical devices and class D in vitro diagnostics.*

In addition, the HSS should also plan for including other technologies of relevance for continued voluntary cooperation, that is:

- any potentially high impact, disruptive, transformative or obsolete technology with focus on patient needs

This includes interventions that do not have a commercial developer such as certain diagnostic approaches, surgical interventions, medical procedures, hospital care (organisational), community care/ programmes, public health interventions (including vaccination programs) and delivery of technologies and a life cycle perspective.

4. Time frame for identification of topics

HTA activities should not delay the introduction of innovative[4] technologies and should contribute to timely withdrawal of obsolete[5] technologies. However, the earlier the identification, the higher the uncertainty about the data. There is a trade-off between an early time horizon, possibly needed for long-term planning and early dialogue, and certainty about the information needed for assessment. For all technologies it is imperative that the HSS monitors innovative and potential disruptive technologies until sufficient evidence for assessment or action is available.

To allow planning of initial joint assessments and early dialogue, identification should be close up to planning of pivotal trials. Typically, for pharmaceuticals this would be in Phase I to Phase II of clinical trials. Exact timeframes are more difficult to provide for other technologies as they may have highly irregular adoption rates.

To allow prioritisation of initial assessments the timeframe for identification should be:

- no later than when a pharmaceutical enters the lists of medicines under evaluation in EMA
- no later than when a device or IVD is anticipated to enter the CE marking process
- no later than six months before the time when pivotal trial data are anticipated to become available

As assessment might influence uptake/use of technologies, a HSS should also provide information when data on effectiveness may lead to changed conclusions (goal: inform a possible need to increase uptake of innovative technology/possible need to disinvest obsolete technologies). Thus, continuous monitoring of prioritised or selected technologies after introduction through a systematic approach would allow a lifecycle perspective of assessments to be supported by the HSS.

5. Information sources for topic identification

Identification should be both proactive (i.e., a range of sources are searched for information) and reactive (stakeholders are allowed to inform the HSS). Examples of sources for emerging and new technologies are provided in table 1. For identification of obsolete technologies different strategies and sources need to be applied (11;12;27).

Table 1 *Sources of information used in identification of new and emerging technologies*

Type of source	Example
Primary sources	• Direct contact with developers through regular meetings • Allowing the developers to enter information in a database (like the UK Pharma screen) • Developers' websites, annual reports, press releases, and conference presentations • Information from market analysts, consultants and commercial research organisations • Commercial pharmaceutical and other specialist health technology media and databases • Public clinical trial registries(e.g. ClinicalTrials.gov and WHO International Clinical Trials Registry (WHO ICTRP)) • Published patent applications (e.g. Espacenet)

[4] An innovative technology may be defined as a new technology potentially providing increased value (compared to existing technology).

[5] Obsolete technology may be defined as an outdated technology that should no longer be used

Secondary sources	• Regulatory bodies* • Commercial and medical publications • Scientific conference proceedings and scientific journals.
Tertiary sources	• Output from existing HSS • EUnetHTA partners • The EUnetHTA database of Planned and ongoing HTAs and systematic reviews (POP database) • Published HTA reports and systematic reviews

*Currently public available information on medicinal products under evaluation can be found on the European Medicinal Agency home page, but there is no database of structured information. Public information on MD and IVD undergoing CE processes is currently not available, this is supposed to change post 2020 by introduction of the EUDAMED database.

Systematic searching primary and secondary sources is very resource intensive, and may require highly skilled personal, sophisticated automatic search algorithms and a sophisticated system for managing the information. There is overlap between sources and a trade-off between completeness and efficiency. Topic identification will depend on the scope and resources available. However, input from developers and other stakeholders should be part of the identification process as described under stakeholder involvement (below). In particular, collaboration between the HSS and regulatory bodies should be explored to assure timely and regular access to structured information. Issues of confidentiality should be clarified. Preferentially, to ensure that the HSS is as transparent as possible, only non-confidential information should be used to populate the data-sets. Some information, including information related to timelines and pricing might be of value for the target of the HSS, but considered as confidential by developers. Special arrangements with developers and regulators, on how to deal with confidential information might be needed. As a rule of the thumb, information that may be cited with a public available source should be considered as non-confidential.

6. Selection

Selection or filtration describes the process in which a set of pre-defined criteria are applied to the identified topics, in order to retain only topics relevant to the pre-determined technology scope and time frame (adapted from EuroScan tool kit (4). Completeness is the goal, all identified technologies defined by the scope should be selected. Selection may need to be performed in several steps: First, to ensure that the technology confines with the technology scope and timeframe of the HSS as such, second to ensure that the technology confines with the scope of a specific activity of the HTA network.

The selection could be based on a simple scoring system (yes/no answer). Selection may be performed by panels of experts and patient representatives appointed for various scopes and therapeutic areas. As large panels may be very resource demanding, it should be explored if a simpler model using a permanent team such as the central secretariat will suffice.

7. Prioritisation

Prioritisation describes the process in which specific criteria are applied to the selected/filtered technologies with the purpose of retaining for assessment (or any other HTA activity) the technologies with greater impact depending on the system's/network's capacity for assessment (adapted from (4). If all selected technologies will be assessed or handled, there is no need for prioritisation. In other cases there will be a need for prioritisation and prioritisation criteria should be

agreed upon. These criteria should be in line with the scope of the EU proposal (15) which suggest that when there is a need for prioritisation, focus should be on:

- *unmet medical need*
- *potential impact on patients, public health, or healthcare systems (e.g. burden of disease, budget impact, transformative technology)*
- *cross border potentials*
- *union-wide added value (e.g. relevance to a large number of Member States)*
- *the resources available to it [to perform the assessments]*

Based on these criteria, the same general focus could be used for all HTA activities throughout the lifecycle of technologies. However, how the variables will be defined or measured needs to be explored. Ranking systems may depend on activity. Complexity of the intervention, organisational impact and safety aspects (hazards) in particular of devices might be used to limit the scope further (selection) or prioritise amongst potentially high impact topics. For cooperation on PLEG, prioritisation could in addition to the general criteria, contain additional criteria such as those described by EUnetHTA JA2 WP7(23):

- Existence of evidence gaps (identified by HS, early assessment or assessment)
- Existence of an explicitly defined research question
- Feasibility of data collection
- No planned or ongoing similar studies (unless the present one will bring additional value)
- The study results are relevant for re-assessment or decision making

Technologies with high impact ranking should be prioritised. The use of explicit ranking systems and tools should be explored.

Complex prioritisation process might be very resource demanding and simplicity should be aimed at. However, since scoring requires specific knowledge in different domains (public health, epidemiology, economics, pharmacy, etc.) ranking should be done by carefully selected and trained committees including at patient and health care representatives.

Committees of those ranking the technologies could be part of the HSS, but decisions need to be made outside of the HSS. Different final prioritisation committees may be established and informed by the HSS depending on activity and level of decision (joint, collaborative, national). Before final prioritisation, stakeholders should be able to provide input to the topic. This could be with regard to the time frame, a letter of interest to provide a submission file and/or views on the potential impact.

8. Type of output to be produced

One main output of the HSS should be a minimal data-set of each identified technology. The minimal data-set should contain a description of the type of technology (pharmaceutical, MD, IVD, other), the name of the technology (generic and trade name if available), the name of the developer and market authorisation holder (MAH) or applicant (pMAH), the intended indication for use (IFU), the developmental status (availability of clinical trials and if applicable phase) and regulatory status. This information should be used for selection (described above) and monitoring of technologies.

In cases were no prioritisation is needed, e.g. if all new pharmaceuticals are to be assessed, there will not be a need for a comprehensive data set. In other cases, e.g. if only a subset of technologies will be prioritised for assessment, or there are no commercial developer, or the scope is reassessment, a more comprehensive data-set may be needed. The aim of a more comprehensive data-set is to

provide sufficient information to allow for prioritisation and ensure transparency of the prioritisation process. Type of information to be included could be more detailed information on mode of action, more information on specific regulatory demands, description of disease, information on current treatment strategies (comparator(s)), potential areas of impact, and more detailed information on ongoing and completed trials. Typically, the comprehensive data-set used for prioritisation does not need to contain clinical trial results or take the format of an assessment report. Rather, it should be explored if a short alert will suffice.

The data-sets should be available in a database and non-confidential information should be made publicly available. The database should give a clear, but easy overview of data and facilitate sorting and tracking of changes. Sources of information should be referenced.

Additional outputs like reports on selected therapeutic areas describing in more detail unmet needs and emerging technologies could be produced on demand.

9. Review of output

Review of output should be part of the HSS quality management system. The aim of the review process should be to verify the completeness and accuracy of the data-sets against referenced sources and any other predefined criteria for quality assurance.

10. Stakeholder involvement

Stakeholders to a European cooperative HSS include regulators, patients and consumers, payers, healthcare professionals, developers (industry, researchers and any other commercial or non-commercial developers of health technology), those holding or applying for market authorisation, or those that in other ways have rights connected to the use of the technology or will be impacted by the use of the technology. Stakeholder involvement should be according to the following guidelines:

- any stakeholder should be able to suggest a topic to the HS identification process
- regulators should be involved in the process of topic identification and the populating and updating of data-sets
- any stakeholder could be contacted upon need to populate and verify the data-sets
- healthcare professionals, payers and patients should be involved in the prioritisation process
- developers should not participate in the prioritisation process
- any stakeholder should be able to provide feedback and be informed on status of HTA activities within the network.

Stakeholder involvement could be both proactive (agreements with the stakeholder to respond upon request) and reactive (possibility of the stakeholder to provide input if wanted). Involvement may be on association level or on individual level. What to choose will depend on resources available for the HSS and the balance between the need for an in depth or broad insight or perspective. To allow reactive stakeholder involvement the main outputs of the HSS should be public available. To ensure efficiency, proactive involvement could be restricted to associations representing specific stakeholders such as experts, patients and regulators. The most representative associations for health professionals, patients and payers need to be identified. For pharmaceuticals, regulator involvement should include agreements with EMA to provide structured information. For MDs and IVDs regulator involvement might (at the moment) be more difficult due to the non-centralized organisation of the CE-marking process. However, it should be less demanding when the EUDAMED database (28) is in place. Developers may need to be contacted directly, but associations may be used to identify individual developers.

11. Frequency of output preparation and updating

Preparation of output and updating of information should contribute to timely HTA activities. Updating the minimal data-sets with emerging technologies (identified before initiation of pivotal trials) should at least be performed once a year, preferentially more often in particular for pharmaceuticals. In addition, the minimal data-sets should be updated iteratively based on continuous scanning for changes in regulatory status and availability of data from pre-selected clinical trials and stakeholder input.

In cases were prioritisation is needed, comprehensive data-sets should be prepared at intervals and time points depending on how critical it is for the activity (assessment) to be aligned with regulatory processes and availability of the technology. The earlier the prioritisation is performed the more uncertainty there will be with regard to the uptake in a regulatory process, availability of the technology and the actual need for initiating an HTA related activity. Thus, early prioritisation may not be very predictable for planning of HTA activities.

Pharmaceuticals are provided with market authorisation (MA) on a monthly basis. If prioritisation for initial assessment is to be performed after the technology has entered the regulatory process, prioritisations should be closely linked to regular updates from EMA and output should be produced accordingly.

12. Implementation

A particular business model has not been evaluated, but scope, timeframes, funding, governance and a central coordinating unit have to be in place. Tender processes rather than voluntary contribution for the whole or individual parts of the system should be considered. Once established, implementation should include quality assurance through transparently shared standard operating procedures (SOPs) covering workflows and responsibilities.

Implementation could be a stepwise process and should at least start with pharmaceuticals, MDs and IVDs to support prioritisation for joint activities including initial assessment and early dialogue. Widening the scope and extension of activities to other areas should be planned for.

13. Evaluation

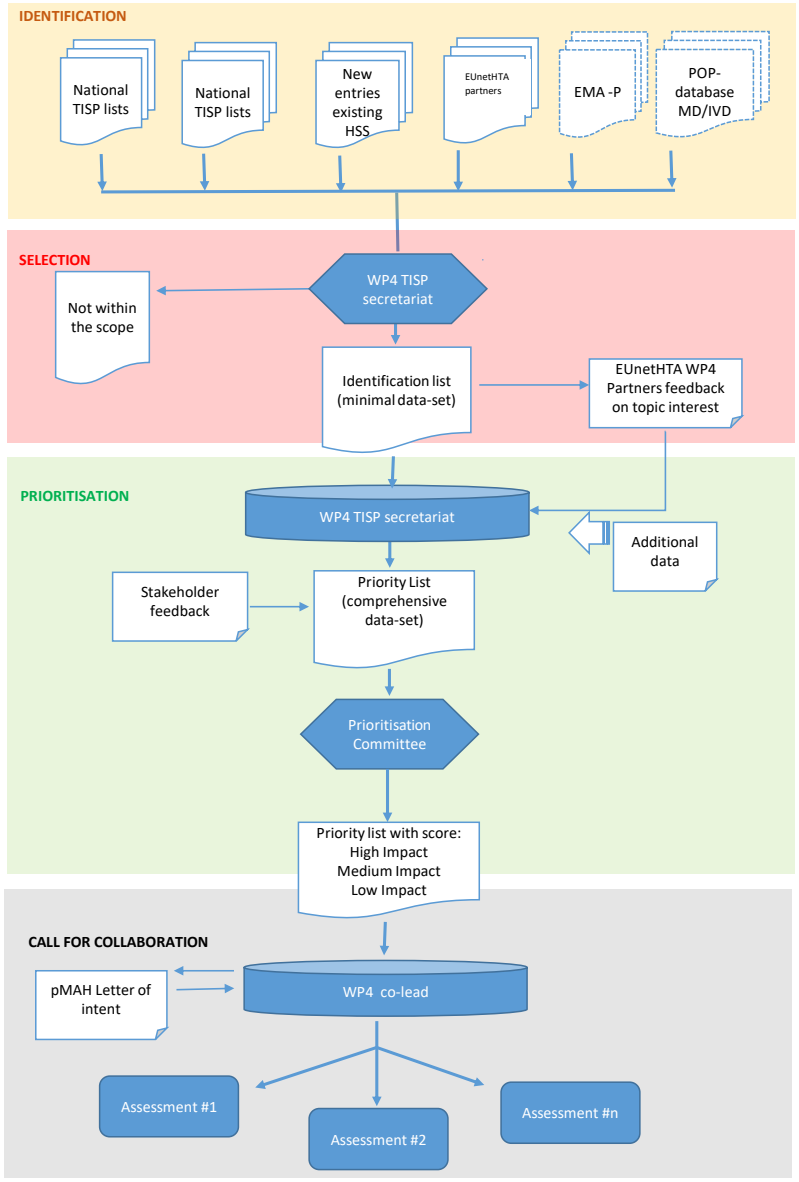
Achievements of proposed objectives should be evaluated , and this should be performed based on predefined indicators of the process (accuracy and completeness, timeliness, usability of outcome, access to information, relevance of criteria) and usage of outcome (number of dossier submissions, number of HTA activities, implementation/uptake, usage of information).

Results 2. A pilot of a workflow for TISP to support EUnetHTA JA3 WP4 activities

TISP workflow for EUnetHTA3 WP4 activities

A workflow for TISP should assure timely identification and prioritisation of HTA related activities. In addition, the workflow should be used to prepare HTA agencies, developers of technologies, payers, patients and other stakeholders for the HTA activities. A suggestion for an overall workflow for EUnetHTA WP4 is presented in Figure 3.

Figure 3 *Workflow for TISP EUnetHTA JA3 WP4 (draft)*



EUnetHTA WP4 HS TISP working group

EMA = European Medicines Agency; P= Pharmaceuticals; MD= Medical Devices; pMAH = prospective Marketing Authorisation Holder, POP Database = Planned and ongoing project database. Stakeholder feedback may include expression of interest and verification of data from stakeholders, including pMAH.

The overall TISP process will be the same for WP4 and WP5 activities. These activities are defined by different time frames and may have different technology scopes. For the pilot we will focus on WP4 activities restricted to pharmaceuticals (joint initial REA) and MDs/IVDs (joint initial REA and collaborative assessments).

Recommendations for the pilot

The same 13 questions used for the draft recommendations were used to define the pilots for TISP.

1. Purpose

The pilot will explore cooperation with existing HSS, EUnetHTA partners ability to share national identification and prioritisation lists, regulatory authorities ability to share structured information, and stakeholder involvement. Experiences from the pilot will guide further EUnetHTA WP4 TISP procedures, and it will be used to inform the final recommendations planned to be available by July 2019.

Those planning and prioritising HTA activities in EUnetHTA WP4, that is the WP4 partners and in addition the EUnetHTA3 Executive board as well as stakeholders expected to provide input to the main target of the pilot.

2. Organisation of the pilot

Authors of the WP4 TISP group will be responsible for conducting and evaluating the pilot. The authors will agree on how to act as central secretariats and a working groups for conducting two strands of the pilot, one for pharmaceuticals and one for OTs, respectively. Details of the organisation will be agreed on in a project plan. Reviewers and stakeholders will be involved in prioritisation of topics and review of the conclusions. The pilot will be performed in a limited time frame, but the workflow and processes could be implemented by EUnetHTA3 WP4. Authors of this report are not responsible for the implementation of the workflow (see below)

3. Technology scope

The scope of the pilot will be restricted to:

1. Pharmaceuticals for joint assessments
2. MDs and IVDs for either joint assessments or collaborative assessments

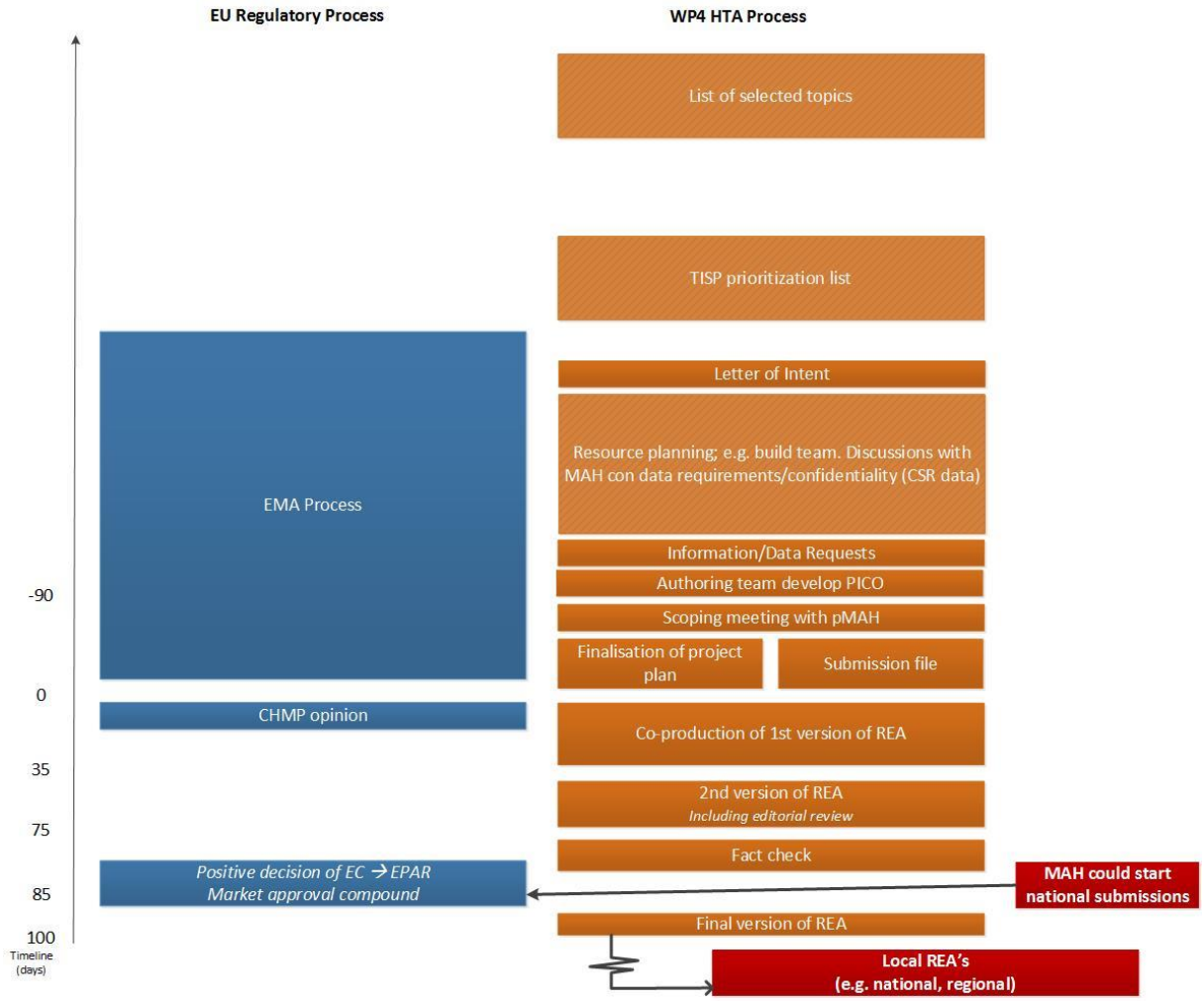
4. Timeframe

A complicating factor for EUnetHTA collaboration are different time horizons for conducting national HTA for different agencies. Thus, to ensure national uptake of joint or collaborative assessments and to avoid duplication of work, prioritisation of assessments by EUnetHTA should be clarified as early as possible.

For pharmaceuticals, the timeframe to be explored by the TISP pilot will be:

- to identify, select and prioritise emerging pharmaceuticals before they enter the EMA regulatory process (see Figure 4)

Figure 4 Timeframe TISP relative to EMA process and Joint Assessment process



EUnetHTA WP4 HS TISP working group

The timeframe for identification of MDs and IVDs will be one of the following depending on technology and available information:

- when a national agency has identified and/or prioritised a topic
- around the time of CE mark
- when pivotal trial data are anticipated to become available
- when a CE marked product is anticipated to be available for use outside clinical trials

5. Information sources

There are currently no resources available for establishing an extensive HSS within EUnetHTA JA3.

For all technologies defined by the scope, the following sources should be explored by the pilot

- EUnetHTA partners and stakeholders should be invited on organisational level to suggest topics

- existing HSS with public available data
- regulatory bodies

For MDs and IVDs additional sources of information should be national identification lists (non-confidential information) and the EUnetHTA POP database

6. Selection (filtration)

The technology scope defines the selection or filtration criteria. For pharmaceuticals, the scope of the pilot will be restricted to initial joint assessment of new medicines as outlined by the EU proposal (15). For OTs the pilot will be restricted to new MDs and IVDs, joint initial assessments as well as collaborative assessments including re-assessments. Selection of identified topics in accordance with the scope will be performed by the WP4 authors based on the identification list. The WP4 authors will produce a selection list that will be distributed to WP4 and WP7 partners.

7. Prioritisation

EUnetHTA JA3 is based on voluntary cooperation, prioritisation of topics for assessment in EUnetHTA JA3 is solely by WP4 partners revealing interest in a topic after a call for collaboration. The pilot may compare three different ways of prioritisation:

A) By means of a call for collaboration amongst EUnetHTA3 WP partners

B) Informed by implicit ranking according to criteria of the EU proposal

C) Informed by explicit ranking providing a score

First partners and stakeholders may be approached with the lists of selected topics and reveal their interest in the topic by means of acting as authors, co-authors and revieweres and for stakeholders to provide input before a pre-specified deadline (A). Feedback from partners can be used as an indication of value for the network members un-informed by ranking. Feedback from developers can be used as an early indication on the ability/interest of the developer to submit a documentation file. Feedback from developers and other stakeholders may in addition inform the production of the more comprehensive data-set.

Meanwhile, the WP4 coordinating secretariat will produce the more comprehensive information (see below). Two prioritisation committees (PCs, one for pharmaceuticals and one for MDs/IVDs) should be established and perform ranking based on the more comprehensive data-sets. Two ways of ranking may be explored, first as high, medium or low impact according to the criteria of the EU proposal (as outlined in the draft recommendations) indicating area of impact by implicit ranking (B), and secondly to use the Pritec ranking tool (29) providing an explicit score (C).The PC members should be recruited amongst the WP4 partners being reviewers of this report, WP7 members and a limited number of members from patient and health professional associations. Results of A, B and C will be compared. Feedback from members of the PCs with regard to ease of concluding (with or without a tool) and the need to modify the tool will be collected.

If needed, EUnetHTA partners and developers could be re-approached with the more comprehensive information and information about the PCs rating and asked to reconsider any negative decisions on interest in topics rated as potentially high impact by the PCs.

8. Type of output

A minimal data-set (defined as the identification list) for selection/filtration should be produced. The list should at least contain the following information:

- Type of technology (Medicinal product; MD; IVD; Other type of technology)
- (International) Non-proprietary Name (generic name)
- Product(s)/Commercial name
- Therapeutic area (s)
- Indication(s) (anticipated)
- Developer/Marketing-Authorisation Holder (MAH)
- Developmental status (Emerging/New; for Pharmaceuticals: pivotal trial number and phase restricted to phase II and III trials; for MDs and IVDs pivotal clinical trial number if available)
- Regulatory status Europe (if applicable/available: Initial market application or extension; First in class; Priority Medicine (PRIME); Accelerated access; Orphan drug etc.; CE mark class
- Regulatory status USA (FDA approval)
- Date of entry and last up-date
- Source of information

For the pilot, the identification list and the resulting selection list may be considered internal documents, typically in excel format. The selection list will contain the same information as the identification list and should be shared amongst WP4 and WP7 partners similar to a call for collaboration (prioritisation mode A, see above).

In addition a more comprehensive data-set (defined as the prioritisation list) should be produced to provide some more details to allow prioritisation. This list should be shared amongst members of the PCs (prioritisation mode B and C, see above). The list could contain the following additional information:

- Expected launch (availability)
- More extensive information about the intervention such as: - the principle/mode of action(pharmacology); formulation; administration; potential co-interventions, organisational consequences such as diagnostics and impact on costs (increased, lower)
- More extensive information about the disease, indication (population) or at least therapeutic area- if possible estimation of target population (number of potential users), epidemiological data and indicators reflecting severity of disease with current treatment (unmet need)
- Relevant comparator or current treatment including cross-border variation in comparator variation in comparator
- Level of evidence: including information on earlier assessment, PICO information about pivotal ongoing and completed clinical trials
- Potential areas of impact(to be provided by members of the PCs):
  unmet need;
  impact on patients (burden of disease, transformative technology potential impact for patients);
  impact on public health;
  impact on healthcare systems (budget impact; high impact for health system);
  cross-border dimension;
- Overall impact (to be provided by members of the PCs)
- Explicit scoring results (to be provided by members of the PCs)
- Comments (to be provided by members of the PCs)

The comprehensive information does not need to be exhaustive, but it may depend on systematic scoping, as well as input from developers, patient and experts. Comprehensive data-sets with cited references should be made publicly available. Either excel sheets or word documents may be used.

9. Review of output

Data-sets produced by one WP4 TISP author will be internally checked by a WP4 TISP author from another agency.

10. Stakeholders and stakeholder involvement

For the pilot, stakeholders should be represented by associations. Involvement in the pilot should be explored by:

- inviting EUnetHTA WP4 partners and stakeholders to suggest topics and reveal interest in selected topics
- involving regulators in topic identification
- inviting commercial developers to verify content of prioritisation lists and provide letters of intent to submit documentation for assessment
- involving EUnetHTA WP4 partners to participate in PCs
- involving patient and health care professional associations in PCs

Notably, developers of technology should not be involved in the selection or prioritisation processes.

11. Frequency of output preparation and updating

For pharmaceuticals, if possible, this should be tested twice with approximately one month in between. For OTs, a workflow with updating the identification and prioritisation lists at least twice a year should be aimed at. One round of TISP will be piloted for OTs.

12. Implementation

The pilot will be conducted in the period October to December 2018 with preparation starting in August. Steps for preparation of the pilot include:

- establishing the central coordinating team of WP4 authors
- translation of the work plan to a project plan
- contacting existing HSS and HS initiatives
- contacting EUnetHTA partners to share the latest national identification/prioritisation list at a certain time-point
- contacting regulators for structured information
- stakeholder are informed about the pilot
- agreement on publishing the comprehensive data-sets on the EUnetHTA
- Excel templates for the minimal data-set are prepared
- Excel or word templates for more comprehensive data are prepared

After the pilot has been conducted a clear commitment from the EUnetHTA executive board is needed for implementation of the workflow in EUnetHTA JA3 WP4. Extension of the pilot to a project beyond December 2018 depends on resources available in WP4. EUnetHTA JA3 implementation could be supported by SOPs generated by EUnetHTA WP6. SOPs could cover.

- Coordination
- Identification and preparation of a minimal data-set

- Updating the data-sets
- The selection process
- Preparation of more comprehensive data-sets
- Prioritisation

13. How can the pilot be evaluated

Endpoints of the pilot will be:

- availability of data from different sources
- regulatory status of data when entering the minimal data-set
- regulatory status of data when entering the comprehensive data-set
- relevance of criteria
- interrater reliability/variation of priority scoring
- expression of interest from commercial developers to provide documentation
- the need for prioritisation
- positive response to call for collaboration.

The time-frame of the pilot is too short to allow for measuring of endpoints like dossier submission, number of HTA, timeliness of HTA, implementation of HTA and usage of outcome, accuracy and completeness. An extension of the pilot to a project lasting one year could allow for some outcomes like dossier submission, number of HTA, timeliness of HTA, implementation of HTA and usage of outcome. However, accuracy (relative to HTAs on High impact technology) and completeness (relative to the scope) would need a far longer time perspective and would be difficult to define.

Discussion

To provide draft recommendations for an HSS to serve a European HTA network beyond 2020, we have used a QA approach. Thirteen draft recommendations have been formulated. The same questions were also used to provide recommendations for a workflow on Topic Identification, Selection and Prioritisation (TISP) for EUnetHTA JA3 WP4 activities, as well as recommendations for a pilot of the workflow.

We (the working group) have not aimed at providing a complete overview on established HS activities or methods that may be used within HS. A limited literature search was performed resulting in inclusion of a few references considered by the authors to represent major updated information of relevance for this working group. The authors and reviewers are all employed by EUnetHTA WP4 partners and recommendations have been made from the perspective of "HTA doers". The field of HS and HTA is a constantly moving target and any recommendations on scope, timeframe and methods will be influenced by changes in both legal aspects such as the EU proposal on HTA (15), policy-recommendations, funding and technology available for conducting the work. Input from stakeholders and lessons from the pilot might influence on the final recommendations to be delivered in June 2019.

The draft recommendations for an HSS beyond 2020 are ambitious, in the sense that an HSS fulfilling all recommendations cannot be realised in short time and without substantial funding and establishment of a professional business model. However, very concrete steps can be taken in the short run, to start with an operational TISP process that supports certain but not all activities and areas of interest for European collaboration on HTA. We suggest that cooperation on HS should at least start with pharmaceuticals, MDs and IVDs using existing sources of information. However, widening the scope and methodological sophistication should be planned for. In addition, a cooperative European HSS should support and promote the implementation of structured national HSS or topic identification selection and prioritisation processes for HTA activities. Notably, the recommendations have been informed by the BeNeLuxA collaboration and their recent IHSI initiative (7;19) cooperation should be explored to avoid duplication of work.

Of particular relevance to benefit from a predefined workflow are the following EUnetHTA activities:

- WP4 joint/collaborative assessments
- WP5 topic identification for Early Dialogues (EDs) and parallel advice with EMA
- WP5 post launch evidence generation (PLEG)/additional evidence generation (AEG)
- WP7 increase the awareness, timeliness and thereby acceptance of joint HTA reports

EUnetHTA JA3 WP4 has experienced a lack of commitment from developers of technologies to suggest topics for HTA as well as some reluctance from HTA agencies to be involved in joint production and uptake of jointly produced HTAs. The reasons for this may be diverse and are not explored in this report. However, timeliness, relevance as well as lack of incentives may be important factors of concern. In addition, the regulatory route of MDs and IVDs does not predict marketing making timeliness of assessment difficult to predict.

We suggest that a workflow that includes systematic identification, prioritisation of topics, and early contact with WP4 partners and stakeholders could increase the number of timely produced joint assessments. To investigate this further we recommend to perform a pilot. Some information, including information related to timelines and pricing might be of value for the target group of HSS, but considered as confidential by developers. Early information shared between a pMAH and a

regulatory body may in many case be confidential, however the information is often available in other sources such as trial registries, patent applications etc. Special arrangements with developers and regulators, on how to deal with confidential information might be needed for a cooperative European HSS. For the pilot there will not be room for any special arrangements and developers will be asked to only share public available information. As a rule of the thumb that applies for both the HSS beyond 2020 and the pilot, information that may be cited with a public available source should be considered as non-confidential.

In EUnetHTA JA3 WP4 prioritisation is the responsibility of the individual agencies. In the recommendations for stakeholder involvement (Recommendation 10) we have stated that developers should not be involved in prioritisation. Originally the authors also stated that regulators should not be involved in prioritisation due to possible conflicts of interests. One problem brought up by reviewers was that some agencies have both regulatory and HTA tasks, and whether this will exclude them from being involved in prioritisation? For the draft recommendations regulators were excluded. However, this is a matter that needs to be further discussed and clarified within the working group. In addition, one could argue that ranking and final prioritisation should be independently from those doing the HTA. Although not possible for the pilot this needs to be discussed for the final recommendations.

The recommended pilot is focused on a TISP process to benefit initial (close to marked availability) assessments of technologies with commercial developers and is very restricted in funding. It will not include methodologically sophisticated HS activities. Thus, completeness with regard to the needs of the European HTA community and a life cycle perspective of technologies is not be the goal of the pilot. However, the pilot will explore the current ability of WP4 and WP7 partners, and stakeholders to contribute to identification and prioritisation in a more systematic way. Stakeholder contact has been a major focus of EUnetHTA and existing contacts on association level will be explored in the pilot. On regulatory level, EUnetHTA has recently signed a three years work plan with EMA where one activity is described as “exploring the opportunities to collaborate on monitoring new medicines approvals (“horizon scanning”)” (10). Contact with EMA will be in particular value for pharmaceuticals that do not follow the “normal 210 days path”, and enter the regulatory process closer to MA. In addition, the regulatory pathway may be slowed down (clock stops) due to unpredictable reasons. Timely and structured information from EMA on this items and sharing this information with EUnetHTA partners is valuable for planning of HTA activities within EUnetHTA. EUnetHTA has also established contact with MD and IVD regulators (30). As the regulatory system of MDs and IVDs are fragmented and under re-organisation, these contacts may currently not be as valuable for the TISP process as the EMA contact. However, the EUDAMED database planned to be launched in 2020 might change the landscape and allow for a more systematic use of information from regulators on MDs and IVDs in a TISP process.

Early dialogue (ED) on devices can only take place before the clinical evaluation for reimbursement admission and only if the pivotal clinical trial has not yet begun. Thus, ED would benefit from earlier identification than is needed for assessment. In many cases, the need for post launch evidence generation (PLEG) may be identified by an initial assessments, thus this activity would depend on identification of topics after or during initial assessment. The need for PLEG might also be linked to the regulatory processes and the ED process. Thus PLEG would benefit from the systematic monitoring of selected technologies from the early emerging phase (before pivotal trials are initiated) to after the initial assessment. Likewise, identification of obsolete technologies does depend on monitoring. We suggest that additional pilots or projects for other activities such as HS for

ED, PLEG and disinvestment should be planned for and could be coordinated by a central HS secretariat within EUnetHTA.

Conclusions

For supporting cooperative and collaborative HTA in Europe beyond 2020, we recommend to establish a HSS following standard operational procedures (SOPs). A coordinating secretariat should act at the central level of the system. Cooperation with existing HSS, HS initiatives and scientific networks should be explored to avoid duplication of work. The purpose of the HSS should be to support planning, timeliness and relevance of the HTA network's activities in a technology lifecycle perspective. The cooperative HSS should at least start with pharmaceuticals, MDs and IVDs for joint assessment as outlined by the EU proposal for regulating HTA. Further extension to any potential high impact (innovative), transformative or disruptive technologies as well as potentially obsolete technologies should be planned for with the focus being on patient needs.

A pilot of a TISP workflow on initiation of EUnetHTA WP4 activities should be performed to explore cooperation with existing HSS and networks, WP4 and WP7 partners' ability to share information from national TISP processes, the use of selection and prioritisation criteria as well as stakeholder involvement. Experiences from the pilot should be used to establish a TISP process for EUnetHTA WP4 activities and inform the final recommendations for a cooperative HSS beyond 2020, and to promote consistency of HS activities.

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Appendix 1

Questions and corresponding recommendations

(Questions are adapted (selected and modified) from the EuroScan Tool kit

Questions	Corresponding recommendation in presentation of the results
Step 1 Identify your customers needs	
1.1 What is the purpose of the EUnetHTA TISP system?	**1. Purpose**
1.2 Who do we intend to inform?	
1.3 What is the scope of the EUnetHTA TISP system (type of technology)? (also related to the scope of EUnetHTA/activity – and future European network and reassessment)	**3. Technology scope**
1.4 What type of output and information is needed? (This question will replace step 6 in the EuroScan toolkit). There might be one type of information needed for selection and more detailed information needed for prioritisation. (Table/excel file?)	**8. Type of output to be produced**
1.5 What are the main stakeholders and how will they be involved in the process? (This question and question 1.6 replaced step 7 in the EuroScan toolkit).	**10. Stakeholder involvement**
1.6 How shall the information be reviewed? Might depend on type of technology. (relates to the output – could be internal check, external or a wider group)	**9. Review of output**
1.7 When and how often shall information be prepared? Might depend on type of technology, source of information and timeliness	**11. Frequency of output preparation and updating**
1.8 How shall the information be distributed?	**8. Type of output to be produced**
Step 2 Time frame	
2.1 What is the time-frame for identification?	**4. Time frame for identification**
Step 3 Identification	
3.1 What sources will be used for identification?	**5. Information sources**
3.2 Who will do the identification?	**2. Organisation of the HSS**
3.3 Who will prepare the information (described in 1.4) needed for selection?	**2. Organisation of the HSS**
Step 4 Selection (filtration)	
4.1 Who will perform the selection?	**6. Selection**
4.2 What are the selection criteria?	
4.3 How is the selection performed?	
4.4 Who will prepare the information (described in 1.4) needed for prioritization?	**2. Organisation of the HSS**
Step 5 Prioritization	
5.1 Who will perform the prioritization?	**7. Prioritisation**
5.6 What are the prioritization criteria?	

Step 6 Organization and resources	
6.1 How can the TISP system be implemented in EunetHTA and post 2020 HTAN?	**12. Implementation and 2. Organisation**
Step 7 Evaluation of the system	
7.1 How can the system be evaluated	**13. Evaluation**