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EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

Pilot for topic identification selection and prioritisation (TISP) - Endpoint evaluation pharmaceuticals

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Developed by WP4 lead partner NIPHNO in collaboration with co-lead partners on pharmaceuticals NOMA and ZIN

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1.	28.11.2019	TISP pilot group on Pharmaceuticals	Draft EPER on TISP pilot for pharmaceuticals	TISP pilot group pharmaceuticals
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EPER= Endpoint evaluation report

1 Executive summary

As part of the EUnetHTA work package 4 (WP) deliverable on Recommendations for Topic Identification Selection and Prioritisation (TISP) this pilot was conducted to explore a workflow for voluntary collaboration on a TISP process based on horizon scanning information (HS) for EUnetHTA joint relative effectiveness assessment (REA) of new pharmaceuticals. The process was designed to be as simple as possible and included three steps: identification, selection and prioritisation of possible topics for REA. The pilot was conducted by a pilot group set up by the TISP WP4 work group according to a pre-defined project plan (available here). A three step process was set up were each step resulted in a product/list: A minimal dataset (MDS), a call for collaboration list (CCL) and the EUnetHTA prioritisation list (EPL). The EPL was merged with the existing EPL from 2018 and published as EPL2 on the EUnetHTA web site. The other products were considered internal documents of the EUnetHTA WP4. Based on the pilot the following conclusions were made by the Pilot group:

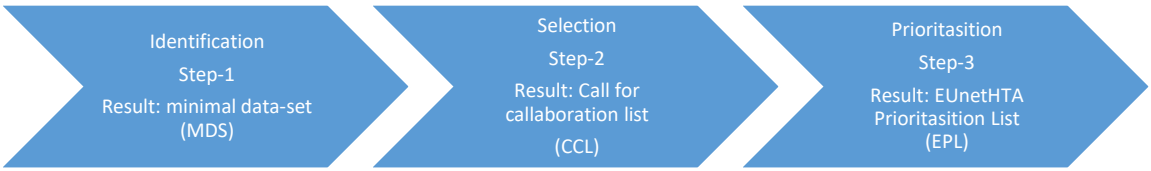
- *A TISP process informing prioritisation of joint REA of new pharmaceuticals is feasible by collaborative means, but can not be performed on voluntary basis alone*
- *The workflow can be conducted within approximately 3-4 months. It should be repeated at least twice a year to help timely identification of topics*
- *The prerequisite for the process to be successful is the presence of a central acting secretariat and the commitment of network members to share data and prioritise topics. Resources needed, if repeating the process twice a year, correspond to at least 60 person days per year for the central acting secretariat*
- *An improvement of the workflow would be to set up agreements with a pre-selected high quality horizon scanning system (HSS), prospective market authorization holders (pMAHs) and the European Medicines Agency (EMA) to specifically serve the purpose of the collaboration*
- *The fields (core elements/ included variables) of future MDSs should be revised based on the experience of the pilot. Most importantly, the field expected launch should be replaced by a best guess on MA or submission to EMA. Furthermore, to reduce duplication of work, the fields should be more aligned with a pre-selected high quality collaborative HSS*
- *For a TISP process to have substantial impact, members of the HTA network need to be able to engage in joint relative effectiveness assessments before knowledge on reimbursement applications or launch of a specific product in a specific country is available*
- *The EPL is currently actively used for acquisition activities by EUnetHTA, but more time is needed to conclude on the value of the TISP process as such*

Results of the pilot was used to inform the final recommendations on a TISP system for European collaboration on HTA beyond 2020.

2 Aims of TISP pilot - pharmaceuticals

The aim of the pilot is to explore a workflow for voluntary collaboration on TISP for joint REA of new pharmaceuticals. The process was designed to be as simple as possible so that it could also be used on a voluntary collaborative basis beyond Joint Action 3. Results of the pilot will be used to inform the final recommendations on a TISP system for European collaboration on HTA beyond 2020.

In short, the process includes three steps: identification, selection and prioritisation of possible topics. Each step results in a product/list (as seen below).



F1 Steps of the TISP process

3 Methods

Organisation of work
The WP4 lead (NIPHNO) and co-leads on Pharmaceuticals (NOMA and ZIN) constituted the TISP working group supported by NCPE, HAS, UCSC and NICE as described in the project plan. Shortly, NIPHNO, NOMA and ZIN acted as a central secretariat organising the TISP process.
Stakeholder involvement was limited to the identification step and selection step as described below.

Identification (step- 1)
In accordance with the project plan, three sources of information were explored:

1) EUnetHTA partners sharing data from existing local or regional Horizon Scanning systems (HSS) or TISP lists informing prioritisation of Health technology assessment (HTA): A questionnaire (available in the project plan) was sent to all EUnetHTA partners on whether they were able to share data from a regional or national HSS or a TISP list.

2) The European Medicines Agency (EMA) (Regulatory authorities): EMA provided an updated report (Excel list) of all ongoing or recently concluded applications for marketing authorisation (MAA), Extension of indication (EoI) and Line extension (LE). The report was solely based on publicly available information. This was based on an agreement made with EMA in December 2018. For details of the information provided see Appendix 1. The report was used to assure completeness of the data, update the information of minimal dataset (MDS), call for collaboration list (CCL) and EUnetHTA prioritisation list (EPL), and to inform the selection process. An update of the EMA reports were requested once.

3) Input from stakeholders: An announcement was made on the EUnetHTA home page and mails were sent to stakeholders (Appendix 2) to inform about the possibility to suggest topics for TISP.

The identification lists were collected and merged by NIPHNO and NOMA and topics were entered into a common form, the MDS. The fields of the MDS were developed by the EUnetHTA TISP group as described in the project plan. Duplicates were removed. The fields of the MDS were completed using the information from the identification lists, inspection of information added as hyperlinks by the sources and if missing, a web-search. The web search included the prospective market authorisation holder (pMAHs) web sites, NHS evidence and FDA. If information was not found fields were left blank due to missing information. The MDS was considered a EUnetHTA internal document shared with the WP4 TISP group on the EUnetHTA WP4 TISP workroom.

Selection (step-2)
According to the project plan, topics to be included in the CCL should fulfil the general scope:

- *medicinal products recently entering the central marketing authorisation (MA) procedure, or anticipated to undergo the central marketing authorisation (MA) procedure within the next 24 months. This includes both new active substances and existing products for which the marketing authorisation is anticipated to be extended to a new therapeutic indication*

In line with the project plan, identified topics anticipated to not fulfil these criteria and topics already handled by EUnetHTA were excluded. Based on pragmatic reasoning, biosimilars, generics as well as selected well defined products of low impact (see results for details) were excluded from the CCL. In addition, some topics were excluded based on EMA submission date and feasibility analysis related to timeliness of assessment.

NOMA performed the selection and created the CCL. The format of the CCL was developed as part of the pilot. The CCL was considered a EUnetHTA internal document shared with EUnetHTA WP4 partners by mail and access to the file in the EUnetHTA WP4 TISP workroom.

Prioritisation (step-3)
The CCL was sent to all WP4 Pharma partners asking them to indicate their interest in the topic. An adjusted CCL with no other information apart from compound name and anticipated indication(s), was also sent to EFPIA in order to gather information about estimated submission dates to EMA.

EUnetHTA WP4 partners could express interest in the topic as:

- *expressed interest in the topic as relevant for national/regional setting*
- *expressed interest in national/regional uptake of a EUnetHTA conducted REA*
- *expressed interest to participate in assessment as author, co-authors or reviewers*
- *no interest*

Interest in topics of the CCL was measured in accordance with the project plan with each yes answer receiving a score of one, and each no answer or do not know answer/open field, receiving a score of 0. This meant that each topic could receive a maximum of three points from each responding partner. The cut of for inclusion was chosen as part of the pilot (not specified by the project plan). First, topics with a total score of 50% or above relative to the maximum score for individual topics (3 X number of responding partners) were included. Some additional topics were included based on high country level score as explained in the result part.

As a last feasibility check on timeliness, some topics were excluded during the preparation of the EPL based on information on submission to EMA received from the pMAH. The final EPL was merged with the EPL1 from 2018 and published on the EUnetHTA homepage (https://eunethta.eu/assessments/prioritisation-list/). EUnetHTA partners as well as other stakeholders were informed about the EPL through e-mails.

Endpoint evaluation
We have reported on the timeline used for the workflow and the following endpoints in accordance with the project plan:

Identification: *Availability of data from different sources and barriers for information sharing; Number of identified topics;* Developmental status of topic when entering the MDS; *Regulatory status of topic when entering the MDS; Information gaps of the MDS*
Selection: *Number of topics in the MDS and CCL; Number of topics excluded from the MDS and CCL and reasons for exclusion; Information on topics in the CCL (Application type EMA, Therapeutic area, Developmental status, Regulatory status)*
Prioritisation: *Level of EUnetHTA partners with expressed interest in a topic. This was reported as a sum of interest on three levels (participating in assessment, relevant for national setting; relevance for national uptake of a EUnetHTA REA on the topic); Information on topics in the EPL (Application type EMA, Therapeutic area, Developmental status, Regulatory status)*
General: *Workload connected with each step.*

Deviations from the project plan:
Prioritisation: We used the sum of expressed interest across the three levels in topic for prioritisation. We did not report specifically on interest of EUnetHTA partners or their preferred roles. This was chosen due to comments indicating that expressed interest may be changed depending on the overall prioritisation and the pMAHs willingness to participate.

We have chosen not to report on the following planned endpoints:
Identification: *The number of times the same topic has been identified by different sources (overlap) should be reported on.* This turned out to be more resource intensive than anticipated by the project-plan and was not systematically measured. This is reflected on in the discussion.
Impact: Response from pMAH should be measured one month after first pro-active contact. As contacting the pMAHs is an ongoing process this endpoint was not reported on. This is reflected on in the discussion.

4 Results

Timeline of the pilot

- *The pilot started 1th of February 2019 by sending out the questionnaire on HSS/TISP lists and the announcement to suggest topics on the EUnetHTA homepage as described above*
- *The deadline to respond was first 1th of March 2019 and then extended to 15th of March*
- *Information from EMA was received twice with the first report with cut off March 1st 2019 and an updated list with cut off May 1st 2019*
- *The call for collaboration was sent out to EUnetHTA WP4 partners 25th April2019 with deadline to respond until the 16th May, 2019. An adjusted CCL was sent to EFPIA at the same time*
- *The EPL was published on the EUnetHTA homepage on 10th July2019*
- *Contacting pMAHs for dialogue on participation is per November 2019 ongoing work*

In conclusion, each round of a workflow from identification to publication of the updated EPL will take at least 3-4 months leaving reasonable time for each step (Identification, Selection and Prioritisation) to be performed on a voluntary basis.

Identification

Availability of data from different sources and barriers for information sharing

According to the project plan the following sources of identification would be explored

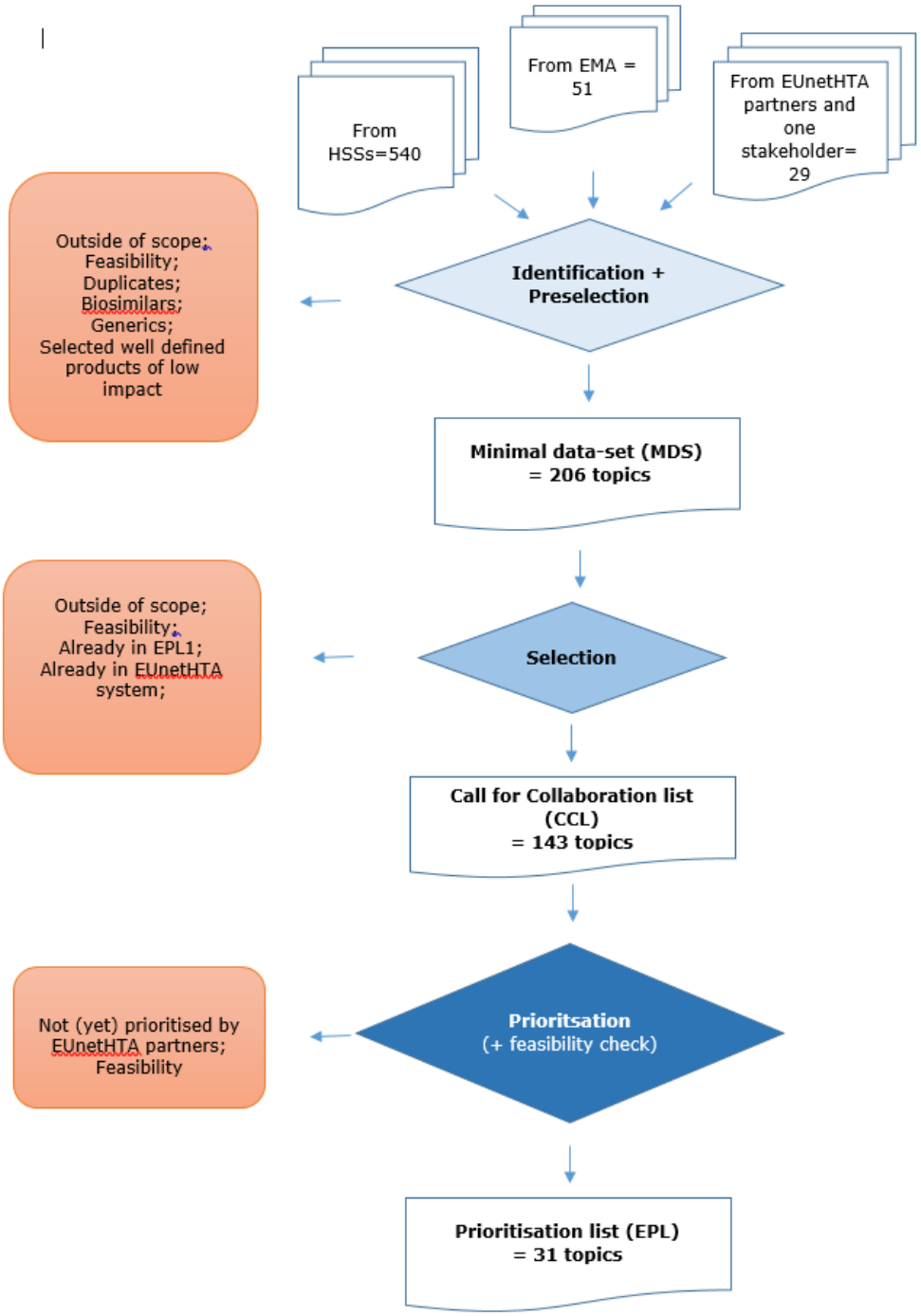
1) *EUnetHTA partners providing data from existing European HSSs and/or TISP-lists*
2) *EMA (Regulatory authorities)*
3) *Suggestions from EUnetHTA partners and stakeholders*

28 EUnetHTA partners from 19 different countries responded to the questionnaire about their ability to share data from their HSS or TISP-lists. Based on information from the responding EUnetHTA partners, ten countries have a national or regional HSS and/or list of topics to inform prioritisation of HTA on pharmaceuticals. EUnetHTA partners from five countries stated that they were able to share data/topics from their HSS for the EUnetHTA pilot as well as beyond 2020 (see table 1).
The response rate corresponds to 66% with regard to response on country level (information was received from 19 countries out of 29 countries with EUnetHTA partners), and 35% with regard to EUnetHTA partners response (28 partners responded out of 81 contacted). Notably, not all EUnetHTA partners are HTA agencies and have information on HSS.

T1 *Countries with HSS or TISP-list informing HTA on pharmaceuticals*

Countries with HSS or TISP-list informing prioritisation of HTA on pharmaceuticals	Share for pilot	Share beyond 2020	Preferred interval for sharing (x per year)
Austria*	Yes	Yes	4
Ireland	Yes	Yes	2
Netherlands	Yes	Yes	2
Norway**	Yes	Yes	2-4
England	Yes	Yes	No preference
Switzerland***	No	Maybe	2
Finland	No	No	-
Italy***	No	Maybe	-
Malta	No	No	-
Scotland	No	No	-

Only oncology, **Only pharmaceuticals identified through publicly available information from EMA, * At the moment sharing is not possible due to confidential data.*



F2 Flowchart of the TISP process for Pharmaceuticals

The numbers refer to numbers of topics processed during the pilot. The same topic may be a compound with one or more indications. One topic can be a line-extension of an existing or excluded topic. In some cases, indications were excluded without changing the total number of topics. Feasibility refers to submission relative to timely EUnetHTA joint assessments (explained in the text). Topics extracted from EMA listings were restricted to topics in the early phase (1-3 months after submission of application). Topics excluded due to feasibility were either excluded based on information on status on the MA process received from EMA or from companies.

The preferred interval for sharing varied from one to four times a year, but most of the respondents preferred two times a year. The main barriers for sharing information was related to confidentiality issues and time line.

Number of identified topics
During the pilot, three agencies involved in EUnetHTA: NICE, England, ZIN, Netherlands and NOMA, Norway supplied lists of topics derived from national HSSs. The HS list from Norway only included products already in the EMA system for more than 3 months and no topics from this list was included. The list of approximately 400 topics received from ZIN was in Dutch and not sorted by the date of entry. Likewise NICE supplied a long list of topics (>400), but these were sorted by the date of entry. Topics on the NICE list with entry prior to July 2018 were previously verified for the first EPL (EPL1) published in 2018 and excluded from the identification list. In total, 140 topics with entry between July 2018 and January 2019 were first included from the English HSS. In addition, NIPHNO received suggestions of topics from the following EUnetHTA partners NCPE (5), SBU (2), NOMA (21) and HVB (1) and one stakeholder (Eurordis; The Voice of Rare Disease Patients in Europe)(19). Numbers within brackets/parentheses is the number of suggestions. Based on prior agreement EMA supplied reports of topics twice. Topics in the EMA reports on ongoing or recently concluded MAAs, EoIs, and LE were sorted according to if the topic was in a first evaluation phase (1 to 3 months after submission of application) or if the application was ongoing (list of question, list of outstanding issues) or concluded. Topics in a first evaluation phase (27 listings for full MAA and 24 for LE or EoI) were included. Based on this, the total number of identified topics was 620.

A pre-selection step was introduced to remove duplicates before merging the topics in a minimal data set (MDS) list. The pre-selection involved checking topics (compounds and individual indications) from the HSS list shared by ZIN against MA data available on the web and the extended selection criteria (see methods above and details given under selection below). Based on this, 98 topics from the ZIN list were translated to English and transferred to the MDS. Of the 140 topics identified as potentially within the scope from the NICE list, only 30 topics with entry in November 2018 to January 2019, were transferred to the MDS. Topics listed before this were excluded without systematic checking all compounds and indications against the ZIN list. This was a pragmatically chosen deviation from the project plan to save resources. Some topics submitted by EUnetHTA partners and the stakeholder were already authorized, these topics were excluded during the pre-selection step. After removing duplicates in the MDS and checking all topics (compounds and individual indications) against the first EMA report and other sources of information as described in the methods section, the initial MDS contained 206 unique topics[1].

Developmental status of topics when entering the MDS
By developmental status we had in mind to describe the status of clinical research (phase I, II or III) and best guess on expected submission date to EMA and launch. When developmental status was identified, substances were most frequently reported to be in phase III trials. However, for many topics this information was resource intensive to find, and the endpoint field was left blank. Where available the information was included in the comment field of the MDS.

Notably launch would be different in different countries and we suggest that this is changed with best guess on MA in quartiles of a year. As therapeutic area was provided we did not see the need for to report a best guess on the first numbers of the ATC code.

Regulatory status
When entering the MDS none of the topics were authorized but might have applied for MA.

[1] One topic is either a new compound (new market authorization) with one or more indications or an extension of indication for a specific product. For this reason one compound can be counted as several topics (in both MDS and CCL) due to different indications.

Information gaps of the MDS
The fields of the MDS were pre-determined by the TISP pilot plan as shown in table 2. Based on the information provided by the sources, followed by a search in NHS-Evidence, the information gap of the MDS most frequently encountered were lack of information regarding ATC code, type of application, estimated launch, estimated submission date to EMA and developmental status.

T2 *Information gaps of the MDS*

Fields of the MDS	**Gaps observed for 206 topics/items**
International non-proprietary name (INN) Name of product(s)	No gaps observed
Product name (if avialble)	Lacking in some cases (not yet available)
MAH/pMAH	No gap observed
Indication (anticipated, including age and sex if applicable)	No gap observed -All topics contained at least one anticipated indication. Information on age and sex lacking in most cases
Therapeutic area	No gap
ATC code (best guess first numbers)	Lacking in most cases – left blank not part of the CCL.
Application type EMA (anticipated): Initial market application (IMA); Line extension (LE); First in class (FC); Priority Medicine (PRIME); Accelerated access (AC); Orphan drug (OD)	Lacking in more than 1/3 of the topics
Timeline clinical research (Information on pivotal trials and trial number(s) if available)	Developmental status. Field left blank and information moved to comment section
Regulatory status	No gaps
Estimated launch (best guess)	Left blank (see comment in the discussion). The field should be changed to best guess on MA or submission date
Comments and hyperlinks to information	Hyperlinks to information available for all topics from NICE, information on developmental status available for approximately half of topics

Selection process
Number of topics in the MDS and CCL
The MDS included 206 topics and the final CCL 143 topics.

Number of topics excluded from the MDS and CCL and reasons for exclusion
A pre-selection step was used to assure that most topics in the MDS were in line with the scope (see methods above). Reasons for excluding topics from entering the MDS in line with the project plan were:

- *Topics with granted marketing authorisation (indication linked)*
- *Topics that had applied in the EMA system for 3 months or longer at the time updating the MDS, were excluded from CCL (time-lines are too short for parallel Joint REA process).*
- *Topics that were too early in the clinical development process and are assumed to apply for MA beyond 2020 (not feasible within EUnetHTA JA3 timeframe)*

The later report from EMA sent in May was used to update the MDS before preparing the CCL. For

topics entering the CCL further duplicates were removed and additional pragmatic exclusion criteria were defined as part of the pilot to restrict the CCL to topics of substantial importance. The following topics were excluded from entering the CCL based on these criteria:

- *Bio-similar compounds*
- *Generics*
- *All call for collaboration 2018 topics (indication linked)*
- *All topics on the first EUnetHTA Prioritisation list from 2018 (EPL1 topics, indication linked)*
- *All topics already submitted to EUnetHTA (all topics that already have been discussed during F2F or TC meetings with the actual pharma company).*
- *Selected well defined products/compounds with assumed low impact (Amoxicilin, ciprofloxacin, Glucagon, exenatide, fluticasone, Formoterol, glycopyronium, budesonide, Indacaterol acetate, glycopyrronium bromide, mometasone furoate, Latanoprostene)*

In addition, based on information on submission date some prioritised topics were excluded from entering the EPL (see below).

Information on topics in the CCL (Application type EMA, Therapeutic area, Developmental status, Regulatory status)
There was a broad range of MAA type (orphan, prime, extension of indication, new market authorisations, etc.) in the CCL. Table 2 reveals an overview of different EMA application types for included compounds of the CCL. The table is based on known/ reported application type from the information sources we have used. We included the information were available. Topics with unknown application type are shown in the last column of the table.

T3 ***Application type EMA in the CCL***

Number indentified topics	**Application type EMA as reported in Call for collaboration list**							
	EoI	IMA	PRIME	AC procedure	Orphan drug	FC	LE	?
CCL 143	25	35	10	3	20	3	3	54

EoI Extension of indication, IMA Initial Market Authorization, AC procedure Accelerated procedure, FC first in class, LE line extension. ?= Application type not known

Therapeutic areas of topics in the CCL were: Cardiology, endocrinology, oncology, psychiatry, neurology, respiratory diseases, infectious diseases, immunology. In the CCL there were topics that had entered the EMA process, but no topic had MA and no topic had been longer on listings than approximately three months on May 1th 2019. Due to limited resources, we did not systematically check the developmental status of topics in the CCL.

Prioritisation process
Level of EUnetHTA partners with expressed interest in a topic.
The CCL was sent to 48 EUnetHTA WP4 Pharma partners in a call for collaboration. 22 EUnetHTA WP4 pharma partners from 18 countries responded giving 62% response rate on country level (18/29 EUnetHTA member countries) and 45% response rate on partner level (22/48 EUnetHTA WP4 partners on Pharma).

All partners expressed interest in at least some topics. Based on expressed interest for national setting, national uptake and/or interest to participate in assessment the max score each topic could get was 66 (3 x 22). First, topics were ranked by total score alone. Topics that had a total score of 50% of max (33 points) or above were included in the first step resulting in inclusion of 29 topics. Secondly, the topics were ranked by both number of countries providing a score and the total score. This ranking was compared to the 29 topics selected by total score alone (step 1 above). Identified

new topics (using 29 as a cut off) were added to the prioritisation list. This resulted in a total number of 36 prioritised topics.

No topic received 0 points. No topic received the top score of 66 points. The maximum score for an individual topic was 42 points and minimum score 20 points. The highest overall score for a topic based on interest for national setting was 12/18 and the lowest score was 2/18. The highest overall score for a topic based on interest for national uptake was 10/18 and the lowest score was 2/18.

Feasibility analysis were performed late in the process in order to secure that prioritised topics with anticipated EMA submission prior to Q3 2020 were included with timelines to fit the EUnetHTA joint HTA process. Based on these analysis, topics that had already applied to EMA and topics reported to early, reported failure or with withdrawn studies were excluded (information received from pMAHs). The latter topics can be included in future EPL iterations. Based on this feasibility analysis the total number of topics in the final EPL was 31.

Information on topics in the EPL (Application type EMA, Therapeutic area, Developmental status, Regulatory status)
Application type to EMA in the EPL were as variated as for the CCL (please see table T3).Therapeutic areas of topics in the EPL were: Cardiology, endocrinology, oncology, psychiatry, neurology, respiratory diseases, infectious diseases, immunology. The dominating therapeutic area was oncology (10 topics). We did not systematically check the developmental status of topics in the EPL. Due to the last feasibility check, no topics in the EPL had MA as per publication date, and no topics was on the listings received from EMA with date May 1th.

Workload connected with each step
Contact with partners in order to receive lists and suggestions
The workload connected with receiving the HSS lists and suggestions was limited to approximately 1 person day.

Creating the MDS
The pre-selection and selection steps were time-consuming. Furthermore, filling in the fields of the MDS with data derived either from the source or searches did take substantial time. Even with a pragmatic approach, depending on search in NHS-Evidence limited to Horizon Scanning and using copy-paste from the sources found, one would expect 5-15 minutes per topic. The time used depended on information provided in the source/suggestion form. Every operation beyond transferring the topic and received information added to the workload. Information on fields not easily found were left blank. To clean up and make a final CCL also required more resources than expected. Likewise, the process from CCL answers to EPL was time consuming, mainly due to the fact that there were many topics on the CCL and that each topic could have more than one indication. The process for feedback from EFPIA (not in the project plan) also added time.

As 620 topics were identified and a total of 206 topics were transferred to the MDS there is a need for approximately ten person days for this step. In total the process from MDS to CCL and from CCL to EPL2 (not included workload of sending CCL to stakeholders and forwarding all answers) took nearly twice as much time as anticipated in the TISP pilot project plan (30 person days instead of 15). Even after getting more experience we consider that an additional 20 person days would be needed giving 30 person days per cycle including sending the CCL to EFPIA and getting response from the pMAHs.

In conclusion, the workload for a central acting secretariat connected with one round of the workflow performed twice a year and approximately the same amount and type of information, is anticipated to be at least 60 person days per year for the secretariat alone.

In addition, resources are needed for partners sharing information and partners prioritising topics. We did not systematically collect data on time spent for sharing information or prioritisation, but at least

one or two person days per responding partner for each step is anticipated. Adding this to the process would probably at least double the resource need of the workflow. Repeating the process would also require up-dating the existing MDS. This has not been included in the pilot. Some reduction is anticipated based on learning, but most importantly more efficient use of identification sources (HSS) would reduce the workload.

Response from pMAH

Response fro the pMAH was a predefined outcome, but is actually not part of the TISP process and details have not been collected as part of the pilot. All pharma companies on the published EPL have been contacted at least once after the first email was sent. The contact with pMAHs is an ongoing process were conferences, telephone conference, webinars and if possible, F2F meetings are being scheduled. So far there is a general positive interest about EUnetHTA activities and a willingness to participate in joint REA.

5 Discussion

We have explored a simple three step TISP process to support prioritisation of joint voluntary collaboration on REAs within the framework of EUnetHTA JA3 and beyond. In the project plan, the only selection criteria (scope) was timeliness with regard to the EMA MA process. This was set to a maximum of 3 months after submission. Prioritisation was based on EUnetHTA partners interest in the topic for national setting, national uptake of HTA or participating in HTA.

To restrict the workload and adjust for feasibility and timeliness of EUnetHTA REA production, some minor modifications of the project plan had to be made. The results revealed that it is possible, to set up a system based upon voluntarily sharing of information, and to use this information to extract a list of topics based on the collaborating partners expressed interest in the topic. The workflow (from identification to publication of the EPL) may be conducted within approximately 3-4 months and resources needed if repeating the process twice a year correspond to at least 60 person days per year for the central acting secretariat. Resources needed for partners sharing information and partners prioritising topics was not measured as part of the pilot, but adding this to the resource need would probably at least double the resource need.

Identification

Identification should assure that relevant topics in scope of the TISP process are identified in a timely manner to ensure that the TISP process contributes to collaboration on the most relevant HTAs and that the HTA process will not unnecessarily delay introduction of innovative medicines. We explored three sources of identification: EUnetHTA partners sharing data from existing HSS/TISP-lists, listings from EMA and EUnetHTA partners and stakeholders proposing topics.

Three EUnetHTA partners provided data from HSSs, but only two of these HSS were in line with the scope of the project. Nevertheless, based on information on the websites of the HSSs from which the responding partners provided data, we can conclude that the systems used a broad range of sources and that most relevant topics should have been identified in a timely manner. However, some topics may be missing based on different scopes of the HSSs relative to the pilot. In particular, with the exception of very large impact vaccines relevant for the Dutch system, vaccines are not in scope of the HSSs contributing with topics. Future models should more clearly indicate if particular therapeutic areas or types of topics are out of scope.

The pilot was conducted with no pre-set agreements on how and when to deliver data. In practice this led to substantial workload for the pilot group, re-entering data probably already available in a structured form in the HSS. To reduce the workload connected with preparing the MDS, a deviation from the work plan was made restricting the final inclusion of topics from the English HSS to only the most recent updates. This was a pragmatic approach based on resource availability and the assumption (personal communication) that the Dutch system, where all data was inspected, used the English system as one of their sources for identification of topics. This approach was chosen for pragmatic reasons, and does not reflect any quality judgment. It should not be used as guiding for future procedures. Rather one should investigate, based on direct contact with the HSSs, to what extent they use the same sources and how duplication of work can be avoided. Additionally, two partners indicated that they could share data in the future, and collaboration with additional HSS with publicly available data, and the latest development of International collaboration on horizon scanning initiative by IHSI (see www.ihsi-health.org/) should be explored for HS serving joint assessments. Furthermore, agreements with the EuroScan initiative (see www.euroscan.org/) might provide a good starting point to set up voluntary collaborative agreements to avoid duplication of work. In the planning phase of this pilot, the IHSI collaboration was not yet fully established, and EuroScan was in a restructuring phase. Thus, no collaborative agreements with these organisations could be set up by the TISP group. In near future this might look differently.

Individual EUnetHTA partners did propose topics, but only one stakeholder was amongst the proposers. The short timelines for topic proposal could be a major factor contributing to this. Future models should more actively promote stakeholder proposals. Several of the proposed topics were not in line with the timeline of EUnetHTA REA assessment, and some would rather be considered proposals for re-assessments and therefore out of scope for the pilot. Pharmaceutical companies did not propose any topics, as this was not a part of the pilot and were never asked to propose topics, but contributed with valuable updates on their products in the CCL. Based on this experience, we would recommend involving pharma companies more actively in the process at an earlier stage. The pMAH might be willing, to share information about their product to be identified, delays in EMA submission process, or change of EMA procedure (application type).

Collaboration with EMA proved very useful. EMA has been very positive and delivered updated information on products submitted to EMA according to data specifications from the TISP group. These data were in particular used for exclusion of identified compounds on the grounds of lack of timeliness of assessments (feasibility assessment). Currently, the information which can be shared by EMA was of less value as it is limited to publicly available documentation which means that it is less suitable for the purpose of identification of products suitable for joint REA. In future models, closer links with the EMA to share horizon scanning information and pipe lines would be very useful if these links can be established. These links could also be made directly between EMA and HSSs.

Based on experience from ZIN the co-lead partner on pharmaceuticals, the best time-point to approach a pMAH for a potential participation in a REA process is probably three to six months prior to the submission of an MA application to EMA.

With regard to timeliness, many topics included by HSSs are identified before this time point. Unfortunately, at the ideal time point (three to six months before EMA submission) many pMAHs consider information on timelines as commercially sensitive. No confidentiality agreements could be made as part of the pilot, and we could only receive public available information. pMAHs often send a letter of intent to EMA 6-7 months prior MA application. This information would be useful for TISP processes. We did send the

In future models, it should be explored if collaboration with a preselected high quality HSS, pMAHs and EMA can based on agreements to share data better aligned with the feasibility timeline for joint REAs.

Selection

Selection should assure that the identified topics are within the scope of the TISP process. In addition, the step was used to identify duplicates and complete the MDS and CCL. Selection was performed in two steps, first a preselection step before merging the identified topics, then after merging and completing the MDS and CCL. Timeliness was the main selection criteria. The pre-selection and selection processes turned out to be more resource demanding than anticipated. Even the few fields included in the MDS, as designed for TISP, provided substantial workload.

There are several reasons for this. Timeliness, duplicates and different topic definitions were a major issue and added to the workload. Notably, two field of the MDS: Best guess on expected launch and ATC codes were left blank. ATC code was not included and not deemed essential for prioritisation. Best guess on expected launch was omitted because it is country specific. Information on timeliness relative to MA is important for work-planning, and as the CCL is expected to provide topics within a pre-specified timeline, the field expected launch in future models could be replaced by anticipated MA or submission to EMA.

Ideally, methods for delivering reliable dates for MA or submission to EMA should be worked out, but anticipated MA or submission to EMA is less sensitive information compared to expected launch, and a best guess on quarterly per year estimates can be made based on public available information. We

introduced an additional step in the process by sending the CCL to EFPIA. This turned out very valuable and could have been introduced at an earlier stage, either by sending the MDS to EFPIA or by closer collaboration with a pre-selected high quality HSS in a more systematic way. Fields (core elements/ included variables) in future MDS list should be revised based on this and aligned with collaborative HSSs assuring that these elements are delivered in more structured ways to avoid re-entering of data. Future models may reduce the workload by pre-set agreements on what data to deliver, how to deliver the data and when to deliver data.

The present work was a pilot so it was natural to limit the selection to products feasible for a joint REA during the EUnetHTA JA3 period. In future models, if resources are as limited as in the pilot, it may be necessary to further specify selection criteria to limit the topics to a smaller range of topics perceived as most relevant for European collaboration. Topics identified at early stage, which are not feasible for JA3, but might be relevant for future European collaboration in HTA and were retained in the MDS. Future models should include a step for "re-selecting" these topics from the MDS.

Prioritisation

Prioritisation should ensure that only the most relevant topics are prioritised. In this pilot, prioritisation criteria were limited to expressed interest in topics at the national level, potential participation in production and national uptake of a European HTA.

28 EUnetHTA partners responded to the call for collaboration. 31 topics with the highest number of positive feedback from EUnetHTA partners and countries were prioritised among 143 selected topics. We conclude that this should ensure that relevant topics are prioritized by for joint REA. However, this way of prioritization does not reflect why partners are prioritizing the topic. We had included a comment field to the CCL for the partners to be used. No partners commented on reasons for prioritisation or lack of information on the topic for prioritisation. Introducing specific and transparent prioritisation criteria would add substantial work-load and was deemed to complex and resource demanding for a voluntary model. This might also increase the need of more specific and comprehensive data on the topic in the CCL.

Using the comment field, several partners indicated that they had difficulties to plan for future resource allocation considering participation in assessments and roles of the team without knowing exactly the timeframe for expected task. They specifically pointed out that the interest in a topic may change. For many EUnetHTA partners, it is challenging to specify exactly at the stage of prioritisation which topics will be assessed nationally or regionally or at what time. Some other partners reported that the decision about reimbursement and HTA-assessment is made on a case-to-case basis so they could not answer the question about relevance at national level. In some countries, companies submit an application to HTA-agencies for reimbursement at which point HTA is initiated. Expected launch and these applications in a particular country is commercially sensitive information and so willingness and ability to share the information can be limited. Some countries will be limited in their ability to take part in TISP or joint relative effectiveness (REA) exercises due to lack of advanced knowledge about whether a company plans to submit an application for reimbursement and therefore whether a topic is a priority for them. Based on these comments, we decided to deviate from the project plan and to not provide data on responses from EUnetHTA partners to participation in joint REAs.

Joint REAs are dependent on MA timelines, it cannot be initiated without an agreement from a company to participate. In an ideal TISP scenario the companies (pMAHs) would be able to provide information about the product, MA dates and launch plans around Europe. This would allow selection and prioritisation exercises to be carried out in a timely manner on topics most likely to be launched in multiple European countries and to add value in multiple European countries. To increase the impact of the TISP process in future models, companies and also national or regional processes for commission of HTA should be encouraged to develop models were joint REAs can be prioritised before information on application for reimbursement or launch in a particular country is available.

6 Conclusions

A TISP process informing prioritisation of joint voluntary collaboration on REA of new pharmaceuticals is feasible by collaborative means. The workflow (from identification to publication of the EPL) can be conducted within approximately 3-4 months. It should be repeated at least twice a year to help timely identification of topics of broad interest to the HTA network members. The prerequisite for the process to be successful is the presence of a central acting secretariat and the commitment of network members to share data, commit to production and uptake. Resources needed, if repeating the process twice a year, correspond to at least 60 person days per year for the central acting secretariat. An improvement of the workflow would be to set up agreements with a pre-selected high quality HSS, pMAHs and EMA to specifically serve the purpose of the collaboration. This is probably not possible on a complete voluntary basis. The fields (core elements/ included variables) of future minimal datasets should be revised based on the experience of the pilot. Most importantly, the field expected launch should be replaced by a best guess on MA or submission to EMA. Furthermore, to reduce duplication of work, the fields should be more aligned with collaborative HSSs. For a TISP process to have substantial impact, members of the HTA network need to be able to engage in joint relative effectiveness assessments before knowledge on reimbursement applications or launch of a specific product in a specific country is available.

The EPL is currently actively used for acquisition activities by EUnetHTA, but more time is needed to conclude on the value of the TISP process as such.

Appendices

Appendix 1 Information fields of the Reports provided by EMA

In the context of the pilot, the report covers all ongoing or recently concluded applications for marketing authorisation (MAA), Extension of indication (EoI) and Line extension (LE). The report was solely based on publicly available information however provides this is a single document for processing rather than numerous PDF files.

MAA ongoing or concluded:

Application Number	Is Orphan Drug	Product INN	Application Status	MAA type	Therapeutic Indication - Summary	Outcome	Outcome Date

MAA 1st evaluation phase:

Application Status	Product INN	Is Orphan Drug	Application Number	MAA type	Therapeutic Indication - Summary

EoI LE ongoing or concluded

Application Status	Product Name	Product INN	ATC Code*	Is Orphan Drug	Application Type	Application Number	Submission Date	Application Scope	MA Holder	Outcome	Outcome Date

EoI LE -1st evaluation phase

Product Name	Product INN	ATC Code*	Is Orphan Drug	Application Type	Application Number	Application Scope	MA Holder

In addition EMA provided a link to the (List of products granted eligibility to PRIME and refer to the tab 'PRIME products (previous)') and an explanatory summary of Milestones and timelines of regulatory assessment procedures and current reporting mechanisms

*ATC code not complete for all entries

Appendix 2 Contacted stakeholders

ORGANIZATION	CATEGORY
Bureau européen des unions de consommateurs-BEUC	CONSUMERS
Health Action International-HAI	CONSUMERS
European Cancer Patient Coalition-ECPC	PATIENTS
European Federation of Allergy and Airways Diseases Patients' Association-EFA	PATIENTS
European Institute of Womens Health-EIWH	PATIENTS
European Rare Disease Organisation-EURORDIS	PATIENTS
European Patients Forum-EPF	PATIENTS
European Multiple Sclerosis Platform-EMSP	PATIENTS
European Public Health Alliance-EPHA	CONSUMERS/PATIENTS/NGOS/HCP
International Diabetes Federation European Region-IDF	PATIENTS
European Organisation for Research and Treatment of Cancer - EORTC	RESEARCH
International Association of Mutual Benefit Societies-AIM	PAYERS
European Social Insurance Platform-ESIP	PAYERS
Council of European Dentists -CED	HCP
Standing Committee of European Doctors-CPME	HCP
The European Association of Hospital Pharmacists-EHAP	HCP
European Union of General Practitioners/ Family Physicians UEMO	HCP
European Society of Medical Oncology-ESMO	HCP
European Forum for Primary Care-EFPC	HCP
European Public Health Association-EUPHA	HCP
European Hospital and Healthcare Federation-HOPE	HCP
European Society of Cardiology-ESC	HCP
Pharmaceutical Group of the European Union-PGEU	HCP
Association of the European Self-Medication Industry-AESGP	INDUSTRY
European Coordination Committee of the Radiological, Electromedical and Healthcare IT Industry-COCIR	INDUSTRY
European Association for Bioindustries-EuropaBio	INDUSTRY
European Confederation of Pharmaceutical Entrepreneurs-EUCOPE	INDUSTRY
European Federation of Pharmaceutical Industries and Associations-EFPIA	INDUSTRY
Medicines for Europe*	INDUSTRY
MedTech Europe (Eucomed)	INDUSTRY
MedPharmPlast Europe, a sector group of the European Plastics Converters-MPPE	INDUSTRY
Plasma Protein Therapeutics Association Europe AISBL-PPTA Europe	INDUSTRY
European Diagnostic Manufacturers Association (EDMA)**	INDUSTRY
ISPOR	RESEARCH

* Medicines for Europe is the former European Generic Medicines Association (EGA)
HCP = Health Care Professional