Recommendations for production process of Relative Effectiveness Assessments after Joint Action 3

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Version log

Version number	Date	Modification	Reason for the modification
V0.1	17 April 2020	First draft report	
V0.2	1 May 2020	Second draft report	
V0.3	18 May 2020	Third draft report	
V0.4	14 Sept 2020	Fourth draft report	Incorporated input from WP4 partner organisations
V0.5	9 Oct 2020	Fifth draft report	
V0.6	20 Oct 2020	Sixth draft report	
V1.0	5 Nov 2020	Final report	
V1.1	28 May 2021	Update of the final report	

This report has been developed by Work Package (WP) 4 Lead Partner Norwegian Institute of Public Health (NIPHNO), Co-Lead Partner for other technologies Austrian Institute for Health Technology Assessment (AIHTA), and Co-Lead Partners for pharmaceuticals Zorginstituut Nederland (ZIN), and the Norwegian Medicines Agency (NOMA).

WP6 Lead Partner (IQWIG) has contributed to parts of the report.

The report has been under consultation by all WP4 partners, where input from 13 partner organisations was received.

List of abbreviations

CHMP	Committee for Medicinal Products for Human Use
CoLP	Co-Lead Partner
CUR	Domain on health problem and current use of technology
DOI	Declaration of Interest
DOICU	Declaration of Interest and Confidentiality Undertaking Form
ECA	EUnetHTA Confidentiality Agreement
EMA	European Medicines Agency
EFF	Domain on clinical effectiveness
EFPIA	European Federation of Pharmaceutical Industries and Associations
EPAR	European public assessment report
EPICOT	Evidence Population Intervention Comparison Outcome Timestamp
EPL	EUnetHTA Prioritisation List
EU	European Union
EUDAMED	European Database on Medical Devices
FAQ	Frequently Asked Questions
GDPR	General Data Protection Regulation
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HTA	Health Technology Assessment
HTAN	Health Technology Assessment Network
ISN	Information Specialist Network
IVDR	In-vitro Diagnostics Regulation
JA	Joint Action
LP	Lead Partner
MA	Marketing Authorisation
MDR	Medical Devices Regulation
OTCA	Other Technology Collaborative Assessment
OTJA	Other Technology Joint Assessment
(p)MAH	(prospective) Marketing Authorisation Holder
P/C&HCP	Patients, consumers, and healthcare professionals
PICO	Population, intervention, comparator, outcomes
PLEG	Post-Launch Evidence Generation
PLS	Plain language summary
POP	Planned and Ongoing Projects
PTJA	Pharmaceutical Technology Joint Assessment
REA	Relative Effectiveness Assessment
SAF	Domain on safety
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SSN	Statistical Specialist Network
RCT	Randomised controlled trial
RoB	Risk of Bias

TEC	Domain on description and technical characteristics of technology
TISP	Topic identification, selection and prioritisation
WP	Work Package

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1 Introduction

1.1 Aim and structure of the report

One of the main objectives of the WP4 Joint Production is to:

Provide recommendations for assessment production process as part of a future model of cooperation on Health Technology Assessment (HTA).

This report aims to give an overview of the work that has been carried out in Joint Action 3 (JA3), our experiences, and recommendations based on these experiences and lessons learned, to fulfil the objective mentioned above. Each of the various aspects of the production process will be presented and include these two parts:

1. the work done and experiences, and
2. recommendations.

The provided recommendations are based on our experiences with a voluntary system and are therefore applicable to a voluntary system. Should any of the recommendations be related to a mandatory cooperation (HTA regulation), we will state that explicitly in the report.

1.2 Target audience of the report

The target audience of this report is the European Commission and EUnetHTA partners. Furthermore, it informs the work on EUnetHTA's White Paper for future model of European cooperation on HTA. The report may also be informative for a wider audience such as stakeholder groups of HTA. The report contains no confidential information.

1.3 Sources of information

This report is based on information exchange and meetings with project managers at Activity Centre Department Leads (other technologies branch), feedback sessions with industry (pharmaceuticals branch), feedback sessions with authoring teams (pharmaceuticals branch), input from partners from WP4 face-to-face and e-meetings, feedback from partner consultations where available, documentation from workshops of the EUnetHTA Task Force on HTA and Medical Devices, and own experiences from WP4 Lead Partner (LP) and Co-Lead Partners (CoLPs). Additional feedback from stakeholder groups from face-to-face meetings and consultations is included where available.

Information regarding participation of partners has been collected from the EUnetHTA website and the EUnetHTA intranet.

WP6 Quality Management, Scientific Guidance and Tools and WP4 created a survey that systematically collects feedback from assessment teams and project managers after the finalisation of each assessment. Information from this survey is also included in this report. In

addition, an evaluation survey on centralised and decentralised project management in other technologies, and a fact check (factual accuracy check) survey and analysis, have informed the report.

1.4 Context of Relative Effectiveness Assessment production

Definition of Relative Effectiveness Assessments

In JA2 (2012–2015), the focus was to strengthen the practical application of tools and approaches to cross-border HTA collaboration. In this project, both full HTAs and Relative Effectiveness Assessments (REA) were conducted. In JA3, the main focus was on the development of process and production of REAs. In addition, Rolling Collaborative Reviews and Rapid Collaborative Reviews have been conducted for COVID-19 diagnostics and treatments, since the EUnetHTA Executive Board decided in 2020 to prioritise activities around COVID-19 to respond to the public health emergency[1]. However, since these products were so recently developed, the current report only focusses on REAs.

In May 2018, the Executive Board decided that WP6 would only create Standard Operating Procedures (SOP) for the production of REAs.

The REAs are assessments concerning the first four domains in the HTA Core Model® only, but may also consider other items, such as ethical, organisational, patient and social, and legal aspects. The four domains of a REA are:

- Description and technical characteristics of technology (TEC)
- Health problem and current use of the technology (CUR)
- Clinical effectiveness (EFF)
- Safety (SAF)

In JA3, a distinction was made between two types of REAs, i.e. Joint Assessments and Collaborative Assessments. The primary differences between the two are that Joint Assessments require a submission dossier from the technology developer, scoping (e-)meeting with the producer, broad stakeholder involvement, and central project management by the CoLPs. On the other hand, in Collaborative Assessments, these aforementioned points are optional, and decentralised project management could also be performed. The idea was that Collaborative Assessments would primarily be assessments of non-pharmaceuticals (referred to as other technologies in EUnetHTA) and should be easier to initiate based on the work programmes of partners.

All pharmaceutical assessments are conducted as Joint Assessments and are coordinated centrally by the WP4 CoLP for pharmaceuticals, ZIN, hereafter referred to as ‘project managers’. Correspondingly, in other technologies, the Joint Assessments are coordinated centrally by WP4 CoLP for other technologies, AIHTA, also hereafter referred to as ‘project

[1] https://eunethta.eu/services/covid-19/

managers'. Collaborative Assessments can also be coordinated by project managers at Activity Centre Departments Leads, i.e. decentralised project management.

Assessments of pharmaceuticals are focussed on single technologies seeking Marketing Authorisation (MA) approval (either for an initial MA or variation/extension of application), and the timing of the work is therefore closely linked to the regulatory pathway around the MA time-point. The assessments are typically produced based on data from a submission dossier submitted by the prospective Marketing Authorisation Holder ((p)MAH). If the (p)MAH omits certain information from the dossier, the assessment team includes a statement in the assessment report that the requested data has not been submitted by the (p)MAH and states the consequences. Within EUnetHTA JA3, the process of handling incomplete data has not been fully clarified. Pharmaceutical assessments are, in principle, only based on the submitted evidence from the (p)MAH. However, the assessment team can decide (on an ad hoc basis) to conduct their own systematic literature search/additional analyses when this is of high importance for the assessment.

In other technologies, the manufacturer can be invited to submit evidence via the "Medical devices evidence submission template" for primarily the TEC and CUR domains (vs. all four domains in pharmaceutical assessments). Hence, the EUnetHTA authoring teams perform the literature searches and conduct the analyses. In addition, assessments of other technologies are less restricted to particular time-points of a regulatory pathway and can also represent re-assessments following additional or new (post marketing) evidence.

Framework of the collaboration and voluntary submission by industry

In the context of EUnetHTA JA3, the REAs are produced in a voluntary framework. EUnetHTA has no legal entity due to the project-based nature of JA3. Also, the activities are only partially funded by the European Commission (60% funding of costs). The remainder is funded by EUnetHTA partners' own budgets. In JA3, the focus is on creating a sustainable process for future collaboration on HTA. One of the key aspects of the collaboration is the usability of the outputs.

In the pharmaceutical branch, a situation arose, where EUnetHTA initiated a Collaborative Assessment on a human papillomavirus vaccine without prior involvement of the pharmaceutical company. The European Federation of Pharmaceutical Industries and Associations (EFPIA) subsequently raised concerns about EUnetHTA being able to start assessments without the initiation of the manufacturer. EUnetHTA, in accordance with advice from the European Commission, decided to focus exclusively on performing Joint Assessments of pharmaceuticals, based on voluntary submissions from the industry (Executive Board meeting in July 2017). Thus, a prerequisite to conducting a Joint Assessment on pharmaceutical technologies in EUnetHTA JA3 has been the receipt of a submission dossier from the (p)MAH. However, within this voluntary framework the (p)MAH was not obliged to submit the information requested by the EUnetHTA assessment team.

2 Summary of recommendations

One of the key aspects for a successful collaboration is ensuring usability of the outputs. Therefore, all recommendations should be considered from this perspective. It should be noted that the recommendations are based on our experiences with a voluntary system. The provided recommendations are not listed in any prioritised order.

Any recommendations related to the establishment or management of a database handling personal information (or similar) involve compliance with the General Data Protection Regulation (GPDR). This comment also applies to the rest of the document.

General recommendations for joint HTA/project management:

- Ensure transparent, unbiased, and efficient processes for topic identification and selection to inform prioritisation of topics for assessments in the European context. Explore collaboration with existing horizon scanning services and networks.
- Make sure adherence to selection criteria for assessment teams is transparent, and, at the same time, continue capacity building (e.g. procedural and methodological expertise) to be able to ensure high production. It is assumed that when full funding is available (provided EU HTA regulation), HTA agencies are better capable of hiring dedicated staff for such assessments.
- Ensure that project management of assessments is predictable and guarantees fairness of procedure. Thus, project management should be conducted according to standardised processes. Necessary procedures, manuals, templates and tools should be maintained. Such tools would be those to keep track of timelines, teams and their individual members, changes, and a timeline calculator.

Stakeholder engagement:

- Ensure engagement with patients/patient representatives occurs early in the assessment process. It is recommended to keep testing different engagement methods and to try to complement different approaches for one assessment. Guidance as to how the results of the patient input should be used and made visible in the assessment should be developed. Documents that are important for patients/patient representatives should be translated into all EU languages to ensure understanding and facilitate participation. Furthermore, a proper process for evaluation of patient involvement should be established.
- Ensure engagement of healthcare professionals occurs early in the assessment process under appropriate confidentiality rules by attending a scoping e-meeting, reviewing of research question, of draft project plan and/or draft assessment report, and by direct contact during the scoping and assessment phase. Incentives (e.g. remuneration and

certificate of participation in an assessment) for healthcare professionals to participate should be created. There should be some flexibility with regards to accepting healthcare professionals with conflict of interest due to the importance of best possible expertise in the assessments.

- Establish a dedicated stakeholder engagement officer/working party/department that facilitates involvement and serves as an external contact point for all joint HTA products. A database of healthcare professionals and patient organisations should be created to maintain a pool of experts to contact for participation in assessments.
- Continue the Conflict of Interest Committee, and maintain and update procedures for the conflict of interest evaluations and handling of Declaration of Interest (DOI) forms. These should be stored in the above-mentioned database.
- Continue the information sharing between European Medicines Agency (EMA) and assessment teams, maintain procedures, and ensure the appropriate confidentiality framework is in place that allows optimal data sharing and usage.
- Continue the collaboration with medical device regulators, while communicating with Notified Bodies aiming at mutual understanding of requirements, processes, and products.
- Ensure manufacturer participation follows a transparent process, where information, submission requirements, templates and guidelines should be easily accessible for the manufacturers. The participation should be guided by an Industry Procedure Manual, which should be tailored to each assessment and contains all the relevant information and timelines.
- Aim at a clear pathway for industry and other stakeholders to raise (and resolve) emerging problems.

Procedures, templates, and methodology:

- Aim that all procedures, templates, and methodologies ensure consistency and usability of the EUnetHTA assessments (e.g. relevant topic selection, useful content of the report, and timely availability). Updates to any of these aspects need to reflect usability and user-friendliness.
- Adapt procedures for assessment production to fit a possible EU HTA regulation.
- Continue to pilot plain language summaries (PLS), ensure usability among target audience and evaluate needed skills to complete a PLS. If necessary, adapt the template to increase usability.
- Ensure further standardisation of methodological rules and procedures (e.g. PICO development, patient input, expressing certainty of the evidence).

- Establish a standing methods working party that regularly evaluates the need for updates or new developments of methodological guidelines, and coordinates the implementation of required revisions and new developments. This group could consist of relevant networks, organisations, and universities. It should be in contact with other relevant methods groups outside EUnetHTA and, where relevant, guidelines of well-established organisations should be referred to. Guiding principles on methodological choices and applicability of specific methods under different circumstances should be decided by the future EU framework on HTA.
- Ensure clear and fair publication and citation policy regarding confidential data, taking into account core principles of HTA (transparent, unbiased, and independent).
- Aim to have a life cycle approach of technologies, thus information from Early Dialogues could be shared with assessment teams, and continue the process of communicating evidence gaps identified in assessments to Post-Launch Evidence Generation (PLEG) activities.

3 The work done, experiences and recommendations

3.1 Topic identification, selection and prioritisation

The work done and experiences

Topic identification, selection and prioritisation (TISP)[2] represents the starting point for HTA. In this respect, an efficient and defined TISP process is an important means to support the aims of European cooperation on HTA. A working group set down by EUnetHTA JA3 WP4 has prepared a set of recommendations for TISP. The working group involved 31 EUnetHTA WP4 partners, volunteering as authors or reviewers, and delivered its report in April 2020[3]. A question-answer approach adapted from the EuroScan toolkit, sharing of selected background literature, collaboration with the EMA, stakeholder input, and pilots[4] on voluntary TISP processes were used to produce recommendations that cover six domains of TISP:

1. Organisation and implementation
2. Topic identification
3. Topic selection and scope
4. Topic prioritisation
5. Stakeholder involvement
6. Evaluation

Voluntary workflows for TISP were piloted in WP4 Joint Assessments for pharmaceuticals and Joint or Collaborative Assessments for medical devices and in-vitro diagnostics. These workflows resulted in the EUnetHTA Prioritisation Lists (EPL), which were published on the website[5].

For the first years of EUnetHTA JA3, despite a pro-active acquisition process, the pharmaceutical industry was reluctant to submit compounds for Joint Assessments. Therefore, the Heads of Agencies group decided in their April 2018 meeting that EUnetHTA should set up an EPL to inform the industry about emerging or new pharmaceutical products identified as relevant for a Joint Assessment. This first version of the EPL (November 2018) was created ad hoc based on national priorities of HTA agencies, as a response to the decision of the Heads of Agencies group. The second version of the EPL (July 2019) was the outcome of the TISP pilot (mentioned above) which followed the TISP project plan (available on the website[6]). Due to the

[2] TISP processes may be of different complexity ranging from solely reactive, i.e. responsive to proposals, commissions or applications, or involve proactive steps. A proactive TISP process can be defined as horizon scanning.
[3] Recommendations for Horizon Scanning, Topic Identification, Selection and Prioritisation for European Cooperation on Health Technology Assessment. Available at: https://eunethta.eu/services/horizon-scanning/
[4] Pilot for topic identification selection and prioritisation (TISP) for pharmaceuticals, Pilot for topic identification selection and prioritisation (TISP) for medical devices and in-vitro diagnostics, Endpoint evaluation other technologies and Endpoint evaluation for pharmaceuticals. Available at: https://eunethta.eu/services/horizon-scanning/
[5] EUnetHTA Prioritisation List (EPL) – Pharmaceuticals: https://eunethta.eu/assessments/prioritisation-list/ (Accessed on 05.03.2020). EUnetHTA Prioritisation List (EPL) – Other Technologies: https://eunethta.eu/assessments/eunethta-prioritisation-list-epl-other-technologies/
[6] https://eunethta.eu/services/horizon-scanning/

EPL, a tailored acquisition approach was developed and the EPL was expected to increase the relevance of Joint Assessments. Eight out of the 16 pharmaceutical Joint Assessments were an EPL compound. Two companies declined submitting a dossier on an EPL compound, because they wanted to see improvements in the implementation numbers first. Other companies proposed to submit an alternative compound, because – due to various reasons – the originally listed compound was not suitable for a Joint Assessment (e.g. due to failed clinical trials or the necessity of certain test not being available in all European countries). The TISP pilot for pharmaceuticals revealed one main challenge: identification and prioritization of relevant topics at the right time. Compounds included in the EPL were prioritised based on the highest number of EUnetHTA partners declaring an interest in participation in Joint Assessment production, and anticipated use of the Joint Assessment at national level. There is a need for further development of criteria for prioritisation of identified pharmaceutical compounds and a robust prioritisation process to better support both future participation in Joint Assessment production and implementation. In addition, several partners reported being unable to commit to Joint Assessments due to national regulations.

For other technologies, topic suggestions in EUnetHTA JA3 have primarily been based on suggestions from partners planning an HTA who would like to undertake this as a EUnetHTA Joint or Collaborative Assessment. Partners have been requested to actively use the EUnetHTA Planned and Ongoing Projects (POP) database to report their planned assessments, and to see if other agencies have been planning/doing an assessment on the same topic as they have been planning. In this manner, the POP database was designed to facilitate collaboration. Also, topics could be proposed by stakeholders (industry, patient organisations, and the public). The majority of these suggestions did not lead to calls for collaboration because they were out of scope or too vague. As assessments in other technologies are not dependent on an industry submission, and as several partners engaged in Collaborative Assessments, the number of projects initiated by June 2020 was 28. However, uptake of the assessments was limited. The pilot for a TISP workflow was set up to see if a more active voluntary topic identification process and an EPL based on this could ease the choice of topic for a Joint or Collaborative Assessment, while increasing the uptake of assessments. The EPL was published in July 2019 and comprised 18 topics. It was based on EUnetHTA partners' interest in topics identified through a public call for proposals, the POP-database, and EUnetHTA partners' lists of potentially relevant topics. No topics were proposed by industry. Three assessments have started based on the EPL. WP4 CoLP AIHTA contacted the agencies who had expressed interest in the topics of the EPL. However, no additional assessments were initiated as the partners had either other priorities, no resources for EUnetHTA collaboration, or the topic became obsolete for them. In the TISP project, we observed that some partners had their topics prioritised once or twice a year, while others had to act on very short notice based on commissions. Partners with the need to act on short notice were not able to react to the EPL. To be successful, changes need to be made in the partners' commissioning systems to be more flexible towards collaboration. This could be achieved with identified topics being presented in a timely manner to those prioritising the topics nationally, rather than the HTA conductors. It should also be

noted that the EPL for other technologies came very late in JA3, and that the relevance of an EPL needs to be further explored[3].

Recommendations

- The main recommendation of the TISP group is that transparent, unbiased and efficient horizon scanning services should inform the prioritisation of European cooperation on HTA.
    - The TISP group specifies that these horizon scanning[7] services[8] should be legal entities with an appropriate confidentiality framework to allow developers of a technology to share information at an early stage.
    - Formalised collaboration with, and learning from existing horizon scanning services, -systems, -initiatives and networks should be explored.
    - The horizon scanning service should use both proactive and reactive approaches for topic identification. This implies that stakeholders should be proactively consulted and that the TISP process is open to public proposals. Those planning and prioritising HTA activities at any level of a European HTA network, as well as individual HTA agencies and stakeholders, should be the target group and audience for the horizon scanning output.
- Based on the experience from the pilots, the TISP group does not recommend EUnetHTA to identify topics solely on a voluntary basis. This means that funding for the TISP step is required.
- The recommendations are generic in the sense that they are valid for different models of European cooperation on HTA. Due to uncertainties regarding these models and legislative regulation, the TISP group was not able to provide recommendations on the ownership and financial responsibilities for horizon scanning and the TISP process, nor detailed criteria for selection and prioritisation. The authors state that these are important areas that remain to be defined.
- Despite uncertainty on a future HTA model, TISP should play a key role helping to identify technologies for assessment in advance.

3.2 Composition of assessment teams

The work done and experiences

Assessment teams are composed of partners volunteering for the different roles. A project manager is always dedicated to the assessment. An assessment team requires the following roles (each role is covered by a different EUnetHTA partner): author and co-author (constitutes the authoring team), and at least two dedicated reviewers. Observer(s) can be added to the team for capacity building. This mode of collaboration was depicted in order to establish trust

[7] In the context of Health Technology Assessment (HTA), horizon scanning is the systematic identification of health technologies that are new, emerging, or becoming obsolete, and that have the potential to affect health, health services and/or society.
[8] Horizon scanning services are defined as legal entities performing horizon scanning.

between the agencies, while gaining experience in differences or similarities of national HTA practices. In addition, this collaboration model allowed more agencies to become acquainted with EUnetHTA procedures, tools, and templates, and thus allowed for capacity building for future assessments.

When a topic is identified for a possible assessment, a call for collaboration is sent to the partners in the relevant branch. The deadline to respond to the call should take no longer than 10-15 working days, but the deadline can be extended if needed (e.g. due to a summer holiday or not having found the required expertise). In order to prioritise between partners, if needed, the WP4 LP and CoLPs created criteria for the selection of assessment teams. These criteria describe the competence that should be covered within the assessment team and can be used when prioritisation is needed between partners. The main criteria for the authoring team are: availability during the timelines, sufficient WP4 budget, no conflict of interest, expertise in the disease area and health technology, and experience and/or knowledge of EUnetHTA procedures and methodology. In addition, there should be relevant expertise regarding information retrieval and statistical analyses within the authoring team, the agencies should commit to use the assessment in the national setting and, lastly, it is preferable to seek geographical spread. For selecting dedicated reviewers, the following criteria have been established: must comprise one information specialist and one statistical specialist, ideally reviewers should have experience with the topic, and, lastly, at least one of the reviewers should have experience with EUnetHTA assessments. The criteria are available on the website[9]. If no information specialist or statistical specialist can be found within the assessment team, the Information Specialist Network (ISN) or Statistical Specialist Network (SSN) can be contacted. These networks could also have a role in building methodological expertise in participating agencies.

Experience of establishing assessment teams has shown that it is not always feasible to cover all the criteria specified above. For pharmaceuticals, it was experienced that not all the national HTA agencies have dedicated information specialists in house, or statistical experts that can review advanced statistical methods. Therefore, the creation of the ISN and SSN was crucial. For other technologies, the experience was that all but one team had an information specialist dedicated reviewer. In the assessment when the dedicated reviewers did not have the required information retrieval expertise, the ISN provided the necessary expertise.

In EUnetHTA, the different roles in the assessment team have the following responsibilities:

- 1 author organisation:
  - Leading role in both the scoping and assessment.
  - Responsible for the content-related process.
  - Ultimate responsibility for quality assurance.
- 1-2 co-author organisations:

[9] https://eunethta.eu/services/submission-guidelines/other-technologies-submission/ (Accessed on 02.04.2020)

    - Support the author in all project phases. Check, provide input, and endorse all steps (e.g. collaboration in literature selection, data extraction, and assessment of risk of bias).
    - Depending on the collaboration mode, responsible for preparing sections independently. Normally we tend to see that co-authors write the TEC and CUR domain and the authors write the EFF and SAF domain. However, this could be different based on relevant expertise within the agencies.
    - Check, provide input, and endorse content of all domains.
- 2-4 dedicated reviewer organisations[10]:
    - Responsible for quality assurance by thorough review of the draft project plan and draft assessment.
    - Review of methods, results, and conclusions based on the original studies included.
- OPTIONAL – observer:
    - This role is specifically designed for partners new to EUnetHTA or who want to learn more about the Joint/Collaborative Assessment production process. Observers will not have an active role, but will have access to all the data.

It has been estimated that the workload for pharmaceutical assessments is around 60 person days for authors, 40 person days for co-authors, and 3-5 person days for dedicated reviewers, but this also depends on the complexity of the topic. The duration of pharmaceutical Joint Assessment production (from receipt of letter of intent until final publication) has shown to lie between 193 and 412 calendar days[11]. The median is 338 calendar days. This period does include the time when we are awaiting CHMP (Committee for Medicinal Products for Human Use) opinion and thus submission of the submission dossier. Therefore, this does not reflect the actual amount of production days.

For other technologies, the estimated workload for assessments is 80 person days for authors, 25 person days for co-authors, and 5 person days for dedicated reviewers. However, the workload is dependent on the complexity of the topic, and this varies between assessments. The duration of assessment production has shown to lie between 141 and 593 calendar days[12]. The median is 427 calendar days. A longer timeline usually means a more complex assessment. However, a longer timeframe can be caused by other factors (in addition or as the main reason), e.g. the work has been paused due to internal resource constraints.

In the beginning of JA3, there were fewer assessments ongoing and numerous partners were usually volunteering for a role in an assessment. Thus, partners had to be rejected for a role in the team. For pharmaceuticals, this period was used to build capacity, and for the first two

[10] In some assessments a larger number of dedicated reviewers have been included to support engagement and capacity building

[11] Number of days from the date of the call for collaboration to publication date of final assessment report. This is based on available information about assessments in April 2020 (N=9).

[12] Number of days from the date of the call for collaboration to publication date of final assessment report. This is based on available information about assessments in April 2020 (N=21).

pharmaceutical Joint Assessments six dedicated reviewers were selected per assessment and 2-3 observers additionally.

For pharmaceuticals, there was an increase in assessments that started in year three of EUnetHTA JA3. As of mid-2019, there were several pharmaceutical assessments ongoing and the project management team experienced challenges with recruiting authors and co-authors for new assessments. For the calls for collaboration after mid-2019, in no instances have partners been rejected for a role as author or co-author, and in six assessments partners have been rejected a role as dedicated reviewer (out of six assessments). In an attempt to increase willingness to actively participate in a pharmaceutical Joint Assessment, WP4 CoLP ZIN gave a training on April 9, 2019. This training aimed to provide insights into the different aspects of a pharmaceutical Joint Assessment, namely explaining the procedures, the Companion Guide, how to set up a PICO (population, intervention, comparator, outcomes), and methodological aspects such as Network Meta Analyses.

Although for pharmaceuticals there were challenges in finding agencies willing to partake an active role in the assessment team, this did not reflect a low overall interest in the topic of the pharmaceutical assessment. Based on feedback from the authoring teams, it became clear that one of the key limitations reflected the high uncertainty in EUnetHTA timelines. HTA agencies can only predict their work plans 3-6 months in advance. Due to regulatory uncertainties (i.e. prolonged clock-stops, reversion of accelerated procedure to regular procedure, or Oral Explanation) the pharmaceutical assessment timelines are regularly delayed from the originally anticipated date for CHMP opinion. On average, CHMP opinion was delayed by 70 calendar days (ranging from -56 to 252 days) compared to the date originally communicated by the (p)MAH in the letter of intent. The lengthy delays resulted in authoring teams being on standby for substantial periods, thereby limiting their availability for their national work plan activities. Therefore, it was decided that the actual work of the scoping phase (i.e. developing the PICO and the project plan) would only start around four months prior to CHMP opinion. The call for collaboration is sent out around six months prior to CHMP opinion, meaning that this will be one month after the day 120 List of Questions has been shared by the EMA with the (p)MAH. Thus, these timelines seem to reflect important regulatory milestones. This (sharing of day 120 List of Questions by the EMA with the (p)MAH) is considered to be a critical time point since this should result in more certainty about the anticipated CHMP opinion date, or should give more clarity on a potential regulatory delay. Other challenges – resulting from authoring team feedback – that could have an impact on the willingness of agencies to participate in an active role are the following:

- Lack of methodological clarity (e.g. missing methodological guidance or standpoint on defining the PICO and advanced statistical methods). Please see further information in Section 3.10.
- Complex procedures with many different steps. Based on feedback from authoring teams, procedures have been adapted.

- Conducting a EUnetHTA assessment requires more work than a national assessment. This is to ensure the assessment can be used by as many partners as possible. Since many partners have many different requirements (e.g. on what information to include and the way of reporting it), the EUnetHTA assessment duration also lengthens.

For other technologies, the experience has been similar, but it has been slightly less challenging to set up an assessment team, although the production in the other technologies branch has been significantly higher overall than in the pharmaceuticals branch. For the calls for collaboration, in nine instances partners have been rejected to become co-author, and in 47 instances partners have been rejected to become dedicated reviewer.

For both pharmaceuticals and other technologies, it could be that the more EUnetHTA assessments are ongoing, the more challenging it is to find partners that have the human resources available to act as author, co-authors, or dedicated reviewers in addition to the regular national HTA work. Naturally, there have been more volunteers for the dedicated reviewer role than for an author or co-author role. A reason for that may be that it requires less human resources. If an agency has participated as observer, they usually subsequently volunteer for the role as dedicated reviewer.

In total, there are 63 partners in the WP. Whereas the minority of partners focus only on pharmaceuticals, around one-third focus only on other technologies, and about half of the partners on both types of health interventions (based on information received from partners at the beginning of JA3 when asking them to indicate whether they would focus on pharmaceuticals, other technologies, or both within the EUnetHTA work).

For pharmaceuticals, nine different agencies have contributed as author, 14 as co-author, and 31 as dedicated reviewer. 33 different partners were involved in at least one of the pharmaceutical assessment teams (38 if including observer roles as well). 22 of those partners contributed in several assessments (26 if including observer roles as well), of which 12 partners participated in different roles in the pharmaceutical Joint Assessments. Of the twelve partners that only participated in one role, ten were included as dedicated reviewer. 10 partners participated as an observer, and five of them stepped up as a dedicated reviewer in another pharmaceutical assessment. The remaining five partners did not step up after having the observer role.

In other technologies, 14 different agencies have contributed as author, 20 as co-author, 29 as dedicated reviewer and seven as observer. 38 partners contributed in any role, 30 partners contributed in several assessments, eight partners contributed in only one assessment in JA3. 23 partners took different types of roles in JA3, and 15 partners participated only in one type of role (there is no pattern to say only dedicated reviewer, or only co-author or author). Four partners became authors or dedicated reviewers after being observers. Three partners did not take on additional roles after being observers, though one partner was an observer in another assessment too.

The selected agencies of all published and ongoing other technology and pharmaceutical assessments can be found on the website[13] (please see the appendix for an overview of the agencies selected per role).

Pharmaceuticals – response to calls for collaboration and formation of assessment teams

35 agencies responded to at least one role, announced via the call for collaboration for a new pharmaceutical assessment.

All authors selected for assessment teams were involved as a co-author or dedicated reviewer in a previous pharmaceutical assessment (or in JA2), thus they had experience with EUnetHTA guidelines, templates and procedures. The same applied for co-authors with the exception of the co-author for PTJA01 and PTJA17[14]. In the case where a less experienced author was accepted, the team was balanced by including an experienced co-author (and in one occasion even two co-authors). The same applied for rather unexperienced dedicated reviewers. In such cases, the group of selected reviewers is balanced with the selection of multiple experienced dedicated reviewers. This is done for educational purposes to secure capacity building and increase involvement of new and less experienced partners.

In some situations, the project management team pro-actively reached out to partners to ask them to consider a role in the authoring team. The management team always considered previous experience in an authoring role, ideally in the same therapeutic area and/or comparable class of drugs. This activity ensured meeting the selection criteria of expertise. The same process was followed in case of a methodologically challenging assessment (e.g. when a network meta-analysis was expected) and the project management team reached out to partners experienced in the respective area.

Other technologies – response to calls for collaboration and formation of assessment teams

40 agencies volunteered to become part of an other technologies assessment team and responded to at least one call for collaboration for a new assessment. 30 agencies volunteered to contribute to an assessment more than twice. 14 agencies proposed a topic for an assessment and subsequently became an author. On average, seven agencies responded to a call for collaboration and applied to contribute in any role. The highest number of applicants was recorded for OTCA06 (18 agencies), the second highest number for OTJA08 (15 agencies), and the third highest number for OTJA10 (11 agencies). The highest number of partners indicating an interest in a topic (indicated that the topic is of relevance in the national setting) was 17 for OTJA08.

[13] https://eunethta.eu/rapid-reas/

[14] EUnetHTA assessments in Joint Action 3 are given a unique identifier in order to allow easy identification of the assessments. Project ID: [PT/OT][CA/JA][00]. PT=pharmaceutical technology, OT=other technology, JA=Joint Assessment, CA=Collaborative Assessment.

In some instances, the project manager directly approached some of the partners to consider being an author, co-author, or dedicated reviewer. This was done in case we were aware that they plan to work on, or have (recently) worked on a similar topic and had valuable expertise in the specific field.

Recommendations

- Ensure clear and transparent selection criteria for assessment teams.
    - Ensure adherence to these criteria, but at the same time encourage capacity building. In other words, do not always select the most experienced agencies, since there is a need to have capacity for a future system with a higher production rate or in case of conflicting production deadlines.
    - The authoring team should include a statistical specialist (if needed). If not, such a specialist should be one of the dedicated reviewers or the SSN should be involved as part of the authoring team.
    - Sufficient funding should be available for the national agencies, so that they can hire dedicated staff for such assessments.
- Keep a database of the responses of agencies and the reason for acceptance/rejection.
    - By means of such a database, one can pool expertise in, for example, therapeutic area and/or class of technology. This is helpful to pro-actively select an assessment team, in a similar therapeutic area/similar class of technologies.
- For pharmaceutical assessments, ensure the timelines reflect important regulatory milestones, while reserving sufficient time to produce high quality reports. It is important to recognise the uncertainty surrounding regulatory milestones at the start of the assessment to prevent unnecessary lengthy authoring team stand-by periods, as this negatively impacts their ability to work on activities from their national work plan. It is therefore also important to keep the regulatory milestones up to date, incorporating (unexpected) accelerations or delays as quickly as possible.
- For other technologies assessments, when planning the timelines the author should search for ongoing trials and preferably adapt the timing of the assessment according to the availability of any upcoming new evidence that is expected to be published from these trials.
- Maintain the ISN and SSN.
    - Ensure that these networks are kept alive (coordination, funds, training to reflect state of the art methods).
- Testing of different procedures to identify assessment teams. For example, testing the timeframe for responding to calls for collaboration to determine a feasible length of time.
- Agencies could be asked to sign up to participate in a certain yearly number of assessments (only if topics are prioritised and known in advance).

3.3 Project management of assessments

This section will present the work done and experiences regarding project management for pharmaceuticals and other technologies separately, due to the different nature of project

management. In pharmaceuticals, the project management is done centrally to mimic the EMA central procedure, to ensure procedural fair industry involvement, and to ensure consistency and timely publication of the assessments, whereas in other technologies the project management can be centralised or decentralised. Many of the assessments are coordinated in a decentralised manner by Activity Centre Department Leads. This reflects the nature of other technologies, since market approval (CE mark) can be granted by different notified bodies that are located in different countries (i.e. there is no central approval) and the time points of market entry can differ from country to country. Furthermore, decentralised project management allows capacity building and enables timely, as well as increased production of assessments that are based on or arising from national interest. Recommendations are provided jointly for both pharmaceuticals and other technologies.

The work done and experiences

Pharmaceuticals

The pharmaceutical assessments (only Joint Assessments) are centrally managed by a main and an alternate project manager from ZIN. The main project manager is the primary point of contact and therefore responsible for all communications related to a specific project. Other tasks include preparation of project documents, chairing meetings, ensuring awareness and importance of SOPs, and monitoring timelines. The alternate project manager is included in all communications and attends all meetings, and is thereby well apprised of the status of the project. If the main project manager is on leave, the alternate project manager takes over the role and coordination.

As mentioned in section 3.2, the number of pharmaceutical assessments increased in year three of EUnetHTA, resulting in the coordination of multiple ongoing assessments with overlapping timelines and deadlines. Due to this increase, the project management team saw the need to standardise the project management tasks and the need to develop a tool to keep track of timelines and upcoming tasks. Therefore, several tools and standardised practices were developed to improve efficiency of project management, via a standardised approach and automated controls on timelines and planning. 3.8 Central maintenance of the management tools allowed rapid and adequate adaptation in case of newly emerged needs or updated procedures.

Since certain aspects of the project management tools that were developed and centrally maintained by WP4 CoLP ZIN are currently not well defined in the existing SOPs (see section 3.8 for more information about the SOPs), the standardised practices and tools are mentioned below:

- Central project management by a main and an alternate project manager.
- General e-mail address that can be accessed by all project managers and is used as archive to store all project-related e-mails.

- Internal Manual for project managers, which includes all the tasks of the project manager in an assessment with links to the relevant SOPs and draft e-mails, and other considerations relevant to the production process.
- Sharing of confidential data is to be checked by a second person. The platform used for sharing (secured mail, SharePoint, etc.) and when and by whom the data was shared and checked is noted in the project management tool.
- Including the project ID (PTJAXX) in all e-mail communications and documents, both internally (assessment team) and externally (with the (p)MAH, patients, clinical experts and EMA), and including version control in all internally (drafts) and externally (final) shared documents. It is important to assign a project ID already when a call for collaboration is sent out.
- Project management tool (timelines in Excel), including:
    - Standardised and automated tools to set up and update project timelines, considering CHMP date and type of EMA application (i.e. initial MA, accelerated, or Type II variation). This sheet is based on a list with all CHMP opinion dates as published by the EMA.
    - Overview sheet of the timelines of all ongoing assessments, including automatic color-coding to make the project manager aware of upcoming or due tasks, and closed projects in a separate sheet with the same format.
    - Project-specific sheets, which automatically creates a Gantt chart showing the timeline and activities per role (project manager, authoring team, dedicated reviewer, EMA, MAH), contact list (including Letter of lntent, DOI/EUnetHTA Confidentiality Agreement (ECA) status, EMA Confidentiality status [only applicable for authoring team] and option to keep track of timeline changes).
- Management tools related to DOI and ECA forms (see section 3.8 for further details).
- Standardised guidance to teams:
    - Standardised emails, referring to timelines and relevant SOPs (including link and log-in credentials to the Companion Guide) whenever needed.
    - Standardised kick-off e-meeting in which the procedures are explained, but mostly used as a way to get to know the team.
    - Provide a standardised template for a slide deck of internal pre-scoping e-meeting and consensus e-meeting to the authoring team.
    - Prior to the scoping face-to-face meeting, start with a pre-meeting without the (p)MAH. During this pre-meeting the project manager explains the objective of the scoping face-to-face meeting again, and discusses important aspects of the Assessment Phase. It is also an opportunity for the authoring team to meet each other in person and discuss any (outstanding) project-specific questions. After the scoping face-to-face meeting, the team continues with a debrief (without the (p)MAH) to share experiences of the meeting and start discussing next steps.
    - When needed, the project manager sets up regular meetings for the authoring team.
    - The project manager informs the team that in case of any disagreements, uncertainties or challenges, they have to reach out to the project manager.

    - Standard folder structure in SharePoint for consistent archiving.
    - Teams are not allowed to share confidential data via e-mail, but are instructed to upload all documents on SharePoint and send a link to the specific document via e-mail. When relevant, SharePoint folders are allocated appropriate access rights to ensure confidentiality.
- Guidance to (p)MAH in the form of an Industry Procedure Manual (see section 3.7 for further details).

Other technologies – centralised and decentralised project management

For other technologies, EUnetHTA assessments are either coordinated centrally by WP4 CoLP AIHTA, or decentralised by WP4 Activity Centre Department Leads. Activity Centre Department Leads are selected HTA agencies across Europe and include AETS-ISCIII, AGENAS, Avalia-t, HIQA, MIZ and NIPHNO. If the assessment is coordinated via Activity Centre Department Leads, the agencies involved will vary and consequently the respective project managers involved may also be different. The Joint Assessments are always managed by project managers at WP4 CoLP AIHTA. EUnetHTA Collaborative Assessments can be managed by WP4 CoLP AIHTA, or by an Activity Centre Department Lead. The purpose of this model was to generate a designated pool of agencies with established roles and growing experience in sustainable collaboration that should enable continuation of joint work after 2021. WP4 CoLP AIHTA offers central training, support, and supervision. Approximately half of all other technologies assessments (i.e. 14 out of 27) were managed decentralised.

In both, the centralised and decentralised project management, the project manager is responsible for organising and moderating the different steps within the production processes and for ensuring awareness of EUnetHTA SOPs. The project manager monitors the timelines, manages the workspace on SharePoint, and is also responsible for most of the communication activities within the assessment. However, in Collaborative Assessments, some of the communication related tasks can also be done by the author, if agreed with the project manager upfront. The SOPs provide guidance on the different responsibilities and where certain tasks can be done by other assessment team members, and where not.

At WP4 CoLP AIHTA, the project managers keep each other posted on the status of the assessments managed or supervised (in case of decentralised assessment management) by them, so that everyone is aware of current status and next steps allowing another project manager to fill, in in case of holiday or sick leave. This is done during internal meetings, which take place at least once a week and on an ad hoc basis, where any challenges or successes are discussed as well. Furthermore, WP4 CoLP AIHTA has a project management tool where all project managers at WP4 CoLP AIHTA indicate the majority of their tasks and timelines. In case of planned leave (holiday), a detailed handover is prepared upfront. All project managers from WP4 CoLP AIHTA have access to the assessment-specific workspace on the intranet.

The centralised and decentralised project management set-up enables the responsibilities of managing assessments to be split up, so that there are not too many overlapping deadlines for one project manager with regard to the assessments. Every decentralised project manager is supervised by a dedicated project manager at WP4 CoLP AIHTA, who provides support and advice where needed. Especially when dedicated SOPs were not yet available, ad hoc email and telephone support is provided. The decentralised project managers are asked to continuously update the dedicated supervisor at WP4 CoLP AIHTA on the status of the assessment and to keep them in copy on important emails.

WP4 CoLP AIHTA has conducted a survey to collect experiences and satisfaction of procedures among the decentralised project managers and authors of assessments. The results showed that authors thought that the project manager role is a separate, well-defined and important role for assessment coordination and production. The decentralised project managers received adequate training from the WP4 CoLP AIHTA, and authors experienced no difference between projects managed centralised or decentralised. The Companion Guide and SOPs are important for guiding standard practice and allowing decentralised project managers to operate independently. Challenges were around extended timelines due to complex topics, external stakeholder involvement, insufficient team communication, and as yet unpublished SOPs resulting in additional central support. Benefits of decentralised management of assessments are: knowledge management and governance to achieve scale, capacity and capability through a designated pool of agencies with established roles, and growing experience in sustainable collaboration of HTA production.

There are several tools and procedures available for project managers:

- The Companion Guide, which contains the SOPs, guidances, and templates.
- Internal Manual, which is continuously being updated to capture changes if new SOPs, guidances or templates are published and/or there is information that is not yet captured in the Companion Guide. The Companion Guide will ultimately replace the Internal Manual as soon as all the information is captured in the SOPs, guidances, and templates.
- Overview of timelines (Excel sheet).
- Overview of partner participation (Excel sheet) to monitor involvement and, if applicable, rejection.
- DOI and ECA forms, Excel template for DOI assessment, and DOI database (see section 3.8 for further details).

Recommendations

These are the joint recommendations for the project management of both pharmaceutical and other technology assessments:

- Continue using the developed tools and standardised practices. This is very important to keep projects running when multiple assessments have to be managed at the same time, potentially with conflicting deadlines. An exchange of experiences, for example with EMA,

could be explored on how they conduct their project management. Guidance tools and documents should be available in one database (e.g. Companion Guide). It is recommended to have all project manager tasks presented in one document and to limit the accessibility of such a document to project managers only.

- Frequent exchange between project managers on status of assessments, challenges and successes i.e. communication is key. One can learn from each other and provide help for solving issues and discussing possible options. This can, on the long run, further enhance consistency in decision-making with regard to project management-related issues, and provide input to changes or improvements on related processes.
- In case of changes to any processes or updates, transparent and rapid communication with project managers is important; training and support should be provided where needed.
- Standardised communications process:
  - Standardised e-mail subject.
  - Standardised version numbering of documents.
  - Internal Manual (as used by the project managers for pharmaceutical assessments) with standard e-mail communications.
- Automated tool to calculate timelines.
- Database to keep track of project specifics (e.g. acceptance/rejecting teams, time/duration of the different phases) to help analyse the process and define future improvements.
- Use a unique code for assessments (e.g. PTJAXX or PTXXJA) in order to facilitate sorting and chronological presentation.

3.4 Engagement with patients/patient representatives

The work done and experiences

The Patients, Consumers, and Health Care Professionals (P/C&HCP) Task Group (TG) was established by the EUnetHTA Secretariat to support the development of a process for patient, consumer, and healthcare provider involvement in EUnetHTA assessments and Early Dialogues. The TG P/C&HCP consisted of representatives from WP1, WP2, WP4, WP5 and WP6 LPs and CoLPs.

A main output of the TG P/C&HCP was the development of the recommendations for patient involvement in REAs[15]. Recommended methods for patient input consist of input via a patient input template, one-on-one conversations, group conversations or participation in scoping e-meetings. This document also explains the purpose of patient engagement.

The TG P/C&HCP had weekly to monthly e-meetings where experiences with and proposals for patient involvement in REAs were discussed. The inputs and perspectives from different EUnetHTA representatives, who were involved in production of assessments, Early Dialogues, dissemination and quality management, were considered in the development of the recommendations. Two face-to-face consulting meetings with stakeholders representing

[15] https://eunethta.eu/stakeholders/patients/ (Accessed on 02.04.2020)

European patient and consumer organisations (from the HTA Network Stakeholder Pool), the European Commission and, on one occasion with EMA, took place. The meetings were held in Diemen, Netherlands on 8 March 2017 and in Brussels, Belgium on 26 January 2018. Furthermore, one e-meeting with patient organisations from the HTA Network Stakeholder Pool took place on 6 June 2019, in order to present the current status of the work done by the TG. In addition, the yearly EUnetHTA Forum provided an opportunity to exchange ideas, discuss challenges and receive feedback. Before publication, the pre-final recommendations were sent to European Patient organisations from the HTA Stakeholder Pool for consultation.

For pharmaceutical assessments, it is mandatory to seek patient input. The project manager coordinates the identification process, facilitates the input approach and documents this in a database. 14 of 16 pharmaceutical assessments successfully involved patients (i.e. patients could be identified/recruited and/or the pursued approach was completed). Pursued approaches were: one-on-one conversation (n=4) and use of online patient input template (n=13). Two assessments were unsuccessful in including patients (one-on-one conversation (n=1), online patient input template (n=1)). In one of the assessments where a one-on-one conversation was conducted, this approach occurred in a very late stage of the assessment phase and thereby limited the usability of the patient input. For two assessments where the online patient input template was used, no responses were received. However, for one of the assessments where no response was received to the online patient input template, the assessment team also had a one-on-one conversation with a patient.

In each other technologies assessment, it is mandatory for the assessment team, together with the project manager, to discuss patient involvement. In case the assessment team, together with the project manager decide not to involve patients, a sound rationale needs to be given and documented. 12 of 27 OT assessments successfully involved patients (i.e. patients could be identified/recruited and/or the pursued approach was completed). For OT assessments, pursued approaches for patient involvement were: (online) patient input template (n=8), one-on-one conversation (n=6), group conversation (n=2), scoping e-/f2f meeting with patients/patient representatives (n=1), and other approaches (i.e. review of draft PICO, review of draft project plan or draft report, involvement as a team member, use of national surveys, prioritisation of outcomes, n= 15). In several assessments, more than one approach was used. However, if one approach was used multiple times within a single assessment, it was still counted as one. Not all led to successful patient involvement in assessments. This was the case for the use of the patient input template (n=5), one-on-one conversation (n=1) and other approaches (review of scope, review of draft project plan or draft report, or feedback on selection and importance of outcomes, n=7). Reasons for unsuccessful recruitment of patients included lack of response or unwillingness to participate, which was the case in seven assessments. Eight assessment teams did not plan for patient input due to tight timelines or lack of a specific patient group organisations.

Patient involvement was shown to be most useful in the scoping phase. Reasons for deviating methods in patient engagement between pharmaceutical and other technologies assessments

are around different nature of topics, timeframes, and the mode of project management. It is to be noted that upon request of the authoring team, different approaches or a combination of approaches can be used.

In total, patient input was received and used for 21 finalized pharmaceutical and other technologies assessments (cut-off date mid May 2021). Currently, patient input is described in the methods section of the report (n=21) and there is a dedicated chapter (n=13) where a summary (verified by the patients) of the one-on-one conversation, group conversation, scoping e-meeting, or key messages of the (online) patient input template results (if approved by the patient organisation who responded) are included. In some assessments, patient input was referenced in the conclusion and discussion (n=8) and in some PTJA, the patient input was also reflected in the PICO table (n=5). In some other technologies assessments, assessment teams referenced/reported the patient input when answering assessment elements/research questions (n= 2). When the draft assessment was reviewed by patient representatives, respective comments and answers from the authoring team were published (n= 1). Questionnaires that were used in group or one-on-one conversations were added to the appendix (n= 4) and in one assessment, complete responses from patient input templates were added.

However, more effort needs to be put into developing recommendations and guidance on how to use and implement patient input in assessment reports in a standardized and transparent manner.

In addition to the recommendations for patient input in REAs, the TG P/C&HCP developed the EUnetHTA Patient Input Template, an information flyer for patients (both available [16]on the website) and an evaluation questionnaire for patients. The EUnetHTA Patient Input Template is in use and has been translated to 22 official EU languages in order to facilitate the completion of the template by patients/patient organisations[17]. The evaluation questionnaire for patients was finalized towards the end of JA3 and only some preliminary piloting of the questionnaire was carried out. Further work on a proper process for evaluation of patient involvement is needed.

Recommendations

- Identification of patient organisations and individual patients proved to be challenging. It might be considered to have:
    - A central database, which is not limited to European umbrella organisations.
    - A central stakeholder/patient engagement officer to facilitate involvement of patients/patient organisations. This person/department could support teams with the identification of relevant patients/patient organisations as well as support in conducting the patient involvement approaches.

[16] https://eunethta.eu/stakeholders/patients/ (Accessed 02.04.2020)
[17] https://eunethta.eu/eunethta-patient-input-template/

    - In addition, national/European patient organisations and individual patients can still be identified by other means (national databases, internet search, via clinicians, etc.)
- Continue to apply the approach that is most useful and feasible for the topic under assessment; encourage teams to involve patients. For pharmaceutical assessments it is recommended to continue to use the online patient input template as a standard approach, but encourage teams to complement this with additional approaches.
- Ensure that the tool used for the online call allows participants to save a draft version of their answers so that they can complete the survey at a later point in time.
- To create further guidance where needed e.g. guidance for one-on-one conversation and/or to provide training to authoring teams who have not had prior experience with patient involvement.
- Translation of relevant documents for patients in order to improve understanding and ease the process of involvement.
- Results of patient input should be included in early stages of the assessment production.
- Guidance should be developed on how to use patient input in assessments and how to make this visible in reports. Set up training/education platform for patients/patient representatives to make them aware of the principles of HTA and European HTA. This could also further explain the engagement methods and how their input is being used.

3.5 Engagement of health care professionals

The work done and experiences

The TG P/C&HCP has developed recommendations for healthcare professional involvement in REAs. As with development of recommendations for patient input, the TG P/C&HCP had weekly to monthly e-meetings. Proposals and experiences with healthcare professional involvement in REAs were discussed. Two face-to-face consulting meetings with health care professional stakeholders took place, one where all stakeholders from the HTA Network Stakeholder Pool attended, and one primarily with healthcare professional organisations. Furthermore, the yearly EUnetHTA Forum provided an opportunity to exchange ideas and discuss challenges. The pre-final version of the recommendations for healthcare professional involvement in REAs was sent for consultation among healthcare professional organisations from the HTA Stakeholder Pool. The consultation period lasted from 12 February 2020 to 4 March 2020.

For pharmaceutical assessments, it is mandatory to seek involvement of clinical experts in the assessments, and this has been pursued for all assessments (n=16). Clinical experts participated in twelve out of 16 assessments, by means of reviewing the project plan and assessment report (n=2) and Question and Answer approach (n=10). In one assessment the identification was unsuccessful. Experiences in the pharma branch have shown that clinical experts are reluctant to partake in reviewing exercises due to resource constraints (most of the clinical experts are practicing medical doctors) and due to the low remuneration from EUnetHTA. In addition, many clinical experts that have expressed interest to participate were rejected due to a conflict of

interest. Often these experts had participated as Principal Investigator in the drug under assessment or a comparator drug.

For other technologies assessments, it is also mandatory to involve clinical experts. Several methods of involvement of clinical experts were applied and tested. In 27 out of 27 assessments, the clinical experts reviewed the preliminary PICO and/or the draft project plan, as well as the draft assessment. In nine out of 27 assessments, the clinical experts participated in a scoping (e-)meeting. Where applicable, the authoring team approached the clinical experts during the course of the assessment in order to pose questions or clarify any open issues. Dedicated SOPs with regard to the review of draft project plan and draft assessment including checklists for clinical experts were created. Experiences have shown that identification of experts can be difficult and time consuming. In some occasions, identified clinical experts needed to be rejected because of a conflict of interest. Looking for experts on the national level or via national databases proved to be most successful.

Recommendations

- The recommendations 'Healthcare Professional Involvement in Relative Effectiveness Assessments' are published on the website[18] (please consult for further information). The recommended methods for involvement of healthcare professionals consist of scoping e-meeting, review of research question (PICO), review of draft project plan and/or draft assessment report, and direct contact during the scoping and assessment phase. The choice of method depends on the timelines of the assessment.
- Identification of health care professionals, without conflict of interest, proved to be challenging. Set up a procedure to accept the involvement of clinical experts with a conflict of interest, if this provides the best expertise for the assessment. This is of particular relevance for assessments on (ultra) orphan diseases where only few clinical experts have expertise in treating the few patients.
- Identification of health care professionals was challenging in general, due to the burden of work on health care professionals and tight timeframes. To support identification, it might be considered to have:
    - A central database. However, clinical experts could still be identified by other means (national databases, internet search, etc).
    - A stakeholder engagement officer to facilitate involvement of clinical experts.
- Consider development of a clinical expert working party in which pre-selected medical societies/clinical expert organisations are included. This working party could be used to discuss procedural updates and to speed up identification.
- Set up incentives for clinical experts to participate:
    - Remuneration.
    - Certificate of participation in an assessment.

[18] https://eunethta.eu/stakeholders/health-care-providers/ (Accessed on 20.04.2020)

- State if clinical expert view differs from the assessment team's view. When experts review a draft project plan or draft assessment, their comments, together with the answers of the authoring team (in a comments form), are published together with the final project plan and final assessment report. This allows transparency. In case the experts are involved via other involvement methods (other than reviewing the draft project plan and/or assessment), other ways to express the view of the expert can be chosen in order to make it transparent, or to address possible disagreements in the discussion part of the report. Additionally, a disclaimer could be added to the documents explaining the role of an expert, and that the assessment team is not obliged to follow the advice given by the expert.

3.6 Collaboration with regulators

Pharmaceuticals

The work done and experiences

In the pharmaceutical branch, important experience was gathered on collaboration with the EMA[19]. One of the deliverables was to set up a framework for alignment of the pharmaceutical Joint Assessment production process with the EMA. A process for collaboration between the EMA and EUnetHTA in the context of joint production under JA3 WP4 was implemented in November 2016, after discussion in the technical meeting of June 2016[20]. This includes identified roles and responsibilities, a confidentiality framework to make the outcome of the regulatory assessment after CHMP opinion available to HTA reviewers, and facilitating a mutual understanding of the outcomes of each decision-making, while respecting the respective remits of each body.

Technical arrangements with the following key principles:

- Parts of the final CHMP assessment report (once adopted) will be provided as well as the relevant Summary of Product Characteristics (SmPC).
- The exchange occurs under dedicated confidentiality arrangements with the recipient.
- The different remits of regulatory assessment and HTA are respected.

Further details and experiences have been reported in the WP4 Milestone 4.4, which has been submitted to the EUnetHTA Secretariat and the European Commission. Next to this framework, a cooperation with the EMA was set up for the WP4 pilot on TISP. In parallel to the TISP working group, EUnetHTA and EMA started a focused discussion on a collaboration. The NIPHNO coordinator was invited in talks with EMA, addressing how EMA could contribute to the TISP

[19] Information on the collaboration between EMA and EUnetHTA can be found here: https://www.eunethta.eu/stakeholders/regulators/pharmaceuticals/. More information on the EMA-EUnetHTA work plan 2017-2021 can be found here: https://www.eunethta.eu/wp-content/uploads/2020/05/EMA-EUnetHTA-work-plan-2017-2021-for-publication_en-.pdf

[20] Minutes EUnetHTA EFPIA Technical Meeting

pilot. Based on this, EMA agreed to provide, in a structured form and at predefined time points, publicly available data on pharmaceuticals in the EMA process.

EMA supplied lists of topics twice during the pilot[21]. The lists included all pharmaceuticals ongoing or recently concluded new MA applications, Extension of Indications, and Line Extensions. The reports were sorted according to whether the topic was in a first evaluation phase (one to three months after submission of application), or if the application was ongoing (list of questions, list of outstanding issues) or concluded. Topics in a first evaluation phase (27 listings for full MA application and 24 for Line Extension or Extension of Indication) were included. Feasibility analyses were performed late in the process in order to ensure that prioritised topics with anticipated EMA submission prior to Q3 2020 were included with timelines to fit the EUnetHTA joint HTA process.

Collaboration with EMA proved very useful. EMA was very positive and delivered updated information on products 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). Based on experience from WP4 CoLP ZIN, the best time-point to approach a (p)MAH for a potential participation in a REA process is probably three to six months prior to the submission of a MA application to EMA. For the identification step, the information which can currently be shared by EMA is of less value as EMA can only share publicly available documentation. In future models, it should be explored whether collaboration with a preselected high quality horizon scanning service, (p)MAHs, and EMA can be based on agreements to share earlier data that are better aligned with the feasibility timeline for joint REAs. This is an important result from the pilot and constitutes the background for recommending that collaborative horizon scanning services should be legal entities with an appropriate confidentiality framework. The data fields of the reports delivered by EMA, as well as the minimal data set used for the call for collaboration (prioritisation) in the pilot, are provided in the pilot Endpoint Evaluation report[22]. These fields (core elements/ included variables) should be revised based on the experiences of the pilot and the collaborative agreements that can be set up. To reduce duplication of work, the fields should be more aligned with collaborative horizon scanning services.

Recommendations

- Structural framework for information sharing between EMA and the assessment team of pharmaceutical Joint Assessments:
  - Ensure this framework respects the different remits (of both regulatory side and HTA side) and occurs under a dedicated confidentiality framework.
  - Once a letter of intent is received from the (p)MAH, the project manager organisation should immediately sign the Confidentiality Arrangement with the EMA since this

[21] Pilot for topic identification selection and prioritisation (TISP), Endpoint evaluation for pharmaceuticals. Available at: https://eunethta.eu/services/horizon-scanning/
[22] https://eunethta.eu/services/horizon-scanning/

facilitates early exchange on regulatory timelines and milestones. This information is crucial to secure a timeline for the establishment of the assessment team (as explained in section 3.2).

- Important to clarify which information can be shared and when. From experience at least the following sections of the CHMP Assessment Report are relevant, as well as the SmPC:
  - Section 2.1 (problem statement), 2.4 (clinical aspects), 2.5 (clinical efficacy), 2.6 (clinical safety), 3 (benefit-risk balance), 4 (recommendations).
- In the confidentiality framework, ensure that the assessment teams can cite the information from the EMA.
  - Since all citations need to be checked and updated according to the available European public assessment report (EPAR), this framework needs to ensure that Joint Assessment teams receive an EPAR with highlighted changes compared to the received CHMP Assessment Report.
- If a future system is to be a legal entity, the entire assessment team should have access to the CHMP Assessment Report and SmPC. Ensure there is a possibility for an information exchange between the CHMP rapporteur, co-rapporteur, and the authoring team of the Joint Assessments.
  - When the production rate increases, it is recommended that this webinar takes place on standard days in the month, e.g. second Tuesday of the month.
  - Questions from Joint Assessment authoring team need to be shared with the EMA at least 3 days in advance of the webinar.
- Involvement of regulator body in horizon scanning and prioritisation exercise: Resources needed would correspond to at least 60 person days per year for the central acting secretariat, supposing the process used by the pilot is repeated twice a year (in case it is repeated more frequently, the resource need would increase). An improvement of the workflow would be to set up agreements with a pre-selected high quality horizon scanning service, (p)MAHs, and EMA, to specifically serve the purpose of the collaboration. This is probably not possible on a completely voluntary basis.

Other technologies

The work done and experiences

In the other technologies branch, WP4 CoLP AIHTA initiated a EUnetHTA Task Force on HTA and Medical Devices in 2017. The aim of this initiative is to identify synergies between market approval (CE marking) and market access (reimbursement and coverage decisions) for high-risk medical devices (class IIb and III, IVD: C and D). An early exchange on requirements for evidence generation between regulation and HTA can contribute to provide early market access of safe and effective medical devices for patients, contain costs for healthcare systems, and ease the burden of manufacturers to comply with different requirements across European countries.

To this end, three workshops of the EUnetHTA Task Force on HTA and Medical Devices were held in Vienna with the aim to explore the synergies between EUnetHTA and Competent Authorities (regulators) responsible for medical devices. Respective presentations and minutes

were published on the website[23]. The first workshop took place on 29 May 2018 and the second on 28 May 2019 where clinical societies and industry were also represented. A third workshop was held online on 4 November 2020. During this workshop, in addition to an update on the progress in implementation of the Medical Devices Regulation (MDR)/In-vitro Diagnostics Regulation (IVDR) and on the status quo of the proposal for a regulation on HTA in the EU, a dialogue on the evaluation on software as a medical device was initiated.

A vision paper was created to further explore the collaboration along the life cycle of medical devices between HTA bodies participating in EUnetHTA and regularly assessing medical devices, the Competent Authorities coordinated in the Medical Device Coordination Group, and Notified Bodies. The vision paper and the documentation of the workshops can be found in the WP4 deliverable "D4.21 Roadmap for coordinated activities on HTA and medical device authorities".

Recommendations

- Continuous activities to identify synergies and collaboration with medical device regulators.
- Cooperation with the Competent Authorities coordinated by the European Commission (DG Santé) under the new MDR/IVDR.
- Continuous communication with Notified Bodies aiming at mutual understanding of requirements, processes, and products.
- HTA agencies to be considered to support clinical guidance documents coordinated by the Clinical Investigation and Evaluation Working Group, and Task Forces.

3.7 Involvement of manufacturers and industry associations

While the mode of interaction with manufacturers is different for other technologies and pharmaceuticals, in both branches manufacturers can be involved. The different procedures and experiences are explained for each branch separately below. Since the fact check (factual accuracy check) is a procedural option in both branches, the section on fact check combines the work done and experiences both for other technologies and pharmaceuticals.

Pharmaceuticals

The work done and experiences

In the beginning of JA3, industry reached out to the project manager for general questions. To make the production process more visible and disseminate answers to frequently asked questions, a specific page on the website[24] was created to guide industry towards information on the production process of pharmaceutical Joint Assessments. This page lists all the currently available templates and describes, in short, the different process steps. More information can be found in the Frequently Asked Questions section on the above-mentioned webpage.

[23] https://eunethta.eu/events/
[24] https://eunethta.eu/services/submission-guidelines/pharmaceutical-submission/

In addition, this page refers to the submission requirements. The submission requirements document is important as it specifies the type of information that is needed for Joint Assessments as well as the citation and publication policy. It is important that this policy is publicly available, to avoid confusion and provide clarity upfront. In December 2018, it was decided that EUnetHTA should publish the core submission dossier in order to be transparent and allow all people who use the EUnetHTA report to be able to see on which information the report was based. Although we distinguish the core submission dossier and attachments to the dossier, the assessment team is free to cite all material submitted by the manufacturer. This is a prerequisite for a transparent and unbiased assessment. Citations from Clinical Study Reports should not be problematic, due to the EMA 0070 policy (meaning that all Clinical Study Reports will be made publicly available within two months after publication of the EPAR). However, industry challenges this policy as they fear this negatively impacts the possibility of manufacturers publishing their data in peer-reviewed journals. As a response, the EUnetHTA Executive Board has discussed if and how EUnetHTA should deal with academic-in-confidence data. The EUnetHTA Executive Board has sent an open letter to journal editors[25] about this topic.

With increasing production of pharmaceutical assessments, the production procedure evolved and became more standardised. In an attempt to keep track of changes in the procedure, templates and/or (methodological) guidelines, and ensure procedural fairness, an Industry Procedure Manual was developed. This manual gives detailed information about the production process tailored to the information needs of the submitting (p)MAH. A general version of the manual was published on the above-mentioned page in June 2020[26]. Once a letter of intent is submitted, the project manager will make the manual product-specific and will share this version with the MAH. The letter of intent marks the official start of a pharmaceutical Joint Assessment and is a letter signed by the (p)MAH expressing interest to submit the respective compound for a Joint Assessment. Furthermore, the letter of intent captures insights into the relevant regulatory milestones as well as the claimed indication to EMA. Once this letter is received, the procedures, templates and guidelines are fixed and can only be changed upon agreement with the participating (p)MAH.

During the first couple of pharmaceutical assessments, it became clear that industry also had to adjust its procedures and communication. To that end, industry is always encouraged to have a ‘kick-off’ meeting with the project management team. This could either be an e-meeting/teleconference, or a face-to-face meeting. In such a meeting, the project management team explains the immediate next steps and the role of the project managers. The industry is also encouraged to appoint a dedicated point of contact who also acts as a project manager for their internal team. In addition, WP4 CoLP ZIN repeatedly encourages industry to set up or increase their internal communication – also with their national affiliates if available – to inform that a Joint Assessment is ongoing and that the company is creating a submission dossier.

[25] https://eunethta.eu/eunethta-open-letter-of-comment/
[26] https://eunethta.eu/services/submission-guidelines/pharmaceutical-submission/

Recently, WP4 CoLP ZIN started to advise companies to use the EUnetHTA submission dossier as a European Value Dossier to be used when developing national submissions. This can most likely enhance implementation of the Joint Assessments. Another aspect put in place to enhance the implementation is that during the scoping meeting (face-to-face or virtual), the authoring team is requested to present their intent to use the assessment and/or submission dossier in their national appraisal processes. Industry is encouraged to bring its national affiliates representing the authoring team countries to the scoping meeting, to start the discussion in an early phase on how the assessment and/or submission dossier can be used in a national process.

To capture the experiences from an industry perspective, WP4 CoLP ZIN developed a survey to capture the feedback of the participating MAH after the assessment is published. This survey aims to capture insights into the highlights and learnings of the process, resource needs to produce the scoping document, submission dossier, and if the MAH found the report clear and fair. Based on the survey results action points for process optimisation have been developed and implemented. To follow up on these results, a feedback dialogue was held in November 2019 (in Diemen) with EFPIA members that participated during PTJA02-12. In addition, a couple of HTA agencies participated in this dialogue. Key messages and action points from the dialogue were brought back to the EUnetHTA Executive Board for discussion and decision-making. Since this meeting was valued by all participants, a similar meeting was held in November 2020.

Despite a pro-active acquisition process, the pharmaceutical industry was reluctant to submit compounds for Joint Assessments. During the first years of EUnetHTA, CoLP ZIN set up a pro-active acquisition process to get new and relevant compounds in for pharmaceutical Joint Assessments. This process included outreach to companies (mostly EFPIA members) and consultancies and offering them face-to-face meetings to explain the process. Other activities included outreach during international conferences and other meetings where industry was present. In some cases, it took over a year to agree with the company that they would submit their compound for a Joint Assessment. When the first EPL was set up, as a response to the Heads of Agencies, ZIN reached out to all companies included on the EPL by sending an official letter and offering a meeting (either via teleconference or F2F) to explain the process and needs. This resulted in a number of new letters of intent. In December 2018, NOMA became a second CoLP for pharmaceuticals to strengthen the acquisition activities towards the pharmaceutical companies for submissions to EUnetHTA. This was decided due to the challenging situation with a limited number of new submissions from pharmaceutical companies and high resource needs for the project management of ongoing Joint Assessments for CoLP ZIN. NOMA continued the acquisition activities as set up by ZIN. After publication of the second EPL, NOMA reached out to all pharmaceutical companies with products on the second EPL[27], by sending an initial e-mail in order to establish primary contact. A reminder was sent since most of the companies replied late or did not reply at all. Few pharmaceutical

[27] https://eunethta.eu/assessments/prioritisation-list/

companies denied further collaboration with EUnetHTA mostly because of unexpected delays in product development. NOMA actively reached out to companies with established primary contact offering e-meetings, telephone conferences or even F2F meetings to discuss submission to EUnetHTA and provide support. Initially, both pharmaceutical CoLPs (ZIN & NOMA) participated in those meetings. Acquisition activities were also performed during international conferences and meetings where pharmaceutical industry was present. All acquisition activities were aligned with production process and there was a very close collaboration between pharmaceutical CoLPs.

Recommendations

Recommendations for acquisition:

Based on acquisition experiences, recommendations on such activities for a future system are as follows:

- Development of publicly available prioritisation list of topics:
  - Targeted communication (via letter and e-mail) to companies on this list.
  - Set up meetings with EFPIA and other relevant umbrella organisations to explain the prioritisation list and the desired result.
  - Reach out to industry and consultancy agencies to meet at relevant conferences (e.g. ISPOR, HTAi, WODC, PPMA).
  - Targeted communication to consultancy agencies to explain prioritisation list, added value for them, and the desired result.
- Standard slide deck to present the process, timelines, and advantages.
- Public information with Frequently Asked Questions relevant for industry participation – page from EUnetHTA can be found on the website[28].
  - The page should also include relevant documents, templates, and point of contact.
- Maintain the Industry Procedure Manual explaining the procedure, timelines, tools and templates that are tailored for the specific assessment.
- Create visibility of the production process.
- Active media releases that announce start of an assessment on the specific compound, submitted by the specific company.

General recommendations for participation of industry in pharmaceutical assessments:

- Easily accessible information explaining the production process and available templates/guidelines.
  - Ideally with an Industry Procedure Manual. As long as EUnetHTA processes, templates and guidelines are regularly updated, we advise to make this manual product specific as soon as an assessment is started, including one page with product-specifics and contact details of the project managers from the MAH and

[28] https://eunethta.eu/services/submission-guidelines/pharmaceutical-submission/

EUnetHTA, and a list of all the procedures, templates and guidelines that are applicable to the specific assessment.
    - Consider adding a standard slide deck as this allows for easy dissemination of information internally within companies.
- Publish a table with fixed dates for submission of letter of intent, scoping document, scoping face-to-face meeting, submission dossier – depends on EMA regulatory milestones (e.g. Day 0 (D0), D120 List of Questions, D180 List of Outstanding Issues, CHMP opinion) – so that it is always clear for (p)MAH when the different phases of the assessment starts. A letter of intent appears to be useful, even in case industry participation is mandatory in a future process, as it acts as an official kick-off of the assessment and it contains a helpful overview of the (anticipated) regulatory timelines.
- When procedures, templates and/or (methodological) guidelines change (e.g. due to previous experiences), these changes should be prevented from being incorporated in ongoing assessments without specific upfront agreement with the respective (p)MAH.
- Participating industry should appoint a dedicated point of contact and alternate point of contact. Ideally, this person should act as a project manager for the industry side.
- Develop recommendations on how industry can/should communicate about the ongoing Joint Assessment work within their organisations (headquarters and national affiliates). This could be supported by, for example, the aforementioned standard slide deck, the Industry Procedure Manual, and leaflets.

Other technologies

The work done and experiences

Frequently Asked Questions and submission requirements have been developed and published on the website[29].

A manufacturer procedure manual has been developed and published on the website[30]. This is a comprehensive document explaining the involvement of manufacturers, the process, timelines, contact points and the documents/tools to be used by the assessment team and by the manufacturers.

Four manufacturers contacted WP4 CoLP AIHTA to enquire about a topic proposal for a EUnetHTA assessment. Of the four, only two submitted a concrete topic proposal.

In other technologies, the use of the submission dossier is optional in Collaborative Assessments and mandatory in Joint Assessments. However, while only optional in Collaborative Assessments, 21 assessments have requested the submission dossier. It has proven to be challenging to receive fully completed submission dossiers from manufacturers in

[29] https://eunethta.eu/services/submission-guidelines/other-technologies-submission/ (Accessed on 02.04.2020)
[30] Procedure Manual Other Technologies Joint and Collaborative Assessments – Manufacturers. Available at: https://eunethta.eu/wp-content/uploads/2020/10/Procedure-manual-JA-or-CA-for-manufacturers-OT.pdf (Accessed on 05.10.2020)

some cases, even though the dossier was requested and 30 working days were provided for completion. Due to the described experience and feedback from authoring teams, as well as the fact that other technologies assessments are never solely submission dossier-based, meaning that literature retrieval and critical assessment is always conducted by the assessment teams, already in JA2 there were initiatives to select questions from the submission dossier for the manufacturers to complete, focusing on the TEC and CUR domains. This has been further encouraged by WP4 CoLP AIHTA in JA3. Nevertheless, information request in any of the EFF and SAF domains in the submission dossier template is allowed, and it is left to the assessment team's discretion which questions they mark for the manufacturers to be filled in.

Identification of relevant manufacturers and their products proved to be challenging. Assessment teams needed to rely on searches on the internet and manufacturer´s websites. Other technologies project managers also approached previously identified manufacturers to get informed about competitors, in addition to asking healthcare professionals to review the list of known manufacturers and products. In a second step, the CE mark status needed to be clarified, something which was not always straight forward. There is no central and complete database for information on the CE marked products available; a new version of the European Database on Medical Devices (EUDAMED) database is planned to be launched in 2022 and will hopefully facilitate receiving required information on CE mark status. If the manufacturer was not willing to participate in the assessment, or no reply was received, assessment teams looked through manufacturers' websites and sometimes also media reports to acquire this information. Additionally, Other technologies project managers aimed at gathering information on use and reimbursement of the relevant technology in European countries. However, manufacturers might not always know themselves or do not want do disclose this information. In such cases, Other technologies project managers asked EUnetHTA partners to provide this information, if they had access to it. In a few instances we approached MedTech Europe (the European trade association representing the medical technology industries, including medical devices, in vitro diagnostics and digital health) for help, but this was not successful, since this information was also not easily accessible and would require significant resources on their side as well.

On 27 May 2019, WP4 CoLP AIHTA organised a technical meeting between EUnetHTA, MedTech Europe, and related industry representatives. Amongst other topics, horizon scanning and the production of EUnetHTA assessments (production process, gap analysis and implementation of assessments) were presented. The respective presentations and minutes were published on the website[31].

Areas for collaboration with regard to horizon scanning identified:

- A framework could be built to provide a safe environment for industry to share information (so that no competitor receives this information) regarding upcoming/future products.

[31] https://eunethta.eu/events/

Areas for collaboration with regard to production process identified:

- MedTech Europe could potentially help (in certain cases, where needed) to identify manufacturers of the intervention/technology that is included in an other technologies EUnetHTA assessment.

Recommendations

- Transparency in the process of topic submission for an assessment, as well as in the involvement of manufacturers in the assessment process is important and should be maintained.
- An easily accessible and up-to-date central database that contains information on manufacturers, products and CE mark status (e.g. EUDAMED), would be essential and help reduce the time needed for scoping. HTA agencies should have access to such a database. In addition, it would also be helpful to have information accessible on use and reimbursement of technologies (optional).
- WP4 other technologies assessment teams experienced some challenges in receiving complete submission dossiers from manufacturers (mainly requested information on TEC and CUR), and therefore we recommend that considerations should be made on how the compliance of the manufacturers with regard to the request (i.e. provision of submission dossier) can be improved. Please note that such details (e.g. a potential mandatory submission by industry) has not been discussed on the WP4 level, since such decisions are of a more strategic level. The submission dossier requirements might also need to be revised based on a potential future regulation. A revision of the submission dossier template – based on the assessment report template developed by the Core Model Working Party - might be considered.
- There should be easily accessible information explaining the production process and available templates/guidelines, ideally with an Industry Procedure Manual. It should be considered to add a standard slide deck to allow easy information dissemination within the companies.

<u>Fact check (factual accuracy check) – pharmaceuticals and other technologies</u>

The work done and experiences

In JA3, WP4 has established a fact check procedure. While conducting assessments, the manufacturer/ (p)MAH is asked to check whether the information presented for the technologies under assessment is complete and correct. Such a fact check has been optional in both Collaborative and Joint Assessments, and its purpose is to highlight any errors or inaccuracies with the factual content of the document that are related to the technologies under assessment. In other technologies, the fact check can be applied to the draft project plan and the draft assessment report. In pharmaceuticals, it can only be applied to the draft assessment report. A fact check guidance was published in the EUnetHTA Companion Guide in

December 2018, with the condition that the fact check procedure would be subject to an evaluation later on.

In other technologies, the manufacturers were asked to provide a fact check of the project plan in 15 of the 24 assessments. The draft assessment report was provided for fact check in 23 of 24 assessments. For two other technologies assessments no manufacturer involvement was applicable, for one assessment no fact check procedure was yet in place. In some instances, the manufacturers were asked, but the project manager did not get any response, or the manufacturers replied that they had no corrections to make. In pharmaceuticals, the fact check was applied for all Joint Assessment draft assessment reports and is planned for all ongoing Joint Assessments as well.

In 2020, an evaluation of the fact check procedure was carried out by WP4 LP and CoLPs and WP6 LP. EUnetHTA's Senior Scientific Officer also contributed to this work. An evaluation survey was run to collect information about the use of the fact check, to determine the usefulness of the fact check, and to find out the impact the received comments had on the project plan/assessment report (both desired and undesired impact). The survey was sent to all partners that had served as an author or co-author on a REA in JA3. In pharmaceuticals, nine author/co-author agencies responded to the survey. In other technologies, 13 author/co-author agencies completed the survey. In addition to the survey, the group conducted a fact check analysis which was a review of draft and final project plans and assessment reports, as well as the corresponding fact check comments forms. The purpose of the analysis was to map how the fact check comments impacted the final project plans and assessment reports. A total of five pharmaceutical assessments and 15 other technologies assessments were included in the fact check analysis part of the evaluation. The results of the evaluation are summarised in a report (finalised in October 2020) that can be found in the Companion Guide.

Recommendations

- The fact check evaluation report should be used to inform EUnetHTA's work on Future Model of HTA Collaboration.
- In the future, there should always be a transparent mechanism for detecting potential errors and inaccuracies in EUnetHTA assessments before publication.

3.8 Procedures

The work done and experiences

In JA2, two procedure manuals on the production of assessments were established. First, an external procedure manual that described the production processes in short and was mainly used by EUnetHTA partners. Secondly, an Internal Manual that was dedicated to the project managers and outlined the different steps that need to be followed by the project manager throughout the production process. Those manuals provided the basis of newly established SOPs, guidance, and detailed process flows, which have been created throughout JA3, and

explain all the different steps from the project start to end. These phases are: scoping and drafting of project plan, assessment phase, finalisation phase, and (general) administration. As soon as a new SOP was created, the respective information in the Internal Manual was deleted and exchanged by the link to the document in the Companion Guide, where all documents, templates, scientific guidance and tools are centrally stored. SOPs and guidance documents were established in close collaboration with WP4 and WP6 partners. There is a dedicated process to develop SOPs, in which there is one creator, one to two contributors, and two to three dedicated reviewers. The development process should take 120 days. The process includes a final check of all SOPs by WP4 LP/CoLPs and WP6 LP. WP4 CoLP ZIN has acted as creator of three, contributor of five, and dedicated reviewer of nine SOPs. WP4 CoLP AIHTA has acted as creator of eight, contributor of four, and dedicated reviewer of six SOPs. WP4 LP NIPHNO has acted as creator of two and dedicated reviewer of 13 SOPs.

In JA3, experiences with regard to the applied processes from the assessment teams and project managers have been collected via the survey for assessment teams and project managers, developed by WP4 and WP6. Experiences have also been gathered from WP4 e-meetings, face-to-face meetings with WP4 partners, and via email. In other technologies, the decentralised project managers have also provided valuable input. In addition, WP4 LP and CoLPs have received some feedback from manufacturers, patients, and clinical experts that participated in our assessments.

Based on the feedback that has been discussed in appropriate task groups, subgroups or between WP4 LP/CoLPs and WP6 LP/CoLP, processes have been amended and further tested.

Herewith, WP4 LP/CoLPs would like to highlight the extensive changes that has been made to the processes in JA3, as compared to JA2:

Scoping:

- In other technologies, the consultation of the manufacturer was limited to a fact check (factual accuracy check) of the draft project plan.
- Removal of the public consultation of the project plan. This was very time consuming in JA2, a limited number of comments were received, and it was agreed that it is a better approach to contact specific stakeholders directly to acquire input.
- In JA3, the project plan is published immediately after the scoping phase ends. This allows for transparency, to have the timelines and the scope available, and to plan national uptake accordingly. For pharmaceuticals this means the project plan is published soon after positive CHMP opinion is adopted.
- For pharmaceuticals: PICO survey was introduced so that all partners could comment on the relevance of the PICO or PICOs proposed by the authoring team.
- For other technologies: PICO survey was introduced as an optional step to give the partners the opportunity to have a say in the scope of the assessment in order to ensure uptake.

However, as this change came late in JA3, there was not enough time to pilot the process as suggested by the PICO FAQ[32].

Submission dossier:

- A document to clarify what is requested from the manufacturer with regard to the submission dossier, to describe the publication and citation policy, was created. This document is applicable for JA3 and might need to be revised thereafter (if a regulation/framework is in place). A main change is that the (for pharmaceuticals: core) submission dossier will be published together with the final assessment report.
- For pharmaceuticals: In the beginning of JA3, the submission dossier was requested close after CHMP opinion. However, to allow for time to check the completeness of the dossier and to ensure timely start of the assessment, the submission dossier is now requested four to six weeks prior to CHMP opinion, depending on the regulatory pathway.

Assessment phase:

- The consultation with the manufacturer is in JA3 limited to a fact check (factual accuracy check) of the draft assessment report.
- Sharing of draft assessments of other technologies: a document outlining the circumstances/prerequisites under which draft assessments can be provided to EUnetHTA partners was created. This document was made available in September 2019[33]. This should prevent duplication of work and enhance the use and implementation of EUnetHTA assessments.
- For pharmaceuticals: a confidentiality framework with the EMA was set up to exchange information under the respective remits and confidentiality (see section 3.6 for further information).

Dissemination of assessments:

- A notification system for publication of project plans and assessments was established, and a dedicated SOP was created to guide the EUnetHTA Communications Officer and the project managers. This includes announcements on social media.
- The alert about publication of assessments includes a request to fill in the Implementation Survey[34].
- For pharmaceuticals and other technologies: a newsletter was created to inform partners about the status of planned, ongoing, and published assessments. In addition, this newsletter summarises any outstanding actions for partners, such as calls for collaboration, PICO surveys, and Implementation Surveys.

[32] https://eunethta.eu/pico/ (Accessed on 26.05.2021)
[33] Instructions on authorship and copyright. Available in the EUnetHTA Companion Guide. Final version was completed in January 2020.
[34] Surveys set up by WP7 to collect information about the use of EUnetHTA assessments. The questions are about whether the assessment was used, and if so, how it was used, and factors that prevented or limited use.

Stakeholder engagement:

- Recommendations for patient involvement ('Patient Input in Relative Effectiveness Assessments') and EUnetHTA patient input template were created (see section 3.4 above).
- Recommendations for 'Healthcare Professional Involvement in Relative Effectiveness Assessments' were finalised (see section 3.5 above).

Declaration of interest and confidentiality agreement:

- The declaration of interest and confidentiality undertaking form (DOICU) was split into two separate forms, a DOI form and ECA form. The new DOI form was developed by WP4 and WP5 jointly (together with the Senior Scientific Officer) and a partner consultation was applied to both the DOI form (to understand which questions to use) and the new DOI guidance (how to assess the DOI information). In the accepted DOI form, further details on potential conflict of interests are requested, as compared to the DOICU form.
- A Conflict of Interest Committee was established so that consistent decisions can be made in WP4 and WP5.
- DOI database was established in order to allow a central storage of DOI and ECA forms[35].
- Procedure guidance for handling DOI and ECA was implemented. The existing procedure guidance from JA2 was extended and a centralised process of collection and evaluation of DOI forms was established.
- Management tools related to DOI and ECA that project managers can use in JA3 are:
    - Excel template for DOI assessments.
    - Template to create an overview of project relevant DOIs (all team members, experts, project management and support).
    - Tool to record decisions made by the Conflict of Interest Committee (see below).
    - DOI database on SharePoint (database to centrally store DOIs and ECAs) with restricted access[36].
    - Guidance document to assess DOI (the guidance, ECA and DOI is available on the website[37]).

General/overall experiences with the implementation/use of SOPs and Companion Guide from a production perspective:

- Allows project managers, especially new staff or decentralised project managers in other technologies, to confidently manage projects.
- Companion Guide allows amendments in different sections/parts and since it is an online tool, changes are available to everyone immediately. Its search function is very beneficial.
- One stop shop: all templates, guidances and process descriptions are stored at the same place.
- It can be burdensome and time-consuming to read through all SOPs and guidances.

[35] https://eunethta.eu/doi/
[36] https://eunethta.eu/doi/
[37] https://eunethta.eu/doi/

- SOPs and guidances do not cover exceptional circumstances; solutions might only be found if one diverts from the SOPs, which are written for standard practice.

Recommendations

- Procedures and SOPs need to be adapted to fit the processes of a possible new framework and should ensure usability of the processes and outputs.
- Some flexibility towards the SOPs and guidances is recommended to allow solutions for situations diverging from standard practices.
- Keep focusing on feedback from assessment teams to further revise the procedures.
- An independent Conflict of Interest Committee is essential and the members need to be carefully selected. For the Conflict of Interest Committee to function, it is essential that a functioning database is operational for the storage and sharing of DOI information.
- A solution should be found in order to allow assessment teams to share full texts/publications from scientific journals amongst team members and project managers without infringing copyright law.

3.9 Templates

This section will present the work done and experiences regarding templates for other technologies and pharmaceuticals separately, and then present jointly for both other technologies and pharmaceuticals regarding the evidence gap table template and PLS template, since these are applicable to both.

a) Templates in the pharmaceutical branch

The work done and experiences

'The Joint Group on the Rapid REA Pharma Process' was set up in 2017 to revise the templates in the pharmaceutical branch of EUnetHTA WP4, based on experiences from assessment teams. This Joint Group revised the letter of intent, project plan, and assessment report templates to increase consistency and transparency of the assessments, but also to better match the assessment team expectations. The revision of the templates was finalised in March 2019 and the revised templates were published in the EUnetHTA Companion Guide. Since then, these revised templates have been in use by the assessment teams of pharmaceutical assessments. An attempt was also made in three different assessments to use the revised submission dossier template. However, due to many hurdles, it was not possible to do so.

Later, based on feedback from industry and assessment teams, the letter of intent has been revised as a shorter and simpler document. The content that was taken out of the document was then moved to the scoping document template as this information is much more relevant to the assessment team in a later stage of the scoping process.

In the EUnetHTA Executive Board meeting in May 2019, the Board decided to set up a subgroup to revise the submission dossier template for pharmaceutical products. In the September 2019 meeting, the Board decided to extend the scope of this subgroup to include the evaluation and

further revision of the assessment report template as well. The subgroup was set up and started its work in November 2019. It was chaired and coordinated by the WP4 LP and comprised 17 members from 13 organisations in 10 countries (per 18 March 2020). Within the subgroup, two smaller teams were established, one to work hands-on with the submission dossier template, and another to work hands-on with the assessment report template.

After thorough initial discussions, the subgroup decided to continue to use the current (from JA2) submission dossier template in all upcoming JA3 assessments. Instead of revising the template, the group collected feedback from EUnetHTA partners on what information and data would be required in a future template. Based on the received feedback, the group provided recommendations for a future (post-JA3) submission dossier template. The Executive Board endorsed this chosen approach at its meeting in January 2020 and approved the finalised recommendations in November 2020. The output of the subgroup was subsequently shared with EFPIA for their feedback. Their feedback was attached as an appendix to the document, but did not lead to any revisions of the content.

To evaluate the assessment report template, revised in March 2019, the subgroup conducted a survey in June-July 2020 to collect feedback on it from the EUnetHTA partners and users of EUnetHTA assessments. Based on the survey results, the subgroup made some very minor changes to the template and shared the rest of the received feedback as recommendations for a future (post- JA3) template. The group also collaborated closely with other EUnetHTA subgroups and task groups to ensure their outputs were mirrored both in the template revision and the recommendations. Furthermore, two subgroup members compared the current EUnetHTA template with tables of contents in published national HTA reports to obtain a clearer picture of the (mis-)alignment between included headings. Results of this preliminary headings comparison exercise were included in an appendix. The outputs of this part of the subgroup work were endorsed by the Executive Board in January 2021.

All deliverables of the subgroup have been included in the EUnetHTA Companion Guide and published on the EUnetHTA website[38].

Minor changes in all templates according to the Instructions on authorship and copyright[39] document have also been performed.

Recommendations

The recommendations of the subgroup for future submission dossier and assessment report templates should be used in future (post-JA3) template revision work.

[38] https://eunethta.eu/services/submission-guidelines/submission-template-pharmaceuticals-submission-template-medical-devices/

[39] Available in the EUnetHTA Companion Guide. Final version was completed in January 2020.

b) Templates in the other technologies branch

The work done and experiences

The major revision of the assessment report template in the other technologies branch was based on the outcomes of the work done by the Core Model Working Party (WP6 activity). The Core Model Working Party was established in November 2018 with the aim to make the HTA Core Model® sustainable for the future. As a first step, the Working Party developed an assessment report template for a EUnetHTA Core HTA of other technologies (all nine domains). The newly developed reporting structure should make the assessment reports easier to read, so as to enhance their further uptake. Moreover, the template should make the assessment reports easier for authors to write by guiding them through EUnetHTA's methodological and procedural requirements, and by providing them with a clear and easy to handle structure. This new assessment template was piloted in two other technologies assessments (REAs) which started in May 2020. To this end, the redundant parts of the full core assessment report template were deleted and/or amended in order to be applicable for the REA reports.

Since the other technologies assessment template is based on the Core Model and the update of the Core Model is within the mandate of the Core Model Working Group, it was decided that WP4 CoLP AIHTA stops the evaluation of the assessment report template and implementation of changes to the template to prevent duplication of work. However, some minor changes have been implemented to reflect decisions taken and implemented through SOPs (information retrieval, data extraction, and risk of bias assessment SOPs), as well as changes according to the Instructions on authorship and copyright document[40], and link to the List of Terms[41] used in EUnetHTA.

Recommendations

- Feedback from piloting the new assessment report template should inform future template revision work.
- The project plan template should be revised in order to further align it with the new assessment report template.

c) Evidence gaps table template

The work done and experiences

In May 2018, WP4 LP and CoLPs, together with WP5B, started to investigate how one could link the evidence gaps identified in EUnetHTA assessments with the work WP5B conducts on Post-Launch Evidence Generation (PLEG). The output of this collaboration was an evidence gaps table template, which was finalised and published in the EUnetHTA Companion Guide in

[40] Available in the EUnetHTA Companion Guide. Final version was completed in January 2020.
[41] The List of Terms was created to contribute to consistent use of terms in SOPs, methodological guidelines, EUnetHTA assessments and related templates. The list is available in the Companion Guide.

February 2020. Furthermore, the evidence gaps table was added to the assessment report templates. The table aims to allow to present the evidence gaps identified during EUnetHTA assessments in a structured and harmonised way. These common evidence gaps could be the starting point of a national or joint PLEG, in which further requirements for PLEG would be defined (dataset to be collected, quality requirements). This collaboration therefore contributes to the lifecycle approach of EUnetHTA's work.

The EUnetHTA Joint Action 2 Position paper on how to best formulate research recommendations for primary research arising from HTA reports and, notably the table no. 3 served as a starting point for the template development work[42]. After the template draft had undergone a number of format changes and structural adjustments, it was shared with the WP5B partners for comments. During the WP4 partner meeting in Diemen on 18 October 2019, the template was also presented to the WP4 partners for information and feedback. The final version was published in the EUnetHTA Companion Guide in February 2020.

The template comprises three parts. The first part contains information about the research question(s) and PICO(s) of the assessment, the second part highlights outcomes where evidence is currently lacking or considered insufficient (based on the assessment results), and the third part indicates additional evidence generation needs (structured according to The Evidence Population Intervention Comparison Outcome Timestamp (EPICOT) framework). The appropriate study design as well as ongoing studies likely to fill in the identified gaps can also be indicated in the third part. The other technologies assessment team completes the table template during the internal review of the first draft assessment, and the author sends it thereafter to WP5B. The pharmaceutical assessment team completes the table template after finalisation of the assessment. Tables are reviewed by the assessment team during the fact check and before publication of the REA report. The third part of the completed table is also published in the appendix of the assessment report.

The table template was piloted in two other technologies assessments and four pharmaceutical assessments (during the JA3 prolongation period). Feedback from authors showed that more guidance is needed to assist the completion of the table. An initial guidance was drafted at the end of JA3[43]. Some authors have also indicated that completion of such evidence gaps table may not be relevant for each assessment topic. In the future, feedback on the usefulness and usability of this template ought to be collected.

Recommendations

Both the evidence gaps table template and the related guidance, developed in JA3, need to be adapted in future work to reflect the outputs of the PICO Subgroup and the Task Group on Common Phrases and GRADE. Furthermore, continuation of piloting of the template is

[42] https://eunethta.eu/eunethta-position-paper-on-research-recommendations-for-aeg/
[43] Available in the EUnetHTA Companion Guide.

recommended to identify further areas of improvement. One should also consider adding some instructions related to the completion of the evidence gaps table template to relevant SOPs.

One should ensure that a link between evidence gaps identified in assessments and PLEG activities exists. Ideally, evidence gaps tables should be completed after the first draft of the report to give the PLEG team the opportunity to provide recommendations on PLEG (core minimum data set and suggestion of data source) on time i.e. before national assessment/appraisal as some HTA bodies will request PLEG at this stage. Furthermore, it would allow interaction with EMA before the finalisation of the regulatory PLEG request. In the future, sharing of information from Early Dialogues (recommendation on PICO could be used as a basis to define assessment scope) to assessment teams could also be tested, in order to attain a more life cycle-based approach for technologies. It would imply industry's acceptance to systematically share Early Dialogue recommendations with the submission dossier.

d) Plain language summary (PLS) and the plain language summary template

PLS of HTA reports may better inform decision-makers, provide useful advice to health care professionals, and empower patient populations. An aim of an HTA PLS is to disseminate and share information to non-HTA experts and researchers such as patients, policy-makers, health care professionals, and the general public.

The work done and experiences

Background research was conducted, including a comprehensive literature review of PLS studies and a review of existing PLS designs, guidelines, and templates. In addition, the formative research involved consultations with several experts from Cochrane Norway who possess experience developing and refining PLSs. These studies, templates, and consultations informed the development process of the HTA PLS.

The next phase was the template development phase involving the creation of a background note, and preliminary design of a PLS template including a general layout with headings, subheadings, author guidance, and suggested standardised text. During this phase, the template was pilot-tested using a published assessment report (PTJA04). The pilot test invited input from the first author, communications and scientific officers, and several researchers working in different HTA offices. The PLS pilot test included more than 10 rounds of editing resulting in substantial revisions to the PLS template. Our experiences showed that it is very difficult to write scientific findings in an easy and understandable language. Therefore, it emphasised the importance that the template gives sufficient guidance on the advised number of words per sentence and also a link to an HTA glossary. Where possible, the PLS template attempts to standardise text so that only project-specific results have to be added.

The fourth phase involved two telephone consultations with individuals recruited from the Health Technology Assessment Network (HTAN) stakeholder pool. The first consultation involved HTA assessors (three from pharmaceutical technologies and three from other technologies, n=6) and invited their feedback on the usability of the PLS template. The second

consultation invited individuals (n=4) from the patient and consumer pillar of the HTAN stakeholder pool. Feedback from each consultation led to a re-design of the PLS template.

The output of this work is a refined version of the HTA PLS template that uses EUnetHTA style, color, and formatting, and provides guidance for assessors and suggests sample text paragraphs.

Recommendations

- Target audience(s) of PLS should be clearly reviewed and defined.
- Risk analysis of unintended consequences (i.e., misunderstanding) of PLS should be conducted.
- Time and writing skills needed to complete a PLS should be reviewed.
- Review process of completed PLSs should be in place to ensure quality and usability of PLSs.
- Training assessors in skills needed to write PLSs may be warranted.
- If a stakeholder engagement officer or department are set up, they should also be involved in maintaining the PLS template as well as developing product-specific PLS (to guarantee consistency and appropriate language).

3.10 Guidelines and methodology

a) PICO subgroup

The work done and experiences

The assessment teams and the project managers in WP4 have noticed during JA3 that within EUnetHTA there has been a lack of agreement on the concept of 'PICO' and its role in the assessment. Furthermore, a guidance on how to develop a European PICO was missing. Therefore, in September 2019 the Executive Board agreed to set up a subgroup to define a standardised process for the development of a European PICO.

Objectives of the subgroup were to:

- Conceptualise EUnetHTA's perspective on the role of the PICO question(s) for EUnetHTA Assessments.
- Define a standard process on how to develop the PICO question(s) for the Assessments.

It was not the objective of the subgroup to provide a methodological guidance on how to develop the PICO question(s).

Deliverables:

PICO Concept Paper to be published in the Companion Guide, explaining EUnetHTA's conceptualisation/perspective of PICO and a standard method and process on how to develop the PICO question(s) in EUnetHTA assessments (including the PICO survey and what to report in

the project plan in terms of the PICO). The subgroup liaised with all other relevant subgroups (e.g. Subgroup on Submission Dossier and Assessment Report Templates of Pharmaceuticals, Common Phrases and GRADE Task Group, and the HTA Core Model Working Party). In addition, the subgroup considered feedback from assessment teams as provided in the assessment team survey or dedicated feedback sessions.

The PICO Concept Paper was endorsed by the Executive Board on 21 October 2020 and subsequently published in the Companion Guide. A PICO FAQ was also created on the website[44] for the public.

Recommendations

- The results of the PICO Concept paper should be taken further in a dedicated SOP to better guide the authoring teams.
- The project plan templates regarding the section on PICO should be revised.
    - Reference to the PICO Concept Paper, as well as reference to the above recommended dedicated SOP (once developed) should be added.
    - Revisions of what to report in a project plan about the European PICO should be considered.

b) Common phrases and GRADE

The work done and experiences

The EUnetHTA Task Group on Common Phrases and GRADE (Grading of Recommendations Assessment, Development and Evaluation) was established in February 2019. The Task Group, which included participants from 13 organisations representing both pharmaceuticals and other technologies, aimed at formulating recommendations on:

- Sentences/words to avoid in the results and conclusions of EUnetHTA Assessments (creation of a negative list of phrases).
- The use of GRADE or other internationally adopted evidence grading system(s) in EUnetHTA Assessments.
- Standardised phrases for describing results and conclusions in EUnetHTA Assessments (creation of a positive list of statements).

For this purpose, the Task Group undertook the following activities:

- A negative list of phrases was compiled from a larger list of phrases that were identified as commonly used in national assessments and other producers of systematic reviews (such as the Cochrane Collaboration). The ‘negative list’ contains phrases the Task Group agreed on should be refrained from being used in assessments, because they might be of limited relevance for, or prejudice, national appraisal and decision making. The sub-deliverable ‘negative list’ was submitted to the Executive Board for information.

[44] http://eunethta.eu/PICO

- The Task Group completed a scoping study of existing international evidence grading systems. The focus was on mapping strengths and weaknesses, and actual use, of the different systems. The study showed that GRADE and its modified versions are more often used than other systems. A meeting with the Task Group and GRADE Working Group was arranged in Diemen on 2 March 2020. It was discussed if and how GRADE could be applied within EUnetHTA assessments, and also what the obstacles could be for different countries and whether any solutions or adaptations were possible. To prepare the meeting, an explorative survey was conducted among the Task Group members. An online workshop to discuss and pilot a set of conditions that could allow a more appropriate use of GRADE within assessments was organized on 11 September 2020. After the workshop, a framework paper on partial use of GRADE was prepared based on the discussions from the workshop and the positions from the partners. This second sub-deliverable was endorsed by the EUnetHTA Executive Board in November 2020.
- The third output of the Task Group, recommendations for presentation of results and conclusions in EUnetHTA assessments, built on the framework paper on partial use of GRADE. This final sub-deliverable focused on providing recommendations for formulations rather than a strict set of standardised sentences (common phrases). It was endorsed by the EUnetHTA Executive Board in January 2021.

All three deliverables have been included in the EUnetHTA Companion Guide and published on the EUnetHTA website[45].

Experiences:

- For the negative list, the Task Group agreed that overall conclusions which are not related to specific outcomes, should be avoided. Specific words should be avoided within the context of drawing conclusions that constitute vague, ambiguous or statistically flawed language.
- The GRADE framework paper presented a proposal on how to partially use GRADE in EUnetHTA context. Partial use of GRADE means that assessment authors use the instrument (i.e. domains) of GRADE to assess certainty of evidence. However, they do not downgrade/upgrade the evidence per GRADE domain or provide any overall judgement of the certainty of the evidence per outcome taking into account all GRADE domains. This ensures flexibility and adaptability so that the assessment can be modified locally to reflect the national contexts.
- The discussions on how to express (un)certainty of the evidence showed that a EUnetHTA assessment should be considered an intermediate product that needs contextualization and adaptation at the national level. In EUnetHTA assessments, context-independent GRADE domains can be formulated more conclusive than context-dependent issues. Conclusions

[45] https://eunethta.eu/tools/grade-and-common-phrases/

should be developed by national HTA agencies before submitting the report to local/national decision-making.

Recommendations

- The outputs and recommendations of this Task Group will need to be transferred into relevant guidelines, SOPs and templates prior to implementation (post-JA3). Drafting a separate methodological guideline on the partial use of GRADE, with the suggested presentation, is recommended.
- It is planned that one of the pharmaceutical assessments (PTJA17) will pilot the partial use of GRADE in June-July 2021. The experiences of this pilot should be used when drafting the methodological guideline on the partial use of GRADE.
- In the future, authoring teams who do not have previous knowledge and experience in GRADE and its domains, should have the possibility for further assistance and training.

c) Methodological guidelines

The work done and experiences

By May 2021, 24 comments on the existing methodological guidelines were submitted via the continuously running survey for assessment teams and project managers ('WP6A.2 Survey'). Comments indicated the need for further guidance or checklists to support specific tasks and pointed to available updates of linked tools. Furthermore, five requests for changes to existing methodological guidelines have been provided by direct contact with the WP6B coordinator or the WP6B.2 Activity Leader. The WP7 Case Study on the use of EUnetHTA Tools and Guidelines collected further requests for the development of new methodological guidelines or the revision of existing ones. All requests for revision of existing guidelines from the different input channels and the comments provided via the WP6A.2 Survey are summarised in Table 1. It should be considered that the feedback needs further reflection when the existing guidelines are updated, or additional guidelines are developed.

Table 1. Requests for updates of methodological guidelines (activity WP6B.2)

Request	Input channel(s)	Summary of comments from WP6A.2 Survey
Update guideline "Process of information retrieval for systematic reviews and health technology assessments on clinical effectiveness"	WP6A.2 Survey Authors' initiative	Guidance on how to develop the PICO and the protocol is missing. Processes are time consuming and their relevance for decision makers is questionable.
Update guideline "Endpoints used for Relative Effectiveness Assessment: Clinical Endpoints"	WP6A.2 Survey Direct contact (e-	Section on how to determine clinical threshold levels should be added.

	mail) WP7 Case study	
Update guideline "Endpoints used in Relative Effectiveness Assessment: Safety"	WP6A.2 Survey Authors' initiative WP7 Case study	Guidance on risk of bias assessment for single arm studies (for safety outcomes) is missing. Guidance on request for/use of safety data from non-RCTs is missing.
Update guideline "Endpoints used in Relative Effectiveness Assessment: Surrogate endpoints"	WP6A.2 Survey	Guideline is really basic and outdated. Different methods should be addressed in different guidelines.
Update guideline "Comparators & Comparisons: Criteria for the choice of the most appropriate comparator(s)"	WP6A.2 Survey	Need for discussion on how to choose the most appropriate comparator and minimum requirement for relevance of comparators.
Update guideline "Comparators & Comparisons: Direct and indirect comparisons"	WP6A.2 Survey Direct contact (e-mail) WP7 Case study	Guideline is severely outdated. Checklist for assessing the quality of NMAs is needed. Instructions on how to present Summary of Findings tables are needed. Need for discussion on specific points. Guidance on critical assessment of evidence from indirect comparisons needed and handling of data of low quality.
Update guideline "Levels of Evidence - Applicability of evidence for the context of a relative effectiveness assessment"	WP6A.2 Survey	Instructions on inclusion of study types other than Randomised controlled trials (RCT) when RCTs are available too is missing. Guidance on how to make scientific conclusions/proper wording is missing (when only Risk of Bias (RoB) is available but no GRADE assessment)

Update guideline "Internal validity of randomised controlled trials"	WP6A.2 Survey	Update needed to reflect revised risk of bias tool Guidance on risk of bias assessment on outcome level is missing
Update guideline "Internal validity of non-randomised studies (NRS) on interventions"	Direct contact (e-mail)	Update needed to reflect new versions of AMSTAR and Cochrane RoB tool.
Update guideline "Meta-analysis of diagnostic test accuracy studies"	WP6A.2 Survey	Update needed to reflect new versions of PRISMA for DTA and QUADAS-2 for comparative studies.
Suggested additional guidelines	WP6A.2 Survey	A Methodological Guideline on screening interventions would be needed in case screening interventions will be assessed regularly on European level.

The need for the development of new methodological guidelines on the following topics has been expressed:

- Procedure for methodological guidelines development and update.
- Critical assessment of clinical evidence.
- Use of real-world data and real-world evidence.
- Complex interventions/technologies.
- Appraisal of emerging technologies.
- Partial use of GRADE.
- Assessment of diagnostic tests.
- Incorporating patients' experience.
- Defining PICO and research questions.
- HTA topic selection procedures.
- Comparison methods for single arm trials.
- Detecting and handling selective reporting bias.
- How to undertake organisational analysis.

Some of the above topics have been discussed in EUnetHTA subgroups or task groups and their outputs have been finalized and published[46].

[46] EUnetHTA framework paper on partial use of GRADE: https://eunethta.eu/tools/grade-and-common-phrases/; PICO FAQ: https://eunethta.eu/pico/; Recommendations for Horizon Scanning, Topic Identification, Selection and Prioritisation for European Cooperation on Health Technology Assessment: https://eunethta.eu/services/horizon-scanning/; Patient Input in Relative Effectiveness Assessments: https://www.eunethta.eu/stakeholders/patients/; SOP "How to Create and Maintain a Methodological Guideline": available in the EUnetHTA Companion Guide

Recommendations

Establishment of a standing methods working party that regularly evaluates the need for updates or new developments of methodological guidelines and coordinates the implementation of required revisions and new developments. This group could consist of relevant networks, organisations and universities. It should be in contact with other relevant methods groups outside EUnetHTA and, where relevant, guidelines of well-established organisations should be referred to. Guiding principles on methodological choices and applicability of specific methods under different circumstances should be decided by the future EU framework on HTA.

4 Appendix

Agencies' roles in assessments

Pharmaceuticals:

Author* – Nine agencies: DVSV (previously HVB), FIMEA (2), HAS (2) INFARMED (3), IQWIG, MIZ (previously AAZ), NOMA (3), TLV (2), ZIN (2).

Co-author** – 12 agencies: AEMPS (3), AETSA (2), AOTMiT (2), DVSV (previously HVB), EUR (Erasmus Universiteit Rotterdam), GÖG, HAS, INFARMED, JAZMP, MIZ (2), NCPE (4), NOMA, SNHTA, TLV, ZIN (3).

Dedicated reviewer – 28 agencies: AEMPS (6), AETSA (2), AIFA (2), AOTMiT (2), DPA/MOH Malta, DVSV (previously HVB), FIMEA (2), FIISC (previously FUNCANIS) (2), HAS (6), HIS (2), INFARMED (3), IQWiG, JAZMP (2), LBI-HTA, MIZ (previously AAZ) (2), HTA Department of SEC of MoH Ukraine (4), NICE (3), NIPN (3), NVD, Regione Veneto, RER (4), SESCS (2), SNHTA (7), SUKL, TLV (2), UCSC Gemelli, UU (Utrecht University), ZIN (2).

Observers – 10 agencies: EKAPTY, EOF (2), EOPYY, GBA, HIS, HTA Department of SEC of MoH Ukraine/ EC of MoH of Ukraine, NCPHA, MoH Malta, SESCS, SUKL.

* The agencies listed here represent the authors responsible for the assessment report. In two joint assessments a change in authoring role occurred: for PTJA11 AIFA stepped down as author around the time of CHMP opinion, due to the COVID-19 emergency in Italy. The authoring role was taken over by NOMA (previously co-author) and the co-author role was taken up by ZIN (new team member); for PTJA07 TLV stepped down as author four weeks before CHMP opinion, due to staffing issues, accepting a co-author role together with AOTMIT (original co-author). The authoring role was taken over by MIZ (new team member). In one assessment the (p)MAH withdrew the MA application. No report for this assessment is available.

** The agencies listed here represent the co-authors responsible for the assessment report.

Other technologies:

Collaborative and joint assessments:

OTCA13 was discontinued in the scoping phase and here not counted.

Author* – 14 agencies

NIPHNO (3), AQuAS, ASI, AIHTA (7), AETS-ISCIII (2), IQWiG, AGENAS (2), AVALIA-T (2), HIQA, DEFACTUM, GÖG, MIZ (2), RER (2), ZIN

Co-author** – 20 agencies: HIQA, AOTMiT, UCSC Gemelli, NSPHMPDB/SNSMPS (5), MoH Slovenia, SNHTA, RER (3), AIHTA (2), Regione Veneto, VASPVT, OSTEBA (2), NIJZ, JAZMP, ASI (2) , NIPHNO (2) GÖG (2), KCE, MIZ, IQWiG, Avalia-t

Dedicated reviewer*** – 29 agencies

VASPVT (6), AQuAS (4), HAS (3), SNHTA (13), Regione Veneto (3), AETS-ISCIII (3), HIQA (3), AVALIA-T (2), NICE (2), ASI , NIPHB, SESCS/Funcanis (4), UCSC Gemelli (2), NSPHMPDB/SNSMPS, GÖG (2), AETSA (2), NIPN/OGYEI (4), DEFACTUM (3), AGENAS (2), HIS (2), MIZ, OSTEBA (3), RER (2), KCE (4), OCSC, AIHTA, IQWIG (3), SUKL, UMIT

Observers – Six agencies: ACSS-IP, AOTMIT (2), EOPYY, MoH Slovenia, VASPVT, UTA

*Counting IAMEV as AIHTA.

*Counting NSPHMPDB and SNSMPS as one.

***Counting SESCS and Funcanis as one. NIPN and OGYEI as one.

Some partners' names have changed during JA3. In this list the most up-to-date names are used. These are: DEFACTUM (formerly MIDT), AIHTA (formerly LBI-HTA), MIZ (formerly AAZ), ASI (formerly HVB).

The selected agencies of all published and ongoing other technology and pharmaceutical assessment can be found on the website[47].

[47] https://eunethta.eu/rapid-reas/