Recommendations for Early Dialogues

Based on the Experience of EUnetHTA Joint Action 3

This document is part of the project/joint action “724130 / EUnetHTA JA3” which has received funding from the European Union’s Health Programme (2014–2020).

DOCUMENT HISTORY AND CONTRIBUTORS

Version number	Date	Modification	Reason for the modification
V1	10/2020	First Draft	HAS, G-BA
V2	11/2020	Document reviewed by EDWP	HAS updated based on the last EDs
V3	03/2021	Updated for response to call for tender	HAS updated based on the last EDs
V4	03/06/21	Share for final review by WP5	Comments by WP5A partners
V5	23/06/21	Final version	Incorporated comments received through final review

Responsibility/role	HTA Body/affiliation
Author	Haute Autorité de Santé, France (HAS)
Co-author	Gemeinsamer Bundesausschuss, Germany (G-BA)
Reviewers	Agencia Española de Medicamentos y Productos Sanitarios, Spain (AEMPS)
	Área de Evaluación de Tecnologías Sanitarias de Andalucía, Spain (AETSA)
	Agenzia Italiana del Farmaco, Italy (AIFA)
	Agència de Qualitat i Avaluació Sanitàries de Catalunya Servei Català de la Salut, Spain (AquAS CatSalut)
	National Institute of Pharmacy and Nutrition, Hungary (NIPN)
	Norwegian Medicines Agency, Norway (NOMA)
	Regione Emilia-Romagna, Italy (RER)

How to cite this document

Please cite this document as follows:

Recommendations for Early Dialogues Based on the Experience of EUnetHTA Joint Action 3. Diemen (The Netherlands): EUnetHTA; 2021. [Date of citation]. Available from: https://www.eunethta.eu

Table of Contents

Abbreviations

AEMPS	Agencia Española de Medicamentos y Productos Sanitarios
AETSA	Área de Evaluación de Tecnologías Sanitarias de Andalucía
AIFA	Agenzia Italiana del Farmaco, Italy
AQuAS CatSalut	Agència de Qualitat i Avaluació Sanitàries de Catalunya Servei Català de la Salut
ATMPs	Advanced Therapy Medicinal Products
ED	Early Dialogue
EDWP	Early Dialogues Working Party
EU	European Union
EMA	European Medicines Agency
EUnetHTA	European Network for Health Technology Assessment
F2F	Face to Face
G-BA	Gemeinsamer Bundesausschuss, Germany
HAS	Haute Autorité de Santé, France
HCP	Health Care Professional
HTA	Health Technology Assessment
HTAb	Health Technology Assessment Bodies
JA	Joint Actions
LoI	Letter of Intent
MOOC	Massive Online Open Course
NIPN	National Institute of Pharmacy and Nutrition, Hungary
NOMA	Norwegian Medicines Agency
PC	Parallel Consultation
PLEG	Post Launch Evidence Generation
RER	Regione Emilia-Romagna, Italy
SME	Small or Medium Enterprise
TC	Teleconference

1. Introduction

1.1 Aim and Structure of the Report

This report aims to provide an overview of the work that has been carried out within WP5A in Joint Action 3 and to provide recommendations based on our experience and lessons learned. 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 report will further inform the work of the EUnetHTA Task Group on Future Model for Cooperation aiming to develop a complete blueprint for future European cooperation on HTA post-2021.

1.2 Target Audience of the Report

The target audience of this report is the European Commission and EUnetHTA partners. It may also be informative for a wider audience such as stakeholder groups of health technology assessment (HTA). This report contains no confidential information.

1.3 Sources of Information

This document contains information pulled from the WP5A Final Report, the Paradigm toolkit, EUnetHTA Guidance for Multi-HTA EDs and Guidance on Parallel Consultations, the EUnetHTA website, the draft EDFM framework document and the WP5A Qualitative Analysis Report.

1.4 Context of Early Dialogues Production

Definition of Early Dialogues

The EUnetHTA EDWP defines an Early Dialogue (ED) as a non-binding scientific advice, before the start of pivotal clinical trials (after feasibility / proof of concept study), in order to improve the quality and appropriateness of the data produced by the developers in view of future HTA assessment / re-assessment.

EUnetHTA EDs provide for an exchange between the Applicant and HTA bodies (HTAb) at an early stage in the development process in order to allow for the integration of HTA requirements (e.g. choice of comparators, relevant outcomes, quality of life, patient groups) in the study design (pivotal trials & post-launch studies) and the economic evidence generation plan. The main objective of EUnetHTA EDs is to gather and provide the common recommendations on how the drug or device could be developed in order to fill HTA requirements across multiple European Member States. However, when consensus is not possible, the views of participating HTA bodies will be made known to the Applicant.

General Aspects and Practical Considerations

- EDs for pivotal studies, before it starts
- Medicines and medical devices
- EDs remain confidential and are non-binding for either of the parties involved.
- 2 ED procedures: Parallel consultation and Multi-HTA
- 2 formats offered: written-only ED and ED with F2F meeting
- One-stop-shop, one coordinating EUnetHTA ED secretariat, dedicated templates for request and Briefing Book, HTAbs coordinated recommendations
- an EDWP Secure systems are used for exchange of documents between company and the EUnetHTA ED Secretariat, as well as between the ED Secretariat and the participating EUnetHTA HTA bodies.
- All participants in an ED (including patients/patient representatives and healthcare professionals) are required to complete Declaration of Interest (DOI) and Confidentiality Agreements form. These documents, together with the DOI handling procedures, are available on the EUnetHTA website.

- Submission formalities are the same regardless of the procedure format. Applicants are advised to review all information available on this website prior to submitting a request.
- All requests (Parallel Consultations and Multi-HTA ED requests) must be made during EUnetHTA's Open Call for EDs. The Applicant must use the template provided on the EUnetHTA website.
- Topics for discussion include **all evidence planned** to be used in the submission dossier for assessment/re-assessment. It is expected that each ED address a combination of the following topics at the same time:
    - Pivotal trial
    - Post-launch studies planned to complete evidence gap anticipated at the time of launch
    - Economic evidence planned as part of future HTA
- Prioritization/selection criteria
- The face-to-face (F2F) meeting venue for an ED depends on the type of request. For Pharmaceutical Products, parallel consultation meetings will take place at EMA (Amsterdam, NL); and Multi-HTA ED meetings will take place either at HAS (Saint-Denis, France) or G-BA (Berlin, Germany) or virtually.
- Some HTA bodies may charge fees for their participation. The EUnetHTA ED Secretariat can provide information on HTA-associated fees. The list is subject to modification at any time.
- IT management tool

Background

Within the framework of EUnetHTA Joint Action 3 JA3 EDs are carried out by work package 5A (WP5A), which is led by HAS (France) and co-lead by G-BA (Germany). EUnetHTA offers Early Dialogues (ED) on clinical and economic evidence generation for both pharmaceutical products and medical devices. EUnetHTA is a one-stop-shop for the involvement of HTA bodies in EDs with the primary contact point being the EUnetHTA ED Secretariat.

General Objectives for EUnetHTA Early Dialogues:

EUnetHTA strives to support generation of good quality evidence for proper HTA. To this end, our objectives include:

- Support developers of health technologies (pharma products and medical devices) by providing a collaborative approach among a wide range of European HTAb to provide consolidated advice on their product evidence generation plans, while also maintaining individual HTAb positions where needed.
- Supply and incorporate patient and clinical expert contributions in the final recommendations provided by HTAb.
- Link EDs to subsequent activities on additional data collection, including the use of patient registries.
- Optimize the interaction with regulators for pharmaceutical products, through parallel EMA-EUnetHTA EDs (Parallel Consultations).

Framework of the Collaboration and Submission by Industry

Types of ED Available

EUnetHTA offers two options for EDs on pharmaceuticals:

1. EMA-EUnetHTA Parallel Consultations: tripartite meetings which include HTAb and EMA together with the company. Prospective and timely advice may allow the Applicant to integrate specific HTA regulatory needs into the development plan and, therefore, fulfil the evidence requirements of both regulators and HTA bodies at the same time. To this end, EUnetHTA, in collaboration with the EMA, offers Parallel Consultations involving both HTA bodies and regulators

2. EUnetHTA Multi-HTA EDs: bilateral meetings between the HTAb and the company.

All EUnetHTA EDs are supported by the EUnetHTA ED Secretariat, thereby benefiting from HTA scientific and administrative coordination, consolidated HTA comments, a concerted effort to find agreement among the EDWP regarding specific issues as well as a consolidated document containing EUnetHTA's Final Written Recommendations. In the case of Parallel Consultations, opportunities for closed discussion amongst HTAbs, and with Regulators, with mutual understanding are maximized.

ED Format

Regardless of the type of ED (PC or Multi-HTA), there is one single procedure. This procedure, however, may follow one of two different formats: Written-only format and F2F meeting format. The decision as to which format the procedure will follow will be decided by the EDWP after review of the Applicant's Draft Briefing Book. This decision will be based on the following criteria:

- PRIME products
- Complexity of development
- Need for an in-depth discussion with the Applicant about the development plan, e.g. in case of unclear development plan or unexperienced companies
- Major issues with the development plan that would benefit from discussion with the Applicant.

For Parallel Consultations, a preliminary exchange on procedure format and associated organizational topics takes place during the monthly Administrative discussion between EUnetHTA and EMA.

In all cases, Applicants are informed of the decision on the procedure format upon reception of the Final Briefing Book by EUnetHTA.

Procedures that ***do not*** require a F2F meeting are approximately 2,5 months in duration starting from reception of the Draft Briefing Book.

Procedures that ***do*** require a F2F meeting are approximately 3,5 months in duration starting from reception of the Draft Briefing Book.

Regardless of the type or format of a EUnetHTA ED, the HTA bodies' final output remains the EUnetHTA Final Written Recommendations.

2. Summary of Recommendations

General Recommendations

Recommendations on the ED Selection Criteria

Based on our experience with the ED Selection Criteria, the following three recommendations are made.

- Open call system, twice per year covering a six-month period, in the case of limited number of possible ED. Although it requires additional preparation up front on the part of the ED Secretariat and the Lead/Co-Lead partners, the Open Call system is more advantageous than the batch system because it allows for better resource allocation and the ED Secretariat is able to influence/refine the ED dates through exchanges with the companies. However, this system can only function correctly if we have a better vision of HTAb resources in advance in order to know how many EDs can be accepted for a given call period. It therefore may be better to do a call twice per year covering a six-month period as this would allow for adjustments or unplanned events such as a pandemic. In the future with possibly higher numbers of EDs, a slot system could be set up (to be further discussed with EDWP as this was more complex for the teams – very difficult resource management).

- Maintain the product Selection Criteria[1]. They were very useful as cooperation added value is mainly to focus on selected/innovative products; they have remained stable throughout JA3. When establishing the criteria, there was concern that they were perhaps too restrictive. Over time however, more and more products being submitted are meeting these criteria and thus we observe it is not as selective as originally thought as evidenced by the fact that we often have more eligible requests than we can accept. The addition of a criterion about innovative methodology is to be investigated with EDWP.
- Finally, we need to work on how to manage similar requests (i.e. multiple requests with a similar MoA or indication) and investigate the possibility to consider indications slots, specific indication-based calls or indication-based workshops following the EMA model.

<u>Recommendations for Different Participants and their Roles in ED Production</u>

- *Enlarge EDWP:* As mentioned in the EDWP description, the relationship developed between the EDWP members opened the door for a revised ED procedure which centralized the main writing of the Recommendations with the Scientific Coordinator with support from the Rapporteur. However, SC/R are selected from the EDWP team and it proved more and more difficult to identify HTAb to take on these important roles. This was aggravated when some HTAb had or decided not to participate in PC. Indeed, as the companies submitted more and more eligible products, it was necessary for the EDWP to refuse products not only due to lack of capacity in the HTAb, but also due to lack of volunteers for the SC and R roles. Therefore, it may be necessary to consider enlarging the EDWP in order to increase ED capacity in the future. Participation in the EDWP has shown to be an excellent capacity building exercise.
- *Training of SC and R:* Furthermore, specific training on the roles of SC and R needs to be further developed, thus allowing for the possibility of additional candidates and taking into account the time required for each role (16 days and 12 days respectively (compared to 6 for an ED participant)).
- S*ystematic monitoring of the quality of all contributions:* A quality assurance system needs to be instituted by the ED Secretariat and acknowledged by the team. Although not a frequent occurrence, it did happen that some EDC members did not fully contribute to the ED. This in turn added to the workload of others and, with the more centralized procedure would then imply additional investment from both the SC and R. The idea of a quality check was developed within the EDFM and this should be explored further. One possible option that is currently under discussion would be to institute a workflow on Sharepoint. According to the description in the EDFM draft framework agreement, during every process of ED, ED Secretariat will interact with the various HTAb involved in the recommendation to ensure compliance with the process (especially due dates) and quality check. The quality check will consist in making sure that every participant in the ED process will contribute to the enrichment of the final recommendation and reflect the specific position of the represented country or region. This quality check aims at guaranteeing the consistency of the various recommendations provided to the Applicant and effective coverage of the various contracting parties (i.e. countries part of EUnetHTA). It may be necessary to define more specific, measurable criteria for checking quality, particularly if a fee for service model is ever implemented.
- *Guidance:* To ensure constant quality and consistency of the advice guidelines of what and how topics have to be covered and databases of points to consider (e.g. country-specific positions) could be considered to develop.

<u>Recommendations on ED Governance</u>

[1] The selection criteria state that the product should aim to bring added benefit to patients, i.e. by: A new mode of action for the indication; AND targeting a life-threatening or chronically debilitating disease; AND responding to unmet need (no treatment or only unsatisfactory treatment available).

The ED Secretariat together with WP5A Co-lead manages the heavy administrative burden of conducting Early Dialogues including but not limited to the development and maintenance of all procedures and related templates and guidance, ongoing quantitative and qualitative analysis, communication (with EDWP, EMA, external stakeholders), presenting at conferences (HTAi, ISPOR, DIA, TOPRA etc.), and insurance of COI compliance. For confidentiality reasons in the context of JA3, declaration of interest forms for each ED participant (internal and external to the network) were assessed by WP5 Lead and Co-lead partners.

- In the future, it is important to include ED in the centralized COI approach currently established in EUnetHTA via the COI Committee.
- The management of external stakeholders should be factored into the role of the ED Secretariat, with support of the national partners, especially those where patient involvement is a well-established part of their national process (in JA3 supported especially by Co-Lead G-BA, NICE, and Spanish colleagues). This last task must be carried out in alignment with national HTAb approaches for stakeholder involvement and this can vary greatly.
- Scientific tasks of ED secretariat to be highlighted .We highlight also that the ED Secretariat is responsible not only for administrative tasks, but also scientific ones (receivability of each ED request submitted, checking the quality of the output (at each step of the ED process), and supporting final consensus and identify subjects of divergence to establish rules adapted to the situation(s), and the training of newcomers to the ED process. We recommend a strategic reflection on these tasks within EUnetHTA and feel that these topics merit an analysis of harmonization of these tasks between WP4 and WP5.
- Perform regular qualitative analysis of EDs: An initial qualitative and quantitative analysis was carried out on the first 21 EUnetHTA EDs. Although it is a cumbersome and time-consuming task, this analysis should be continued on a regular basis to support the evolution of the ED procedures and methods, alignments of HTAbs and impacts. A systematic evaluation of the quality of the output has been implemented during the prolongation period and this provides for a regular evaluation of the EUnetHTA ED deliverables. The evaluation of output should consider, whether the advice had an impact on study design (if there were advice to change it) and, if the product got an assessment, whether the advice is reflected in the assessment (critique in the assessment was already anticipated in advice?). This analysis requires two scientific project managers to double check the work done by each of them, similar to a peer-review system.

The output of such analysis could support evolution of the procedure and guidance on systematic recommendations in specific cases.

Stakeholder Engagement

<u>Recommendations for Engagement with Patients and Patient Representatives</u>

- Patients or consumers involvement in ED should be systematic
- Consolidate guidance on how to conduct Interviews

The ED Secretariat implemented and tested three different approaches to patient involvement in EDs throughout JA3. The different approaches worked well, however one drawback is that the patient interview aspect works best when done by HTAb who have experience with involving patients. Nevertheless, many of those who did not have this experience in the beginning have gained it through interviewing patients in their role of SC/R.

In addition to guidance about how to conduct the patient interview, we recommend that the interview guide be adapted for each procedure to include problems already identified by the HTAb – particularly in the case of an expert participating in the entire procedure.

- Improve product information

Furthermore, we recommend systematic sharing of the Briefing Book with the concerned ED stakeholders including (particularly for patients) information concerning the sections that are most important for them to read. This will also facilitate the interview.

We encourage as much interaction as possible with the HTAb – in particular by encouraging patient participation in the HTAb List of Issues e-meeting and the pre-F2F meeting if the ED is following the F2F Meeting Format. In the case of a product following the Written-Only Format, encourage their participation in the HTAb meeting on the List of Issues or Draft Recommendations. Patent engagement in HTAb meetings prior to a F2F meeting needs to be tested and the best implementation might vary between the 3 different approaches in practice.

- Transparency: Regardless of the procedure format, we recommend transparency of patient input in the appendix of the Final Recommendations and clearly noted input within the body of the report.
- Further develop guidance on patient engagement in EDs:
- We have begun and recommend further developing guidance around patient involvement in Early Dialogues. This guidance could take different forms (i.e. information sheets, short videos, online presentations) and includes topics such as:
- What are EDs and why take part?
- Revise and customize on an ED basis the interview guide used by SC/R when interviewing patients
- Guidance regarding the recruitment of patients
- Patient guidance for participating in both virtual and F2F meetings
- Revision of patient feedback collection

Given the success we have experienced in recruiting patient participants directly, our recommendation is to continue this approach. This approach, together with the guidance documents described above may be the key to identifying the types of patients we prefer to see participate. Each participant has their role within an ED be it HTA, Regulatory or patient. Participating patients should have expertise on the disease and ideally some knowledge of the clinical development process. The purpose of an ED is to have a focused discussion on clinical development and not burden of the disease. While disease burden certainly influences the discussion, it is not the primary discussion topic nor is the difficult reimbursement situation in different countries. An ED is not a place where patients should advocate to get better treatment or support further reimbursement.

While patient input has impacted recommendations, some of their recommendations has shown to be less taken into account. In the future, patient's input could benefit in being presented following PICO framework so HTAb could better refer to patient's feedback when making recommendation on each item.

- Develop the use of PROs: We recommend PROs to be a systematic topic of discussion during EDs.

<u>Recommendation for Engagement with Health Care Professionals</u>

A transparent approach needs to be implemented for HCP experts much as there already is for patients.

<u>Recommendations for Collaboration with Regulators</u>

- Favor PC procedure for pharma, but maintain multi-HTA:

Although the majority of the EUnetHTA EDs carried out in JA3 were done in parallel with EMA, some companies may prefer to request a Multi-HTA ED. We have observed for instance that SMEs often are less familiar with HTA and thus request advice only after having received feedback from the EMA and the FDA.

The sequential timing might be a lost opportunity. To offset this and promote PC, multiple steps have been implemented during JA3

1. Increasing communication between EUnetHTA ED Secretariat and EMA.
2. Communication with the companies to encourage that the different advices be within a similar timeframe.
3. Over time, the increased communication with EMA allowed also the ED Secretariat to successfully lobby for using PICO as an organizational framework for the List of Issues and thus the F2F meeting (as the List of issues serves as the main list of subjects to address during the meeting)

The above modifications should be continued in the future. The benefits of Parallel Consultations, as identified through the qualitative analysis presented above lead us to recommend that PCs should be prioritized over Multi-HTA. This prioritization would not only encourage further understanding between HTAb and regulators but would be more efficient. That said, there are companies who prefer the Multi-HTA approach therefore it should be maintained as an option for early advice from HTAb.

- Explore collaboration for EDMD with the expert panel.

<u>Recommendations for Involvement with Manufacturers and Industry Associations</u>

- A better overview of available human resources at HTAb: Industry demand for EUnetHTA EDs far exceeds the supply. To this end, we need to better manage industry expectations regarding the number of ED to be carried out. This will require also better insight into the actual capacity of the HTAb and, perhaps, a commitment from their side to carry out the number of EDs agreed upon.
- A fee-for-service system is needed: The implementation of a fee-for-service mechanism would only underline this need.
- Complete ED requests forms. Although it has already been integrated into the revised procedure being implemented during the prolongation, we recommend the inclusion of additional details in the ED Request Form in particular PRO (validity of the tool included in proposed development with MCID), on PLEG (anticipated gap at launch, remaining research questions, additional core data set to be collected)…and maintaining the possibility to request additional information up until the F2F meeting in order to provide the best recommendations.

As noted particularly in the above section on Patient involvement, we recommend the systematic agreement from industry to share their Briefing Book with ALL external experts involved in a procedure provided each has an approved EUnetHTA DoI and CU.

- Share ED final recommendations with the JA team: EDs should be part of the JA submission dossier. As with a Joint Assessment, a EUnetHTA ED is centered around the PICO. We would recommend that a legally acceptable solution (respecting confidentiality and conflict of interest rules) be identified to share EUnetHTA ED Final Recommendations with the JA team, following the model used by EMA, for products that are jointly assessed in the future. The purpose of this is not to render the recommendations binding, but to provide the JA team with a PICO that has already been agreed upon by multiple HTAb as basis for discussion as recommendations may evolve over the time.

Procedures, Templates, and Methodology

<u>Recommendations for Procedures and Guidance Pharmaceutical EDs</u>

In general, the current pharmaceutical ED structure, with 38 EDs completed, works well and is aligned with EMA. Therefore, we do not recommend any major modifications. Any change recommendations would be more internally (do we centralize the procedure, do we do written-only EDs going forward).

These are questions that are currently being examined in the prolongation and the procedure will be updated according to what is most efficient for all participants. As an example, we need to see if the centralized procedure should be retained following its implementation. Two EDs have already been conducted using it and following the prolongation, there will have been a total of seven. Feedback needs to be collected from the EDWP ad Analysis will be needed to understand if the centralized procedure functions as planned, saves time, and makes the task less complicated and time consuming, in particular for the SC/R.

The open call system that was implemented for EDs carried out during the prolongation was successful in alleviating the pressure on resources previously experienced by the participating HTAb. It also facilitated the recruitment of patient experts. We therefore recommend formalizing in writing the call procedure and the eventual pro-active recruitment of EDs if interesting subjects are able to be identified in advance (for instance through discussions with companies where pipeline is discussed).

EDFM

The financial sustainability of EDs should be achieved. For the EDFM framework to work, an organism to function as the "banker" must be identified; otherwise a new approach must be developed. The draft EDFM framework has been developed by WP5A Lead and Co-Lead together with experts on European law (Eubelius) and the business case consultant KPMG (both renowned partners). The framework is in theory ready and available as soon as a "banker" could be identified. Based on the experience from attempting to implement the EDFM, we recommend that the "banker" role not be undertaken by an HTA organism. Industry is ready to pay, particularly if this will increase ED capacity. Notably, the fee amount evaluated by the EDFM was considered "acceptable" by industry.

On the other hand, if implemented, the EDFM will add to the workload of the ED Secretariat particularly in terms of coordination and compiling the information necessary for the banker, but also and most importantly for ensuring the quality and the implication of each participating HTAb.

We highlight that even if it were decided today to implement the EDFM, it will take up to 6 months to have it up and running due to the need to identify an organism for the bank, revision of procedures to integrate that organization, not to mention the required signatures from all participants. Significantly, if a new mechanism must be developed, we are looking at a much longer period, likely 6 months minimum that would be needed. The operation time period of a mechanism would likely need to be at least 2 years in duration to justify the work to establish it.

Finally, and most importantly, a sustainable mechanism will not be possible in the future without a legal framework.

EDMD

There is much less demand currently for EDMD than for pharmaceutical MD.

- a communication campaign is likely necessary if we wish to increase the numbers.
- Further explore synergies with the MDR expert panel.

<u>Recommendations for Templates</u>

- Regular review of documents. The templates and guidance documents used in the framework of EUnetHTA EDs must be reviewed and revised at least once annually, if not every six months. While modifying documents linked to Multi-HTA EDs (both pharma and medical devices) is rather straight-forward, the modification of anything linked to Parallel Consultations for

pharma is more complex as it involves not only EUnetHTA but EMA. During the prolongation, the use of the ED Request Form during the open call allowed us to make certain modifications, for example requesting more detailed information at the start in order for the EDWP to have a better informed basis on which to make their decision on acceptance of a product. Going forward, we recommend reviewing the current Briefing Book Template as the information requested is sometimes repetitive. These changes can be done quickly for Multi-HTA but will require discussion and negotiation with EMA in order to modify the parallel consultation version.

- The modifications regarding HTA only in the PC procedure should be done in an easier manner.

Recommendations for Method Adaptation

A formal quality assurance system to evaluate the quality of the final deliverable needs to be established and parameters of how to measure this need to be defined including a mitigation procedure in case the ED fails the QA.

- Room for improving the process; Based on the findings above, overall room for improvement and simplification of the ED process should be explored to propose a concept for further modification of the advice procedure. Recommendations for this include:
    - Some adaptation of the briefing book to ensure sufficient information on PLEG and PRO/HQol is provided by the company
    - While different approaches were observed to make recommendations on PRO/HQoL, subgroup, and statistical analyses, further exchanges are needed between EDWP members to discuss the rationale for the differences. This discussion could help to achieve further consensus.
    - Statistical support by dedicated expert group (WP4 expert group for example) and maybe also closer exchange with EMA on stats could also improve alignment.
    - Systematic recommendations should be further communicated

- Monitor the ED impact. The impact of the ED process is observed but we should consider further monitoring it. Unfortunately, industry feedback questionnaire is often missing due to many companies never returning the completed document. Time is needed in order to see the effect of an ED on development. Perhaps this should be further discussed with industry.

IT tool

It is necessary to have a robust management tool and database on EDs

Going forward, the ED Secretariat would benefit greatly from an improved utilization of Sharepoint and perhaps even the integration of Teams to share information with different stakeholders. This is particularly important given first, the lack of a functioning extranet and second, the latest change in functioning at EMA. Until November 2020, Eudralink (an EMA resource for secure email) was used for exchanging all information between EUnetHTA and EMA and EUnetHTA and companies for parallel consultations. This system will no longer be used in Parallel Consultations and thus a EUnetHTA solution via Sharepoint and/or Teams is necessary. A workflow solution should also be envisaged to better monitor each step of the process and ensure quality.

Recommendations for Communication

Together with the recommendations made above, particularly some of those for communicating with patients, we would recommend the creation of a MOOC on the ED process.

Hand in hand with managing the expectations of industry is how we communicate them. It may be necessary to review how this is done and develop more efficient means of communication, such as an email newsletter to which interested companies subscribe.

3. The Work Done, Experiences, and Recommendations

3.1 JA3 ED Production

The Work Done and Experiences

From launch in March 2017 through May 31, 2020 122 official requests for Early Dialogue were received from industry. From those requests, 39 products received EUnetHTA advice. Of the 39 products, 32 EDs were carried out in parallel with EMA, 6 were Multi-HTA EDs and there was one ED for a Medical Device. Table 1 below provides a breakdown of the EUnetHTA advice provided by therapeutic area.

Table 1: EUnetHTA EDs by Therapeutic Pathway

Total Requests for Early Dialogues (119*) in JA3			
Therapeutic Field (indication)	**Multi-HTA Early Dialogues** (23 requests)		**Parallel Consultations** (94 requests)
	Pharmaceutical Products (6 accepted requests)	**Medical Devices** (3 requests)	**PCC/PC[2]** (32 requests)
Cancer	2 (completed)	1 (completed)	10 (completed)
Metabolic disorders		1 (withdrawn by applicant)	
Neurodegenerative disorders	1 (completed)		4 (completed)
Viral disease	1 (completed)		1 (completed)
Other	2 (completed)	1 (withdrawn by applicant)	16 (completed) 1 (withdrawn by applicant)

**Including 2 requests for qualification in parallel with EMA not included in the therapeutic field breakdown*

In addition to the products above, 26 other products received Individual Parallel advice (i.e. not benefiting from EUnetHTA funding).

We note that: 17/119 (14.29%) requests came from SMEs (resulting in seven PCs); 19/119 (15.97%) were requests for ATMP products (resulting in ten PCC/PC, one Multi-HTA [note: the EDWP agreed that an additional product met the selection criteria but, due to resource constraints, had to be refused]. 33/119 (27.73%) were requests related to products with an Orphan designation, resulting in 13 PC and 3 Multi-HTA.

A qualitative analysis was performed on the first 21 EUnetHTA EDs (comprising 18 PCs and 3 Multi-HTA EDs), using July 31, 2019 as the cut-off date and including ED50 (F2F in June 2019). Results of this analysis allowed us to make certain diagnoses of the situation and fed our reflection on recommendations for the future. Some of the data extracted from this analysis are mentioned in several sections of this report.

[2] As of July 2020, all consolidated Parallel Consultations were referred to as PC

3.2 ED Governance

Secretariat and Project Management of EDs

The ED Secretariat is composed of a full-time project manager, a part time scientific project manager and an assistant at HAS. The Secretariat was also supported by one project manager from G-BA. It is responsible for the overall management of the activities related to the performance of the EDs and carries out the following tasks:

i. Practical coordination of EDs;
ii. Explication procedure etc. and assistance for newcomers;
iii. Update documents, guidance, template, FAQs
iv. Management of the ED intranet and tools including Sharepoint access to restricted areas, creation of ED work areas (including calendars, reminders, workflow), provision of secure mechanisms for exchange of documents with Applicants that cannot use the EMA system (e.g. for Multi-HTA EDs or after the EMA stopped its Eudralink system);
v. Serve as single point of contact for HTA Bodies, Industry (and EMA in case of Parallel Consultations), and other stakeholders including patients and healthcare professionals (HCPs);
vi. Monthly and ad-hoc e-meetings with EMA to discuss and negotiate Parallel Consultation procedures, timelines, templates, explain HTA principles PICO, etc.
vii. Respond to all questions regarding EDs including those from Applicants, the European Medicines Agency, HTA Bodies, as well as external stakeholders such as HCPs, patient experts, HCP organisations, patients' organisations, etc.;
viii. Verify the receivability of ED Requests and refer receivable ED Requests to the EDWP for an assessment of the eligibility of the concerned pharmaceutical product for an ED; inform the Applicant and EMA in the case of a Parallel Consultation about the receivability and acceptance of the ED Request (as decided by the EDWP);
ix. Monitor the quality and the consistency of EDs including but not limited to insuring the scientific quality of the final recommendations insuring all participating HTAb have taken part in each step of the process, insure the templates are used and used correctly, insure the respect of deadlines as provided in the ED-specific timetable;
x. Request, manage, and review all DOI and CU documents for ED participants including HTAb members, and patient and HCP experts with G-BA as co-lead partner. The product, indication and any information provided by the company regarding an Early Dialogue is confidential. Thus, detailed assessment by all members of the COI Committee is not possible. For this reason, COI judgement for WP5A needs to be done by WP5 only. ED participants (HTAb and experts) are in the situation of providing advice (consultancy) to company therefore conflicts are considered only if participants have a stake or interest in a competitive technology which could adversely influence their recommendations.
xi. Engage patients and patients' representatives (with the exception of German patients' representatives, who will be engaged via G-BA) and HCPs to identify participants to provide expert input related to i.a. the condition, treatment and expectations of patients and the proposed development protocol; sign the necessary agreements (EUnetHTA DOI and CU, HAS contract for compensation, etc) with European patients' representatives and HCPs;
xii. Provide reports on the activities including quantitative and qualitative analyses of the EDs performed; communicate about the activities (through conferences, publications, etc.) in collaboration with G-BA as Co-Lead Partner.
xiii. Creation, modification of ED information and content for the EUnetHTA website including but not limited to FAQs, descriptive text, guidelines, timetables.
xiv. Communication on EUnetHTA EDs at international conferences via posters, presentations, and panels.

xv. Management of WP5A budget spending and estimations

The ED Secretariat worked on continually improving the ED Work Area on Sharepoint. In the beginning there was a good amount of difficulty and we needed to remind participants at each step what they needed to do and how to access documents. This improved with better understanding of the procedure and an initial reorganization of the work area.

Throughout JA3 the ED Secretariat responded to questions and inquiries from industry both by email and telephone. To respond more effectively to these inquiries an FAQ was developed and maintained on the EUnetHTA website.

A shared the qualitative analysis was carried out by HAS and G-BA. The process was arduous, but the collaboration between the two HTAb was very useful as the qualitative analysis is subjective in nature and needs peer review to maintain impartiality. The contribution of G-BA within the ED Secretariat also allowed us to have draft templates that were founded on consensus from 2 experienced HTAb that do EDs with different procedures. This helped us to take into account different work mechanisms and requirements prior to presenting a draft to the larger EDWP. The team prepared standardized templates for emails, timeline calculations for retro planning, and procedural templates.

A medical writer was retained to review all Final Recommendations for clarity and consistency in language.

Nevertheless, one lasting frustration is the lack of means. This frustration is not only coming from industry (not enough EDs accepted or not enough slots) but also with EMA (needing to regularly algin with EMA timelines even if they do not match those of the HTAb), and internally (in particular due to staff constraints).

Over time, it became evident that the ED Secretariat needs to regularly check the outputs of each step of the ED procedure. Indeed, this mechanism was integrated into the proposed EDFM. In general, the ED Secretariat must verify the quality and consistency of the document, from ensuring that the comments and notes have been deleted and that patient input has been integrated. Finally, when there were moments of misunderstanding or disagreement on a topic within the EDWP (in particular between the SC/R) the ED Secretariat acted as arbiter. We note also that a medical editor was integrated into the ED process about mid-way through JA3 and this has assisted the ED Secretariat in guaranteeing the consistency of the recommendations that are provided.

Recommendations

The ED Secretariat together with WP5A Co-lead manages the heavy administrative burden of conducting Early Dialogues including but not limited to the development and maintenance of all procedures and related templates and guidance, ongoing quantitative and qualitative analysis, communication (with EDWP, EMA, external stakeholders), presenting at conferences (HTAi, ISPOR, DIA, TOPRA etc.), and insurance of COI compliance. For confidentiality reasons in the context of JA3, declaration of interest forms for each ED participant (internal and external to the network) were assessed by WP5 Lead and Co-lead partners.

- In the future, it is important to include ED in the centralized COI approach currently established in EUnetHTA via the COI Committee.
- The management of external stakeholders should be factored into the role of the ED Secretariat, with support of the national partners, especially those where patient involvement is a well-established part of their national process (in JA3 supported especially by Co-Lead G-

BA, NICE, and Spanish colleagues). This last task must be carried out in alignment with national HTAb approaches for stakeholder involvement and this can vary greatly.

- Scientific tasks of ED secretariat to be highlighted .We highlight also that the ED Secretariat is responsible not only for administrative tasks, but also scientific ones (receivability of each ED request submitted, checking the quality of the output (at each step of the ED process), and supporting final consensus and identify subjects of divergence to establish rules adapted to the situation(s), and the training of newcomers to the ED process. We recommend a strategic reflection on these tasks within EUnetHTA and feel that these topics merit an analysis of harmonization of these tasks between WP4 and WP5.
- Perform regular qualitative analysis of EDs: An initial qualitative and quantitative analysis was carried out on the first 21 EUnetHTA EDs. Although it is a cumbersome and time-consuming task, this analysis should be continued on a regular basis to support the evolution of the ED procedures and methods, alignments of HTAbs and impacts. A systematic evaluation of the quality of the output has been implemented during the prolongation period and this provides for a regular evaluation of the EUnetHTA ED deliverables. The evaluation of output should consider, whether the advice had an impact on study design (if there were advice to change it) and, if the product got an assessment, whether the advice is reflected in the assessment (critique in the assessment was already anticipated in advice?). This analysis requires two scientific project managers to double check the work done by each of them, similar to a peer-review system.

The output of such analysis could support evolution of the procedure and guidance on systematic recommendations in specific cases

3.3 Different Groups and their Roles in ED Production

The Work Done and Experiences

The ED work package was Led by HAS and co-Led by G-BA. Partners in the WP were kept updated regarding advances in the workplan through an annual meeting. These meetings were supplemented by meetings of the Early Dialogues Working Party (EDWP). Additionally, and until the prolongation period, when an ED was accepted by the EDWP all WP5A partners were informed and invited to respond to a call for participation. This action was discontinued during the prolongation period due to lack of resources.

Early Dialogues Working Party

The Early Dialogues Working Party ("EDWP") is essential to the functioning of EUnetHTA Early Dialogues. The EDWP is composed of permanent and experienced HTAb members and its membership will remain unchanged for the duration of the EUnetHTA prolongation period.

The EDWP is currently composed of the following HTA Bodies: AEMPS (with the support of regional agencies AQuAS-CatSalut and AETSA), G-BA, HAS, NIPN, NICE, NOMA, AIFA/RER (RER is back-up for when AIFA does not participate). The diverse composition of the EDWP is one of its key strengths and allows EUnetHTA to provide Final Recommendations that consider the specificities of each national situation, while also providing a consolidated response to Applicants.

The EDWP is the standing working party of the HTA Bodies for the performance of the EDs and is responsible for the following tasks:

i. assess the eligibility of ED Requests in view of the Eligibility Criteria and report to the ED Secretariat on the eligibility and acceptance of the ED Requests;
ii. provide feedback to the ED Secretariat on draft guidance documents and templates as shared by the ED Secretariat;
iii. participate systematically in the performance of the EDs;

iv. monitor and report on the quality and the consistency of EDs to the ED Secretariat;
v. engage national experts in the framework of EDs, who cooperate on a voluntary basis.

The HTA Bodies agree to take on with the roles and obligations of Scientific Coordinator and Rapporteur and to participate in all EDs (with exceptions for products outside their remit, etc).

Due to the confidential nature of the information contained in a Letter of Intent and an ED Request form, each individual participating on behalf of an HTA Body in an ED must provide a completed and signed copy of the EUnetHTA Declaration of Interest and Confidentiality Agreements prior to receiving any information regarding an ED or a request for an ED.

The EDWP was constituted by a call to all WP5A participants. The primary requirements were that the HTAb was experienced in EDs and that they had budget to participate in all EDs. The original composition was as follows: AIFA (with RER as alternate), G-BA, HAS, NICE, NIPN, RIZIV-INAMI/ZIN (Shared Seat). After year 3 of JA3 both RIZIV-INAMI and ZIN withdrew from the EDWP. At the same time new HTAb entered. After doing the work of the EDWP for nearly two years without the status or voting rights as an EDWP member, NOMA and TLV entered with a shared "Nordic" seat and Spain entered led by AEMPS and including also Spanish regional agencies AETSA and AQUAS.

At the end of JA3, the EDWP composition included 7 HTAb as outlined at the beginning of this section. For the JA3 prolongation period, TLV decided not to continue as an EDWP member and, due to Brexit, while NICE remains an EDWP member, their participation is limited to Multi-HTA EDs.

The experience of the first two years of EDs allowed the EDWP members to gain confidence in each other and to better understand the positions and requirements of each HTAb. Without this foundation of understanding, it would not have been able to move toward a more centralized procedure as was done in the last half of JA3 year four. The EDWP was instrumental also in reviewing all procedures and templates drafted by the ED Secretariat and actively proposed modifications to templates, and work methods.

Early Dialogue Committee

The Early Dialogue Committee (EDC) is composed of members of the EDWP and of other HTA bodies that are participating voluntarily in a specific ED. The composition of the EDC can vary in function of the specific ED, depending on the particularities of the concerned ED and (the scope of the) remit of the different HTA Bodies. If the pharmaceutical product involved in the ED falls outside the scope of an HTA Body, this HTA Body will not be part of the EDC for the ED related to that pharmaceutical product.

The EDC is responsible for providing written feedback on every step of every ED procedure, namely the following tasks:

(i) review and provide feedback on the list of issues proposal from the Scientific Coordinator (SC) and the Rapporteur (R) prior to the List of Issues e-meeting (in case of F2F Meeting Format);
(ii) provide national-level specificities, if necessary, during the e-meeting;
(iii) review the finalized consolidated list of issues (in case of F2F Meeting Format);
(iv) discuss Applicant's Written Response to the list of issues and draft recommendations during the pre-face to face meeting(s) (e-meeting) (in case of F2F Meeting Format);
(v) review final written recommendations

EDC members are official only once their EUnetHTA Declaration of Interest form and Confidentiality Agreement have been submitted to and reviewed by the ED Secretariat. Only at that point do they

have access to any element of the Letter of Intent or are they provided access to the EDC work area which provides access to the dossier and associated documents through Sharepoint.

During the prolongation period, the decision was taken to include only EDWP members in the EDs and thus the EDC. This decision was because the budget for the prolongation period was limited and we had to negotiate to be able to conduct a number of EDs based on an estimated cost. Were able to estimate the costs needed for the prolongation due to work done with the EDWP members in preparing the Early Dialogues Financing Mechanism. Due to the diminishing and sporadic involvement of non EDWP members in the first 40 EDs, it was very complicated to try to estimate the impact of their potential involvement on the budget needed.

Pre-prolongation, all WP5A members were solicited to participate in an ED. They were solicited regardless of whether it was a Multi-HTA or Parallel Consultation. Following the decision by the EDWP as to whether to accept an ED, a Call for Interest was sent to the WP5A partners. They had 3 days to respond to the request and thus join the EDC. On average 6 HTAb participated in an ED. The table below provides an overview of the WP5A HTAb who participated the 38 EUnetHTA Early Dialogues for pharmaceutical products.

Table 2: HTAb Participation in EUnetHTA EDs

HTAb Participation in the 38 EUnetHTA EDs for Pharmaceutical Products		
WP5A Member	**Number as Full Participant**	**Number as Observer**
AEMPS	27	
AETSA	8	
AETS-ISCIII	1	
AIFA	18	
AQUAS	11	
G-BA	33	
HAS	36	
HVB	2	
INFARMED	2	
JAZMP	2	1
NCPHA	0	1
NICE	28	
NIPN	35	
NOMA	23	
RER	11	
RIZIV-INAMI	9	
TLV	12	
ZIN	2	

While there was a wide array of HTAb who participated over the JA period, this participation was sporadic at best and often, even for EUnetHTA EDs. Nevertheless, the HTAb who were involved were often those with less ED experience, and thus their participation was a good exercise in capacity building.

Early Dialogue Scientific Coordinator

An Early Dialogue Scientific Coordinator (SC) is nominated for each ED. The SC is responsible for the following tasks with a workload estimate of around 16 working days:

i. Draft and consolidate the written requests for clarification if needed, in collaboration with the ED Rapporteur; request clarifications from the Applicant at any time throughout the procedure;

In case of Written-Only Format:

ii. Prepare the slides and chair the e-meeting on the draft positions, in collaboration with the members of the EDC;
iii. Exchange on draft positions with the European Medicines Agency during the closed e-meeting
iv. Consolidate the final written recommendations, in collaboration with the ED Rapporteur;
v. Validate the final written recommendations, in collaboration with the ED Rapporteur, based on the feedback from HTA Bodies and the medical editor.

In case of F2F Meeting Format:

ii. Draft the list of issues, in collaboration with the ED Rapporteur;
iii. Prepare the slides and chair the e-meeting on the list of issues and draft positions, in collaboration with the members of the EDC;
iv. Finalize the consolidated list of issues, in collaboration with the ED Rapporteur, based on the feedback received during the e-meeting;
v. Discuss the consolidated list of issues with the European Medicines Agency during the pre-face to face meeting;
vi. If applicable, interview "European" expert identified by the ED Secretariat;
vii. Compile the draft written recommendations, in collaboration with the ED Rapporteur, with relevant adaptation based on the response of the Applicant to EUnetHTA list of issues, in preparation of the face to face meeting(s);
viii. Chair face to face meeting(s) on behalf of the members of the EDWP;
ix. Consolidate the final written recommendations, in collaboration with the ED Rapporteur, based on the discussion during the face to face meeting(s);
x. Validate the final written recommendations, in collaboration with the ED Rapporteur, based on the feedback from HTA Bodies and the medical editor.

Multiple approaches have been tested in identifying partners for this role. While at first the partners were against a rotation schedule, after years 2 and 3 it became evident that it would not be possible to continue without one. A fixed rotation was implemented for the EDs carried out under the prolongation period. The advantage in the prolongation was that EDs were selected and programmed over a 9-month period. This allowed not only for most partners to take on multiple roles at different times, but also for them to know what the product would be, thus making sure the human resources are available in advance.

Table 3: HTAbs as Scientific Coordinator in EUnetHTA EDs

EDWP Members	Number of times as Scientific Coordinator
AEMPS	1
AIFA	0
G-BA	16
HAS	9
NICE	3
NIPN	0
NOMA	7
RER	2
RIZIV-INAMI	0

ZIN	0

EARLY DIALOGUE RAPPORTEUR

An Early Dialogue Rapporteur ("ED Rapporteur") is nominated for each ED and supports the ED Scientific Coordinator and works in close collaboration with the ED Scientific Coordinator. The estimated time commitment is 12 working days.

The ED Rapporteur shall be responsible for the following tasks:

i. Review the written requests for clarification if needed; request clarifications from the Applicant at any time throughout the procedure;

In case of Written-Only Format

ii. Assist ED Scientific Coordinator to prepare the slides and chair the e-meeting on the draft positions;
iii. Exchange on draft positions with the European Medicines Agency, in collaboration with the ED Scientific Coordinator during closed e-meeting;
iv. If applicable, interview "European" expert identified by the ED Secretariat (in coordination with ED Scientific Coordinator);
v. Review the final written recommendations;
vi. Validate the final written recommendations, in collaboration with the ED Scientific Coordinator.

In case of F2F Meeting Format

ii. Review the list of issues;
iii. Review the finalized consolidated list of issues;
iv. Assist ED Scientific Coordinator to prepare the slides and chair the e-meeting on the draft positions;
v. Discuss the consolidated list of issues with the European Medicines Agency, in collaboration with the ED Scientific Coordinator;
vi. If applicable, interview "European" expert identified by the ED Secretariat (in coordination with ED Scientific Coordinator);
vii. Discuss the Applicant's written response to the list of issues, in collaboration with the ED Scientific Coordinator, in preparation of the face to face meeting(s);
viii. Prepare the presentation and chair the closed pre-face to face meeting(s) (e-meeting);
ix. Co-chair the face to face meeting(s) on behalf of the members of the EDC;
x. Review the final written recommendations;
xi. Validate the final written recommendations, in collaboration with the ED Scientific Coordinator.

Quality acknowledged by team and ED Secretariat in case lack of quality imply further investment from other parties like rapporteur or one specific participant.

Table 4: HTAbs as Rapporteur in EUnetHTA EDs

EDWP Members (including former members)	Number of times as Rapporteur
AEMPS	1
AIFA	2
G-BA	9
HAS	10
NICE	7

NIPN	2
NOMA	2
RER	0
RIZIV-INAMI	0
TLV	1
ZIN	0

Recommendations for Different Groups and their Roles in ED Production

- Enlarge EDWP: As mentioned in the EDWP description, the relationship developed between the EDWP members opened the door for a revised ED procedure which centralized the main writing of the Recommendations with the Scientific Coordinator with support from the Rapporteur. However, SC/R are selected from the EDWP team and it proved more and more difficult to identify HTAb to take on these important roles. This was aggravated when some HTAb had or decided not to participate in PC. Indeed, as the companies submitted more and more eligible products, it was necessary for the EDWP to refuse products not only due to lack of capacity in the HTAb, but also due to lack of volunteers for the SC and R roles. Therefore, it may be necessary to consider enlarging the EDWP in order to increase ED capacity in the future. Participation in the EDWP has shown to be an excellent capacity building exercise.
- Training of SC and R: Furthermore, specific training on the roles of SC and R needs to be further developed, thus allowing for the possibility of additional candidates and taking into account the time required for each role (16 days and 12 days respectively (compared to 6 for an ED participant)).
- Systematic monitoring of the quality of all contributions: A quality assurance system needs to be instituted by the ED Secretariat and acknowledged by the team. Although not a frequent occurrence, it did happen that some EDC members did not fully contribute to the ED. This in turn added to the workload of others and, with the more centralized procedure would then imply additional investment from both the SC and R. The idea of a quality check was developed within the EDFM and this should be explored further. One possible option that is currently under discussion would be to institute a workflow on Sharepoint. According to the description in the EDFM draft framework agreement, during every process of ED, ED Secretariat will interact with the various HTAb involved in the recommendation to ensure compliance with the process (especially due dates) and quality check. The quality check will consist in making sure that every participant in the ED process will contribute to the enrichment of the final recommendation and reflect the specific position of the represented country or region. This quality check aims at guaranteeing the consistency of the various recommendations provided to the Applicant and effective coverage of the various contracting parties (i.e. countries part of EUnetHTA). It may be necessary to define more specific, measurable criteria for checking quality, particularly if a fee for service model is ever implemented.
- Guidance: To ensure constant quality and consistency of the advice guidelines of what and how topics have to be covered and databases of points to consider (e.g. country-specific positions) could be considered to develop.

3.4 ED Selection Criteria

The Work Done and Experiences

While the choice of what type of ED (Parallel Consultation vs. Multi-HTA) is up to the Applicant, the decision as to the acceptance (or not) of a request for Parallel Consultation or Multi-HTA ED is up to the EDWP. This decision is based on the application of the EUnetHTA Selection Criteria. Within EUnetHTA, resources (not only financial, but also human) are finite. While EMA rarely declines a product scientific advice, this is not the case with EUnetHTA. With this in mind, a set of selection criteria was established at the outset of JA3 by the EDWP. These criteria were then published on the EUnetHTA website and included in EUnetHTA ED Guidance for transparency. The EUnetHTA Selection Criteria state that the product should aim to bring added benefit to patients, i.e. by:

- a new mode of action for the indication; and
- targeting a life-threatening or chronically debilitating disease; and
- responding to an unmet need of patients (no treatment or only unsatisfactory treatment available).

In addition to the above, the phase 3 studies must not have already started and the product should be within the remit of all members of the EDWP.

The Applicant can be granted a right to access an ED procedure by a decision of the EDWP to accept its ED Request. The decision is taken with a simple majority of the votes cast by the members of the EDWP. In order to be able to consider an ED Request acceptable, the EDWP should take into account the following principles:

(i) maximum 2 EDs should be running per month (within a maximum of 12 EDs per year) with the additional selection made (in cases multiple products are eligible) based on whether there are other products recently developed in a similar indication and whether or not the EDWP has already evaluated a product in a similar indication;

(ii) the selection of EDs should be as diverse as possible - selected EDs should represent a wide array of topics, therapeutic areas, etc. (e.g. orphan, ATMPs, antibiotics, oncology).

From April 2017 through June 2020[3], EUnetHTA EDs functioned on what was referred to as the "batch" system. Following the published timelines for Parallel Consultations and Multi-HTA EDs, companies submitted a Letter of Intent in order to be considered for an ED for that month. After the submission deadline, the EDWP members evaluated all requests received for that period as a "batch" and decided which product(s) to accept. This evaluation was carried out without any knowledge as to which came in first or last and each request is weighed against the published EDWP Selection Criteria. In some batches, multiple products were eligible, while other times only one or even none.

In the beginning, as many as 4 products were selected during a particular batch. This quickly became unsustainable, especially since new products were arriving every month and most often at least one was accepted. In Y4 of JA3, only 1 product was selected per month, if any. This change was initially due first to lack of resources for specific indications but was soon exacerbated by the Covid-19 pandemic resulting ultimately in the temporary suspension of EDs from February 2020 through June 2020. The batch review process was intended to make it easier for the EDWP to choose products, as they could evaluate several at the same time. However, without foresight as to what would be coming the next

[3] While the batch system was in place this whole period it was effectively suspended from March 2020 through June 2020 due to the COVID-19 pandemic.

month, it also made it difficult for HTAb to organize resources and compounded the already complex task of identifying Scientific Coordinators and Rapporteurs for all accepted products.

To address this issue and to fill the slots for the 8 EDs approved by EX Board through May 2021, the EUnetHTA ED Secretariat held an Open Call to industry from July 7 – August 15, 2020. The aim was to select the 8 products over the summer that would benefit from a EUnetHTA ED to be conducted during the JA3 prolongation period. Primary selection of products was carried out during the summer in order to restart ED activities in September 2020.

Recommendations

Based on our experience with the ED Selection Criteria, the following three recommendations are made.

- Open call system, twice per year covering a six-month period, in the case of limited number of possible ED. Although it requires additional preparation up front on the part of the ED Secretariat and the Lead/Co-Lead partners, the Open Call system is more advantageous than the batch system because it allows for better resource allocation and the ED Secretariat is able to influence/refine the ED dates through exchanges with the companies. However, this system can only function correctly if we have a better vision of HTAb resources in advance in order to know how many EDs can be accepted for a given call period. It therefore may be better to do a call twice per year covering a six-month period as this would allow for adjustments or unplanned events such as a pandemic. In the future with possibly higher numbers of EDs, a slot system could be set up (to be further discussed with EDWP as this was more complex for the teams – very difficult resource management).
- Maintain the product Selection Criteria[4]. They were very useful as cooperation added value is mainly to focus on selected/innovative products; they have remained stable throughout JA3. When establishing the criteria, there was concern that they were perhaps too restrictive. Over time however, more and more products being submitted are meeting these criteria and thus we observe it is not as selective as originally thought as evidenced by the fact that we often have more eligible requests than we can accept. The addition of a criterion about innovative methodology is to be investigated with EDWP.
- Finally, we need to work on how to manage similar requests (i.e. multiple requests with a similar MoA or indication) and investigate the possibility to consider indications slots, specific indication-based calls or indication-based workshops following the EMA model.

3.5 Engagement with Patients and Patient Representatives

The Work Done and Experiences

The methods by which WP5A involved patients was developed is a hybrid model. At the outset of JA3, patient experience within the EDWP members was minimal. The two exceptions were NICE and G-BA however both used very different approaches. In that context we wanted to test multiple possibilities ex NICE wants patient in meeting and G-BA no, this we came up with 3 approaches as presented in table 5 below.

[4] The selection criteria state that the product should aim to bring added benefit to patients, i.e. by: A new mode of action for the indication; AND targeting a life-threatening or chronically debilitating disease; AND responding to unmet need (no treatment or only unsatisfactory treatment available).

Table 5: Hybrid Approach to Patient Involvement in EUnetHTA Early Dialogues

Approach	Patient Deliverables
Approach 1: Patient/ patient representative interviewed regarding the disease and their experience.	• Minutes of the interview • Patient contribution visible in final EUnetHTA recommendations • Feedback questionnaire and interview
Approach 2: Approach 1 + discussion with local HTAB regarding submission file (without applicant).	• Minutes of the interview • Patient contribution visible in final EUnetHTA recommendations • Feedback questionnaire and interview
Approach 3: Approach 2 + discussion with all participating HTABs regarding the submission file and participation in the F2F meeting with the applicant.	• Minutes of the interview • Patient contribution visible in final EUnetHTA recommendations • Share final EUnetHTA recommendations • Feedback questionnaire and interview

The approaches are based on a combination of those used across different HTAb. They were discussed within the EDWP and published on the EUnetHTA website.

In terms of recruiting patients, this is begun once the EDWP decision on eligibility is final. At that point, the EUnetHTA ED Secretariat begins contacting European and national associations to identify potential patient experts. Throughout JA3, the ED Secretariat tested centralizing requests through a European network of associations and in parallel directly contacting national and European organizations. While patients were identified through both mechanisms, a significant majority of the patients were identified via direct contact with national and European patient associations. This result is likely due to a much faster response time (sometimes same day) but also due to a better acceptance regarding the compensation rules (no payment for services), Conflict of Interest, etc.

As soon as a patient is identified, which may take from a day or two to over a month, the ED Secretariat contacts them to schedule an introductory interview to discuss their potential involvement and to explain the following:

- EUnetHTA and what we do
- The difference between HTAb and Regulators
- What an ED is and what is expected of their participation
- answer any questions they may have regarding the process, EDs, etc.

The patient Interview is generally conducted by the Scientific Coordinator and Rapporteur. However, it can also be done by any of the participating HTAb, particularly if the interview is to be conducted in the national language. The interview may take place at any time from reception of the Final Briefing Book up until one week prior to the EUnetHTA e-meeting on draft positions (if Written-Only Format) or the pre-F2F Meeting (if F2F Meeting Format). Prior to the telephone interview, the patient receives a copy of the Patient interview guide. This allows them to know in advance the questions to be asked and, if desired, to pre-complete the guide. Following the interview, the patient/patient representative receives a draft of the minutes of the interview and the finalized version is circulated to the entire EDC so that everyone has the patient feedback. In addition, the minutes of the interview are included in

final EUnetHTA recommendations and (except for approach one), the patient receives a copy of the EUnetHTA Final Recommendations. In all cases, the ED Secretariat conducts a final feedback interview with the patient(s) in order to receive their feedback on the process but also in order to provide them any additional feedback.

Since Q2 2017 122 requests for EDs have been received. Of these 122, 38 have been "EUnetHTA" EDs (PCC or Multi-HTA). The patient involvement process officially began in Q1 2018 and since then 31 of the 38 "EUnetHTA" EDs have had patient participation (i.e. at least one approach used) and in several instances multiple approaches used (up to three patients).

Table 6: Patient Involvement in EUnetHTA EDs

Approach	Number of EDs	Number of patients/ED
Approach 1	7 EDs	7 patients
Approach 2	21 EDs	25 patients
Approach 3	12	13 patients

Results from the post-ED patient feedback questionnaires

The information in this section is based on the feedback questionnaires received from 23/33 patients having participated in a EUnetHTA ED through May 31, 2020. Of the 33 patients, is noted that all German patients (14) were recruited by G-BA whereas the other patients were recruited by the ED Secretariat (16) with assistance in 6 cases from Eurordis and France Assos Santé. NICE also contributed by recruiting 3 patients/patient representatives. In nearly 2/4 the cases (73.91%) the patient was recruited through a patient's association; the remainder were contacted through the G-BA department of Patient Participation.

Although all but 5 participants indicated that they had not received any kind of training in preparation for the ED, patient satisfaction with the process was overwhelmingly positive, notably:

- 19/23 were clear regarding the ED general objectives
- 20/23 had a clear understanding of what was expected from them
- 19/23 felt that their participation made a difference (note: 3 noted they were indifferent and one did not respond to the question).

In terms of the feedback provided on the documents used during the process, all but 3 (20/23) utilisied the interview questionnaire to prepare for the interview, 17/23 indicated they read the entire briefing book, while 2 indicated that they did not because it was too complex. While several of patients suggested it would be helpful to have a summary or bullet points highlighting the main aspects of the study design, they also underscored that a "simplified" version only was not desired. For them, it was important that they have the option of reading the entire document, or not. The interview questionnaire was appreciated for its flexibility in the conversation; but also for providing the participant with an idea of what kinds of questions to expect during their interview with the Scientific Coordinator and Rapporteur.

A significant 22/23 indicated that they felt they had ample opportunity to express their opinion during their participation in the procedure. The remaining participant did not respond to the question.

While it is not always feasible, the overwhelming majority would prefer to participate throughout the procedure and in the F2F meeting with the company. They appreciated the interaction with the HTAb throughout the process and the inclusion of their responses in the annex of the EUnetHTA Final Recommendations. Ideally, a short MOOC (30 min) would be nice to have to provide patients/patient representatives more information concerning EDs, the role of HTA in the development lifecycle.

Additionally, in our qualitative analyses (21 EDs of which 16 had patients), we assessed the main topics where patients/patient representatives contributed to the ED process and the reflection of their input in the EUnetHTA Final Written Recommendations. Their contributions mainly focused on the choice of population to be included (inclusion/ exclusion criteria), comparator, and outcomes (almost in all ED). However, they also provided input on study duration and the intervention itself. While patient input was well integrated in final recommendation, the last item on intervention was often less considered. Feedback from patients on potential difficulties of future treatment usage (frequency of administration, acceptability of injection, convenience of oral treatment, convenience of concomitant exam etc.) were frequently not mentioned in the recommendations. Issues related to current treatment administration (need for hospitalization or specific test or issue of access to treatment) that could become future concomitant treatment were also often not taken into account. The importance of specific symptoms was also often not taken into account or only at country level (individual HTAb recommendations).

As with all ED participants, patient experts must also complete the EUnetHTA DOI and confidentiality forms. In only one instance was a patient refused participation due to a conflict of interest and in that case the person in question had assisted in the product development. It should be noted also that sometimes it was very difficult to identify a patient to participate and other times, although one was identified, they decided not to participate (time constraints, administrative burden, low monetary compensation)

The ED Secretariat, as well as multiple EDWP members contributed to the Paradigm project specifically in contributing resources developed within EUnetHTA JA3 to the Paradigm Patient Engagement Toolbox. This exercise allowed us to have exchanges with HTAb outside of EUnetHTA, to exchange documents and templates, to refine our language, and to confirm and promote our methods.

Recommendations

- Patients or consumers involvement in ED should be systematic
- Consolidate guidance on how to conduct Interviews

The ED Secretariat implemented and tested three different approaches to patient involvement in EDs throughout JA3. The different approaches worked well, however one drawback is that the patient interview aspect works best when done by HTAb who have experience with involving patients. Nevertheless, many of those who did not have this experience in the beginning have gained it through interviewing patients in their role of SC/R.

In addition to guidance about how to conduct the patient interview, we recommend that the interview guide be adapted for each procedure to include problems already identified by the HTAb – particularly in the case of an expert participating in the entire procedure.

- Improve product information

Furthermore, we recommend systematic sharing of the Briefing Book with the concerned ED stakeholders including (particularly for patients) information concerning the sections that are most important for them to read. This will also facilitate the interview.

We encourage as much interaction as possible with the HTAb – in particular by encouraging patient participation in the HTAb List of Issues e-meeting and the pre-F2F meeting if the ED is following the F2F Meeting Format. In the case of a product following the Written-Only Format, encourage their participation in the HTAb meeting on the List of Issues or Draft Recommendations. Patent engagement in HTAb meetings prior to a F2F meeting needs to be tested and the best implementation might vary between the 3 different approaches in practice.

- Transparency: Regardless of the procedure format, we recommend transparency of patient input in the appendix of the Final Recommendations and clearly noted input within the body of the report.
- Further develop guidance on patient engagement in EDs:
- We have begun and recommend further developing guidance around patient involvement in Early Dialogues. This guidance could take different forms (i.e. information sheets, short videos, online presentations) and includes topics such as:
- What are EDs and why take part?
- Revise and customize on an ED basis the interview guide used by SC/R when interviewing patients
- Guidance regarding the recruitment of patients
- Patient guidance for participating in both virtual and F2F meetings
- Revision of patient feedback collection

Given the success we have experienced in recruiting patient participants directly, our recommendation is to continue this approach. This approach, together with the guidance documents described above may be the key to identifying the types of patients we prefer to see participate. Each participant has their role within an ED be it HTA, Regulatory or patient. Participating patients should have expertise on the disease and ideally some knowledge of the clinical development process. The purpose of an ED is to have a focused discussion on clinical development and not burden of the disease. While disease burden certainly influences the discussion, it is not the primary discussion topic nor is the difficult reimbursement situation in different countries. An ED is not a place where patients should advocate to get better treatment or support further reimbursement.

While patient input has impacted recommendations, some of their recommendations has shown to be less taken into account. In the future, patient's input could benefit in being presented following PICO framework so HTAb could better refer to patient's feedback when making recommendation on each item.

- Develop the use of PROs: We recommend PROs to be a systematic topic of discussion during EDs.

3.6 Engagement with Health Care Professionals

The Work Done and Experiences

WP5A aims to engage with HCP. Unfortunately, the only experience had in this area pertains to Medical Devices. The one EDMD that was performed involved a clinical expert throughout the ED procedure and this involvement was considered a success and of added value by all HTAb participants.

While efforts have been made to include HCP in pharmaceutical EDs, this has not been easy nor very successful. The primary issue that most HTAb are already including their own experts, in an informal

manner. It is compounded by the fact that some see the clinical expert input as being directly related to the local standard of care and the national situation. This, it was complicated to involve a common clinical expert. This information was transmitted to HCP stakeholders during stakeholder meetings.

During the prolongation additional effort will be made to include HCPs.

Recommendations
A transparent approach needs to be implemented for HCP experts much as there already is for patients.

3.7 Collaboration with Regulators

The Work Done and Experiences
Collaboration with EMA began in 2016 and resulted in the first milestone: launch of Parallel Consultations in July 2017. Since that time, the EUnetHTA ED Secretariat and EDWP have processed 98 requests for Parallel Consultations, including 2 registry qualification requests, culminating in 32 pharmaceutical Early Dialogues.

To manage the volume of ED requests, transmit important decisions by the EDWP to EMA, schedule meetings (e-meetings and F2F meetings) for accepted EDs a monthly teleconference is held between the EUnetHTA ED Secretariat and the EMA Scientific Advice Secretariat.

Ongoing qualitative analysis on alignment EUnetHTA/EMA (Issues raised and final recommendations. Analyses ongoing)

Recommendations

- Favor PC procedure for pharma, but still keep multi-HTA:

Although the majority of the EUnetHTA EDs carried out in JA3 were done in parallel with EMA, some companies may prefer to request a Multi-HTA ED. We have observed for instance that SMEs often are less familiar with HTA and thus request advice only after having received feedback from the EMA and the FDA.

The sequential timing might be a lost opportunity. In order to offset this and promote PC, multiple steps have been implemented during JA3

1. Increasing communication between EUnetHTA ED Secretariat and EMA.
2. Communication with the companies in order to encourage that the different advices be within a similar timeframe.
3. Over time, the increased communication with EMA allowed also the ED Secretariat to successfully lobby for using PICO as an organizational framework for the List of Issues and thus the F2F meeting (as the List of issues serves as the main list of subjects to address during the meeting)

The above modifications should be continued in the future. The benefits of Parallel Consultations, as identified through the qualitative analysis presented above lead us to recommend that PCs should be prioritized over Multi-HTA. This prioritization would not only encourage further understanding between HTAb and regulators but would be more efficient. That said, there are companies who prefer the Multi-HTA approach therefore it should be maintained as an option for early advice from HTAb.

- Explore collaboration for EDMD with the expert panel.

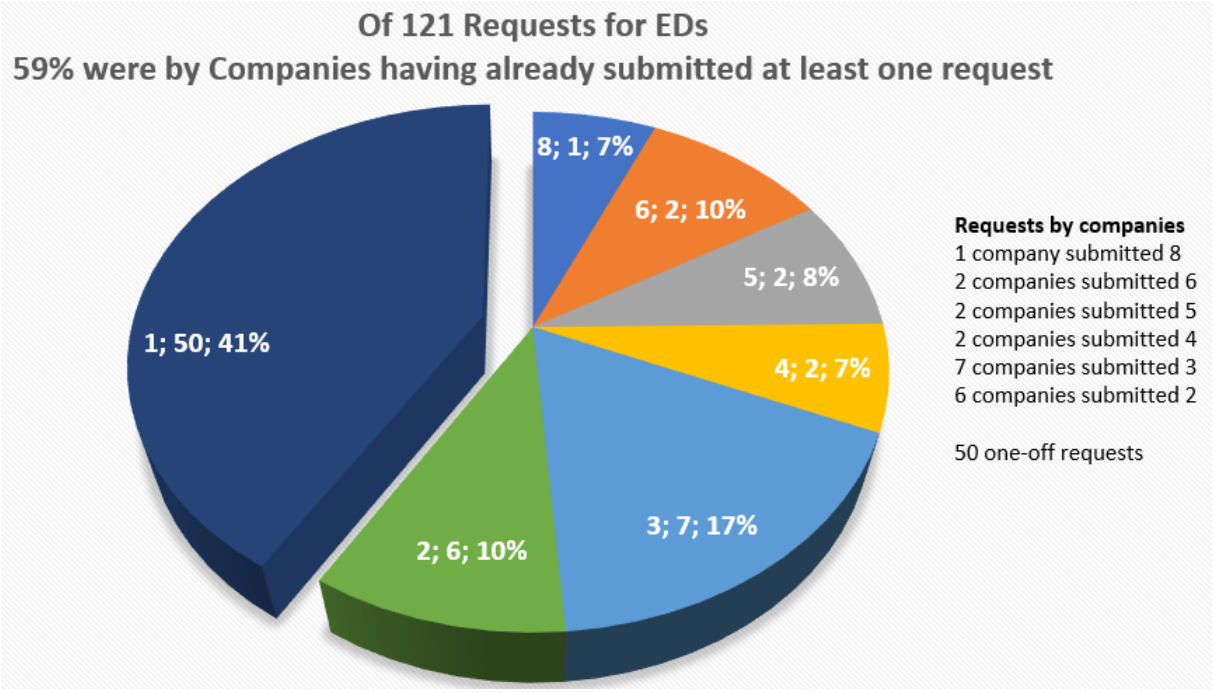
3.8 Involvement with Manufacturers and Industry Associations

The Work Done and Experiences

During JA3 and the prolongation period, 70 different companies, applied for a EUnetHTA ED, for a total of 122 ED requests, with 59% of these companies submitting multiple ED requests during JA3.

One company made 8 (6.61%) requests and an additional 30 (24.79%) requests were made by six companies (2 companies making 6 requests (9.92%), 2 made 5 requests (8.26%), and 2 made 4 requests (6.61%)). The 6 most prolific ED requesters all represent big pharma; only 17/119 (14.29%) requests came from SMEs (resulting in seven PCs). An additional 21 requests (17.36%) represented 3rd requests by 7 companies and 12 companies made 2 requests (9.92%) for ED. The graphic below illustrates this breakdown.

Graph 1: Companies Making Multiple Requests for EDs



The line of communication with the ED Secretariat and manufacturers was always open. Depending on the number of EDs ongoing at any given time, multiple calls and/or emails could be responded to in a day. Although many questions were answered related to ongoing EDs, this does not represent the majority of contact with industry. More often than not they were seeking to determine if a product was suitable (or even eligible) for an ED, sometimes they needed the ED process clarified or had a specific scientific question, and other times they presented their pipeline.

This kind of communication requires that the ED Secretariat take every precaution to ensure that confidentiality is maintained.

The WP5A Lead (HAS) and Co-Lead (G-BA), conducted an analysis of the Briefing Books received for the first 21 completed "EUnetHTA" EDs (3 Multi-HTA, 18 PC) for pharmaceuticals showing:

- ⇨ The PICO criteria and study design were discussed in almost all the EDs, health economics topic was addressed in more than half of the EDs and Post Launch Evidence Generation (PLEG) in one third of the EDs.
- ⇨ A high percentage of alignment between HTAb with more than 80% of full alignment (which

does not prevent supplementary national specification) on all PICO items except for recommendations on PRO where approaches could differ between agencies performing health economics evaluation and those focusing on clinical evaluation.

⇨ A good signal of better evidence for future HTA since modifications were already proposed by the Applicant in 12 out of 21 (57%) EDs after receiving the EUnetHTA List of Issues. This includes major changes like the addition of a study (2/21), changes of comparator (3/21), design adaptation (8/21), primary endpoint choice (5/21) but also population criteria, intervention, and other outcomes. Further clinical development adaptations can be expected after applicant have received the final EUnetHTA recommendations.

During JA3 the ED Secretariat regularly presented the status of EDs during EUnetHTA Stakeholder meetings, at the annual EUnetHTA EFPIA meeting and at international conferences where industry was present. While planning the EDFM, the Secretariat reached out to EFPIA in particular in order to communicate the status of the mechanism and to gauge industry tolerance for fees. Further communication was carried out when launching the Open Call to select the EDs to be carried out during the prolongation period.

Following each ED, the ED Secretariat requested that the applicant complete a short questionnaire about their experience with EUnetHTA EDs. Unfortunately, the rate of return of these questionnaires was low and often those returned were not fully completed. The ED Secretariat was therefore unable to fully properly analyze the input received. The questionnaire will need to be revised in the future to increase likelihood of receiving completed responses. Nevertheless, the feedback in general from industry (at end of meeting, by email, etc.) by the ED Secretariat was very positive and this is demonstrated through the increase in demand for EDs.

Recommendations

- A better overview of available human resources at HTAb: Industry demand for EUnetHTA EDs far exceeds the supply. To this end, we need to better manage industry expectations regarding the number of ED to be carried out. This will require also better insight into the actual capacity of the HTAb and, perhaps, a commitment from their side to carry out the number of EDs agreed upon.
- A fee-for-service system is needed: The implementation of a fee-for-service mechanism would only underline this need.
- Complete ED requests forms. Although it has already been integrated into the revised procedure being implemented during the prolongation, we recommend the inclusion of additional details in the ED Request Form in particular PRO (validity of the tool included in proposed development with MCID), on PLEG (anticipated gap at launch, remaining research questions, additional core data set to be collected)…and maintaining the possibility to request additional information up until the F2F meeting in order to provide the best recommendations.

As noted particularly in the above section on Patient involvement, we recommend the systematic from industry to share their Briefing Book with ALL external experts involved in a procedure provided each has an approved EUnetHTA DoI and CU.

- Share ED final recommendations with the JA team: EDs should be part of the JA submission dossier. As with a Joint Assessment, a EUnetHTA ED is centered around the PICO. We would recommend that a legally acceptable solution (respecting confidentiality and conflict of interest rules) be identified to share EUnetHTA ED Final Recommendations with the JA team, following the model used by EMA, for products that are jointly assessed in the future. The purpose of this is not to render the recommendations binding, but to provide the JA team with

a PICO that has already been agreed upon by multiple HTAb as basis for discussion as recommendations may evolve over the time.

3.9 Procedures and Guidance

The Work Done and Experiences

Pharmaceutical Products

Two primary types of ED are available for pharmaceutical products: Parallel Consultations (tripartite with EMA, EUnetHTA HTAb, and the company) and Multi-HTA EDs (bilateral between EUnetHTA HTAb and the company). The option of which type of ED to pursue is up to the company, however regardless of the type of request, the company submits their request to the ED secretariat by the published deadline. Once all submissions have been received for the deadline, the ED Secretariat compiles the requests, the Scientific Project Manager drafts an overview of the requests and all the information is transmitted to the EDWP for decision via the EDWP are in Sharepoint. The EDWP has 5 working days to evaluate all the requests against the EDWP Selection Criteria and each EDWP member organization completes an evaluation form for each request that includes their decision as to whether or not it should be accepted and their reasoning for that decision. The ED Secretariat compiles the decisions and informs the EDWP, the company(ies), and (for Parallel Consultation) EMA of the outcome. In the case of a negative response, the applicant is informed of the reasoning behind the EDWP decision. The reasons for refusal can be multiple including pivotal trial ongoing, not a novel mode of action, outside remit of certain agencies, etc. Once a product is accepted, all communication between the EDWP and the company and/or with EMA is done through the ED Secretariat.

EUnetHTA EDs were launched once a procedure had been defined and written. The ED procedure was based on experiences from JA2 and the SEED Consortium. The ED was based on all participants writing concurrently and the SC/R were then charged with consolidating the responses.

This approach proved very time consuming and it soon became evident that this procedure needed to evolve to something more centralized, it was a necessary step as it allowed the HTAb to build a rapport and better understand each other's positions on different subjects. Toward the end of Y4 the new, centralized procedure was ready to be tested. The revisions made resulted in a workflow not so different from that of a Joint Assessment with the Scientific Coordinator and Rapporteur acting in a similar fashion as an author/co-author and the rest of the EDC acting as reviewers. It was however very important to maintain the possibility for each HTAb to add their own nuances to the final report based on national specificities that are not covered by the consolidated recommendation. The revisions also permitted us to request additional information from industry regarding PROs, PLEG and to organize the related templates according to PICO. The Written-Only Format of the ED procedure was also added

For the prolongation, only Parallel Consultations and Multi-HTA EDs are available with both culminating in a the consolidated EUnetHTA Final Recommendations. The primary differences in the prolongation period are:

- Instead of reviewing monthly submissions from industry, an open call for submissions was held over the summer and the EDWP selected products (based on the EUnetHTA Selection Criteria) in September;
- On the basis of the draft briefing book, the EDWP then decides whether the request requires a F2F meeting with the company (highly complicated dossier, major issues identified by HTAb) or if the product can follow the Written-Only format which indicates that there are no major issues with the company's proposed development plan.

As a result, the length of an ED is effectively reduced from a systematic 4,5 months in duration to 2,5 for a Written-Only Format and 3,5 for a F2F Meeting Format.

Medical Devices

The workflow for a Medical Device Early Dialogue (EDMD) is very similar to that of a pharmaceutical ED with one significant difference. Instead of submitting a Letter of Intent or an ED Request Form (for an Open Call) the company submits a draft briefing book. This document is reviewed by the MD team at HAS and they provide initial feedback as to the acceptability of the request. If the request is deemed acceptable, it is then circulated to the entire EDMD Working Party for their feedback. If at least three HTAb are willing to actively participate in the ED, the participating HTAb will provide consolidated feedback on the dossier to the company. The modifications requested in this feedback must be included in the Final Briefing Book. Following submission of the Final Briefing Book, the procedure is the same as that for pharmaceutical products.

Table 7: Overview of EUnetHTA EDs in JA3

ED#	EDWP Decision	Pharma or OT	Participating HTABs	Scientific Coordinator	Rapporteur[5]	Start[6]	End[7]
ED01	Multi-HTA	Pharma	AETSA, G-BA, HAS, INFARMED, NICE, NIPN, RER, ZIN, TLV (ZIN Secretariat, EMA as observers)	HAS	G-BA	2017-04	2017-09
ED02	Multi-HTA	Pharma	AEMPS, G-BA, HAS, NIPN, NOMA, RER, RIZIV-INAMI (ZIN Secretariat and EMA as observers)	HAS	G-BA	2017-07	2017-12
ED10	PCC	Pharma	G-BA, HAS, NICE, NIPN, NOMA, ZIN	HAS	G-BA	2017-09	2017-12
ED11	PCC	Pharma	AETS-ISCIII, AIFA, G-BA, HVB, HAS, NICE, NIPN, NOMA, RIZIV-INAMI	HAS	G-BA	2017-09	2017-12
ED14	PCC	Pharma	AEMPS, AIFA, AQuAS, G-BA, HAS, NICE, NIPN, NOMA, RIZIV-INAMI, (JAZMP (SI) as observer)	HAS	G-BA	2017-11	2018-03
ED15	PCC	Pharma	AEMPS, AETSA, G-BA, HAS, NICE, NIPN, RER, RIZIV-INAMI, TLV (NCPHA observer)	G-BA	HAS	2017-12	2018-05
ED16	PCC	Pharma	AEMPS/AQUAS, AIFA, G-BA, HAS, NICE, NIPN, NOMA, RIZIV-INAMI	G-BA	HAS	2017-12	2018-05
ED17	PCC	Pharma	AEMPS-AETSA, G-BA, HAS, NICE, NIPN, RER, RIZIV-INAMI, TLV	G-BA	HAS	2018-01	2018-06
ED19	Multi-HTA	Pharma	G-BA, HAS, NIPN, NOMA, RER, RIZIV-INAMI	G-BA	HAS	2018-01	2018-06

[5] If multi-HTA or PCC

[6] Start refers to the following: Date of reception of Letter of Intent for PCC/Multi-HTA EDs pre-August 2020, Date of reception of Draft Briefing Book for PC/Multi-HTA post-August 2020, Date of reception of Final Briefing Book for EDMD

[7] Sending of final recommendations

ED20	PCC	Pharma	AEMPS, AIFA, AQuAS, G-BA, HAS, NIPN, TLV	G-BA	HAS	2018-01	2018-06
ED22	PCC	Pharma	AEMPS/AQUAS/AETSA, AIFA, G-BA, HAS, NICE, NIPN, TLV	G-BA	NICE	2018/02	2018-07
ED27	PCC	Pharma	AEMPS, AIFA, AETSA, G-BA, HAS, NICE, NIPN, NoMA	G-BA	NICE	2018-03	2018-08
ED32	PCC	Pharma	AIFA, G-BA, HAS, NICE, NIPN, TLV	NICE	HAS	2018-04	2018-09
ED35	PCC	Pharma	G-BA, HAS, NICE, NIPN, NoMA	NICE	G-BA	2018-05	2018-10
ED42	PCC	Pharma	AEMPS/AETSA, HAS, G-BA, NIPN, NoMA, RER	AEMPS	HAS	2018-10	2019-03
ED43	PCC	Pharma	AEMPS, AIFA, HAS, NICE, NIPN, NOMA, RIZIV-INAMI	NOMA	NICE	2018-10	2019-03
ED45	PCC	Pharma	AETSA, AIFA, AQUAS, G-BA, HAS, NICE, NIPN, NOMA, RIZIV-INAMI	NOMA	NICE	07/12/2018	29/04/2019
EDMD 201801	EDMD	OT	AQUAS, AVALIA-T, HAS, NICE, RER, SNHTA, TLV (G-BA as observer)	HAS	-	2018-07	2018-12
ED46	PCC	Pharma	AEMPS, G-BA, HAS, NICE, NIPN, NOMA	G-BA	NICE	18/01/2019	03/06/2019
ED47	PCC	Pharma	AEMPS, HAS, NICE, NIPN, NOMA	NOMA	NICE	18/01/2019	03/06/2019
ED48	PCC	Pharma	AEMPS, AIFA, G-BA, HAS, NIPN, TLV	HAS	AIFA	18/01/2019	08/07/2019
ED50	PCC	Pharma	AEMPS, G-BA, NICE, NIPN, RER	RER	G-BA	15/02/2019	17/07/2019
ED51	PCC	Pharma	AEMPS, AIFA, G-BA, HAS, JAZMP, NICE, NIPN, RIZIV-INAMI	G-BA	NIPN	15/03/2019	06/08/2019
ED55	PCC	Pharma	AEMPS, AIFA, G-BA, HAS, NICE, NIPN, NOMA, TLV	G-BA	NOMA	17/04/2019	20/09/2019
ED58	PCC	Pharma	AEMPS, AETSA, AIFA, G-BA, HAS, NICE, JAZMP	G-BA	(NICE)	17/05/2019	18/10/2019
ED64	PCC	Pharma	AEMPS, AIFA, G-BA, HAS, NICE, NIPN	G-BA	(NICE)	17/05/2019	18/10/2019
ED66	PCC	Pharma	AEMPS, AQUAS, HVB, NICE, NIPN, NOMA, RER	RER	NOMA	14/06/2019	18/11/2019
ED76	PCC	Pharma	HAS, NICE, NIPN, NOMA	NOMA	HAS	09/08/2019	13/12/2019
ED77	PCC	Pharma	G-BA, HAS, NICE, TLV	G-BA	HAS	09/08/2019	13/12/2019
ED80	PCC	Pharma	AEMPS, AIFA, HAS, INFARMED, NICE, NIPN, NOMA	NOMA	(NICE)	06/09/2019	31/01/2020
ED81	PCC	Pharma	AIFA, G-BA, HAS, NICE, NIPN, TLV	HAS	TLV	06/09/2019	31/01/2020
ED82	Multi-HTA	Pharma	G-BA, HAS, NICE, NIPN, TLV	G-BA	(NICE)	04/10/2019	06/03/2020
ED91	Multi-HTA	Pharma	AEMPS, AIFA, AQUAS, G-BA, HAS, NICE, NIPN, NOMA	G-BA	HAS	14/01/2020	2020-05

ED92	PCC	Pharma	AEMPS/AQUAS, HAS, G-BA, NIPN, NOMA, RER	NOMA	NIPN	14/02/2020	2020/06
The four products below were accepted through the open call held July 3 - Aug 15. As of 19/10/2020 they are considered ongoing as of the reception of their draft briefing book and column "H" represents the date it will be submitted. To note, there is now no longer a letter of intent submitted to EUnetHTA, but an ED request letter and it is submitted during the open call.							
ED104	PC	Pharma	AEMPS, AQuAS, G-BA, HAS, NIPN, NOMA, RER	G-BA	AEMPS	04/09/2020	25/11/2020 (Written-Only Format)
ED105	PC	Pharma	AEMPS, AIFA, AQuAS, G-BA, HAS, NIPN, NOMA	NOMA	AIFA	07/12/2020	26/03/2021 (F2F Meeting Format)
ED112	Multi-HTA	Pharma	AEMPS, G-BA, HAS, NIPN, NOMA	NICE	G-BA	08/03/2021	25/06/2021 (F2F Meeting Format)
ED117	PC	Pharma	AEMPS, G-BA, HAS, NIPN, NOMA	HAS	G-BA	11/01/2021	23/04/2021 (F2F Meeting Format)

Guidance documents

Multiple guidance documents have now been produced for Early Dialogues including guidance for:

- Parallel consultations
- Multi-HTA EDs (pharma)
- EDs for Medical Devices
- Roles of the Scientific Coordinator and Rapporteur in a pharmaceutical ED

These documents provide detailed information about the roles of each actor and the steps of the ED process.

Further documents should be produced as mentioned earlier in this document, including but not limited to guidance for patients/patient representatives participating in an ED and guidance for HTAb newcomers to the ED process.

Much like the templates, guidance documents must be reviewed and updated on a regular basis in order to reflect any modifications in the procedure or makeup of participating HTAb.

Sustainability

One of the largest hurdles during JA3 has been the establishment of a sustainable mechanism for Early Dialogues. The selected approach is described in detail in D5.4. One of the key questions at the outset of the joint action was whether a fee-for-service model would be acceptable to industry. Through our exchanges with industry, the interest in such a model had been confirmed. A Framework Agreement commented and agreed by the EDWP, legal experts (Eubelius) and business consultant (KPMG), was delivered in June 2020 and could in theory serve as the basis for a contractual agreement to set up an EDFM. While the framework (including fees) for the EDFM has been developed, it could not be piloted during JA3 due to the lack of an agency to function in the role of the EDFM Secretariat, the “banker” for the framework. Due to the complexity of setting up the EDFM, unless there is a regulation implemented by the European Commission going forward, it might be difficult to find a new organization to act in this role. Additionally, and in order to ensure a transparent system with clearly

defined roles, WP5A recommends that the organization acting as the EDFM Secretariat ('bank') be an independent institution – not an HTAb that is also interested in participating in the scientific part of the activity. Another key lesson learned from the development and attempted implementation of this deliverable is that without a legal framework (i.e. a joint action, or a contract such as was used to create SEED or a Regulation), a sustainable model may not be possible. In the absence of JA3 or an EU Regulation, a legal framework is a necessity.

Recommendations

Pharmaceutical EDs

In general, the current pharmaceutical ED structure, with nearly 40 EDs completed, works well and is aligned with EMA. Therefore, we do not recommend any major modifications. Any change recommendations would be more internally (do we centralize the procedure, do we do written-only EDs going forward). These are questions that are currently being examined in the prolongation and the procedure will be updated according to what is most efficient for all participants. As an example, we need to see if the centralized procedure should be retained following its implementation. Two EDs have already been conducted using it and following the prolongation, there will have been a total of seven. Feedback needs to be collected from the EDWP ad Analysis will be needed to understand if the centralized procedure functions as planned, saves time, and makes the task less complicated and time consuming, in particular for the SC/R.

After the prolongation period, an evaluation should be done comparing the batch system for EDs that was in place the first 3 years and the open call system that was implemented for the prolongation. Should the results of that evaluation be positive, we recommend formalizing in writing the call procedure and the eventual pro-active recruitment of EDs if interesting subjects are able to be identified in advance (for instance through discussions with companies where pipeline is discussed).

EDFM

The financial sustainability of EDs should be achieved. For the EDFM framework to work, an organism to function as the "banker" must be identified; otherwise a new approach must be developed. The draft EDFM framework has been developed by WP5A Lead and Co-Lead together with experts on European law (Eubelius) and the business case consultant KPMG (both renowned partners). The framework is in theory ready and available as soon as a "banker" could be identified. Based on the experience from attempting to implement the EDFM, we recommend that the "banker" role not be undertaken by an HTA organism. Industry is ready to pay, in particular if this will increase ED capacity. Notably, the fee amount evaluated by the EDFM was considered "acceptable" by industry.

On the other hand, if implemented, the EDFM will add to the workload of the ED Secretariat particularly in terms of coordination and compiling the information necessary for the banker, but also and most importantly for ensuring the quality and the implication of each participating HTAb.

We highlight that even if it were decided today to implement the EDFM, it will take up to 6 months to have it up and running due to the need to identify an organism for the bank, revision of procedures to integrate that organization, not to mention the required signatures from all participants. Significantly, if a new mechanism must to be developed, we are looking at a much longer period, likely 6 months minimum that would be needed. The operation time period of a mechanism would likely need to be at least 2 years in duration in order to justify the work to establish it.

Finally, and most importantly, a sustainable mechanism will not be possible in the future without a legal framework.

EDMD
There is much less demand currently for EDMD than for pharmaceutical MD.

- a communication campaign is likely necessary, if we wish to increase the numbers.
- Further explore synergies with the MDR expert panel.

3.10 Templates

The Work Done and Experiences

As a starting point, many templates were adapted from JA2/SEED and EMA, in particular the Letter of Intent and Briefing Book templates. Rapidly it became necessary to create additional templates for nearly every step of the process in order to organize the EDs and guarantee their continuity and quality.

As a result, the following templates were created by the ED Secretariat and/or by the EDWP members themselves.

- Letter of Intent (two versions, one each for Parallel Consultation and Multi-HTA)
- Template for requesting Clarifications on the Draft Briefing Book (for all pharmaceutical EDs)
- Briefing Book Template (two versions, one each for Parallel Consultation and Multi-HTA)
- Template for the List of Issues to be sent to the company (three versions, one each for Parallel Consultation and Multi-HTA and one for EDMD)
- Draft Positions and Issues Template (for all pharmaceutical EDs) for the e-meeting to discuss the List of Issues (if F2F Format) or the Draft Positions (if Written-only)
- Templates for the EDC an Applicants for step-by-step timelines for each kind of ED (PC, Multi-HTA, EDMD) and for the two formats (Written-Only and F2F Meeting) for pharma EDs.
- Standardized template for the SC/R to use in preparing the pre-F2F HTAb meeting
- Patient interview guide based on the HTAi questionnaire (note: beginning with the prolongation this document is customized for each ED by the ED Secretariat scientific Project Manager)

The templates are available for all to download in the EUnetHTA Early Dialogues Document Library located in the Early Dialogues are of Sharepoint. Anyone with access to the ED page has access to this library.

In order to continually improve the ED process and the patient involvement process, the ED Secretariat developed feedback questionnaires for patients and industry. These questionnaires have guided modifications to the relevant procedures.

Recommendations

- Regular review of documents. The templates and guidance documents used in the framework of EUnetHTA EDs must be reviewed and revised at least once annually, if not every six months. While modifying documents linked to Multi-HTA EDs (both pharma and medical devices) is rather straight-forward, the modification of anything linked to Parallel Consultations for pharma is more complex as it involves not only EUnetHTA but EMA. During the prolongation, the use of the ED Request Form during the open call allowed us to make certain modifications, for example requesting more detailed information at the start in order for the EDWP to have a better informed basis on which to make their decision on acceptance of a product. Going forward, we recommend reviewing the current Briefing Book Template as the information requested is sometimes repetitive. These changes can be done quickly for Multi-HTA but will

require discussion and negotiation with EMA in order to modify the parallel consultation version.

- The modifications regarding HTA only in the PC procedure should be done in an easier manner.

3.11 IT tool

The Work Done and Experiences

AT the outset of JA3, the development of an IT Tool was planned. Several options were discussed internally between Lead and Co-Lead partners ranging from creating a Microsoft Project file to adapting a system used internally at HAS. The problem was that those options would require either time or money (or both) that was not available. The ED Secretariat's experience in using Sharepoint led to the decision to build the "tool" in Sharepoint. The tool will allow the ED Secretariat to better manage EDs all along the process, using functions that are rather frequent within Sharepoint. The Quality assurance mechanism (via metadata or a workflow, for example), reminders for partners for each ED, a facility to securely exchange files and information with external experts, archiving of completed dossiers – this is all possible with the tool we already have available within EUnetHTA.

Although the modifications needed have been discussed several times, implementation has yet to be carried out.

Recommendations

It is absolutely necessary to have a robust management tool and database for EDs. Going forward, the ED Secretariat would benefit greatly from an improved utilization of Sharepoint and perhaps even the integration of Teams in order to share information with different stakeholders. This is particularly important given first, the lack of a functioning extranet and second, the latest change in functioning at EMA. Until November 2020, Eudralink (an EMA resource for secure email) was used for exchanging all information between EUnetHTA and EMA and EUnetHTA and companies for parallel consultations. This system will no longer be used in Parallel Consultations and thus a EUnetHTA solution via Sharepoint and/or Teams is necessary. A workflow solution should also be envisaged in order to better monitor each step of the process and ensure quality.

3.12 Method adaptation

The Work Done and Experiences

As mentioned earlier a comprehensive qualitative analysis was undertaken examining the first 21 EDs performed which aims to identify topics covered by ED and some methodological issues HTAb could have faced which may have impacted the quality of final recommendations.

<u>a. Topics Covered</u>

An evaluation was performed to determine if all important domains of a development plan were addressed during the procedure. The intent was to explore if the Applicant-addressed relevant issues in the raised questions were taken up by EUnetHTA during the process. To do so, recurrent topics addressed in the questions from the Applicant and in the EUnetHTA List of Issues from HTAb were explored according to domains and subdomains.

All EDs addressed the domains population and outcomes, and almost all EDs addressed the sections comparator and study design. While the Applicant often did not ask specific question related to intervention (only for half of the EDs), HTA often raised issues on this topic, most of the time in relation

with concomitant/add-on therapy or targeted labeling. The topic PLEG was in the majority of the EDs not addressed by the Applicant. HTA added it twice to their List of Issue while the Applicant did not evoke the topic. HTAb also added the topic of global strategy of clinical development plan (questions on this topic raised by Applicant half of the time while HTAs wanted to discuss it in more than 75% of the cases). Health Economic questions were asked in half of the Briefing Books by the Applicants, HTAb invited the Applicants to discuss the topic more frequently.

Table 8: Topics addressed in EUnetHTA EDs

	Question Applicant	EUnetHTA List of Issues
Population	21/100%	21/100%
Intervention	12/57%	19/90%
Comparator	19/90%	19/90%
Outcomes	21/100%	21/100%
Study Design	20/95%	20/95%
PLEG	6/29%	8/38%
Health Economics	12/57%	14/66%
Clinical Development Plan/other	12/57%	16/76%

Population

A systematic discussion on inclusion and exclusion criteria was initiated by the questions from the Applicants. However, discussions around subgroups (or stratification/ biomarkers) and also regarding generalizability of the results were raised by HTAb while these topics were not addressed in the Applicant's questions.

Outcomes

On outcomes usually generic questions from the Applicant covered all outcomes subdomains and were thus addressed by both Applicant and HTAb with almost the same high frequency. In some cases, there were more detailed questions raised by the HTAb regarding the relevance of PRO/QoL chosen for the certain indication without any illustration by the Applicant on the rational for choosing a specific scale vs. other existing scales available. Adverse Events were usually not addressed by the Applicant (5/21) but were raised as a specific issue twice more often by HTAb (10/21), even more frequently than by EMA (7/21).

Study design

Main discussion on study design were about study duration/long-term data collection (13/21 LoI HTAb) and issues related to the statistical analyses plan (20/21 LoI HTAb). Both items were usually also addressed initially by the Applicant. Time point and frequency of data collection was a topic more frequently brought up by HTAb (8/21 vs Applicant 4/24 and 2/21 for EMA).

In comparison to the questions in the Final Briefing Book submitted by the Applicant, HTAb more frequently raised issues on intervention (most of the time in relation with concomitant/add-on therapy or targeted labeling), PLEG, overall clinical development plan and health economics.

The differences between issues raised by HTAb and questions asked by applicants show that HTAb expect a more global discussion on the impact of the new treatment and associated development needed instead of focusing on specific items of the proposed protocol. This is also reflected in the volume of questions from the company that is sometimes be very high (EX:50+) in some dossiers, focusing on minute details while the HTAbs expect to discuss a maximum of 10-12 major issues.

Issues raised by HTAb on interventions are related to the need for a complete overview of place of the new product in current treatment algorithm which is often not clearly stated in the dossier submitted by the company. Similarly, when HTAb raise questions on PLEG and health economics, it is connected to HTAb's need for anticipation of the short-term and long-term clinical and economic impact. PLEG proposals by industry, when shared, often do not provide a sufficient level of detail. As a prerequisite of for PLEG discussion the ED submission must include the following elements: rationale for gap, research question (that needs to be answered), detailed plan of evidence generation including the design of the post-launch study, minimum core set of data and sources industry plans to provide.

b. Alignment between HTAb

To evaluate how clear the Final Written Recommendations were delivered and how they reflected the needs of Applicants, the level of commonality among HTAbs in their recommendations was analyzed.

Overall, there was a high rate of alignment between HTAb with more than 80% alignment: Full or Full* on all items with the exception of outcomes where recommendations on PRO in particular showed partial alignment in 90% of cases. The Full* category with national specificities accounted in majority for recommendations on population, comparator, primary and secondary outcomes and statistics. The majority of Full alignment without any specificities were detected for the topics: global clinical development plan, PLEG, intervention and study duration.

However, especially for the subdomain on PRO/QoL, most of the time only partial alignment was stated in the common recommendations. This could be partially explained by an insufficient level of detail (relevance, validation, minimum important difference (MID)) in the briefing book that results in different views amongst HTAb. However, it is certainly also due to different approaches in terms of QoL assessment that became visible between those HTAb that are doing economic assessment and partners that do not include economic aspects in their assessments. For example, in this context, the G-BA requests the SF-36 as a general quality of life questionnaire while other HTAb prefer ED-5D. This is a divergent approach to the assessment but does not manifest major differences between HTAb in terms of the relevance allocated to quality of life data. All partners emphasize that quality of life is a major topic for HTA and that Applicants need to provide relevant data for this item. PROs in general are not addressed by all HTAb in detail. This is also a difference in the advice procedure of the partners as some (e.g. G-BA) provide feedback on all the suggested PRO by the company while others provide more general feedback.

MID discussion can also be difficult on specific scales and thresholds, necessitating very intensive research which cannot be done by all HTAb.

Differences in approach to populations targeted in the assessment by HTAb later on were not so obvious due to high level discussions on relevant population and relevant comparators where relevant subgroups are identified and the respective Standard of Care (SoC).

The level of detail for feedback on statistics also differs between partners which could be due to a lack of expertise in this area for some partners involved or the limitation to involve only a certain department in the production of an ED without close contact to other departments that might be more experience in statistical methodologies. A detailed and predefined statistical analysis plan (SAP) was stated of importance by most HTAb: specific cut-offs, robust method, hierarchical analysis etc. should be laid out in detail by the Applicant to enable a detailed judgement – communicate clearly to industry what is needed

Significance of results was most important, especially on hard outcomes like overall survival (OS) = gold standard

Areas with commonalities or divergent approaches for HTAb will be addressed in detail in the following section.

c. Commonalities and topics with divergent approaches for HTAb

Systematic recommendations by HTAb - commonalities

POPULATION
1) Biomarkers
Systematic recommendation by HTAb to collect data on
- predictive value and clinical usefulness of biomarkers to support threshold choice - usage in practice to inform on generalizability of the targeted population
2) Choice of exclusion and inclusion criteria
Systematic recommendation by HTAb in oncology:
- Recommendation to enlarge ECOG criteria - Suggestion of pre-definition or stratification for subgroups related to histology grade, previous treatment including surgery/radiotherapy, biomarkers
INTERVENTION
- Systematic recommendation by HTAb to collect data on treatment maintenance and rational for treatment duration in particular for oncology drugs
COMPARATOR
OUTCOMES
Systematic recommendation by HTAb on
1) General comments:
- Necessity to consider separate endpoints in case of composite endpoint - Hierarchical testing advised by some agencies (HAS, Spain, NIPN)
2) PRO/QoL
- SF-36 systematically recommended by G-BA - EQ-5D-5L systematically recommended by HTA doing economic assessment - Alert regarding issue of missing data for PRO and difficulty of interpretation especially in case of open design trial
3) Outcomes in oncology
- OS as primary outcomes commonly recommended
- Recommendation to capture detrimental QoL due to AE
- EORTC is well accepted with loss of function/pain/fatigue identified as important symptoms to monitor
STUDY DESIGN/CLINICAL DEVELOPMENT PLAN
- Single arm study not accepted in oncology - Intra-individual comparison accepted exceptionally for ATMP - For oncology development: risk of drop out/ cross over and impact of subsequent therapy - In case of conditional market approval, challenge for recruitment in ongoing phase III

Topics with divergent approaches for HTAb

POPULATION
1) Biomarkers
- Some HTAb do assess while others don't - Some will assess the performance; others will only focus on the cost associated for economic evaluation of the product - A priori all HTAb are interested in prognostic value and impact on eligible population in real practice
2) Subgroups
- Stratification or pre-definition of subgroups always only mentioned of some potential subgroup of interest and need for inclusion of them in RCT
INTERVENTION
- Need for monotherapy data only combination not enough
OUTCOME
PRO
o Only high-level feedback without a specific position on each proposed PRO - partially explained by lack of detailed info of PRO/scales proposed (rational for choice and validity/MCID)
STUDY DESIGN
Statistical recommendation
o Not all HTAb give recommendations on statistics o The importance of pre-defined statistical analysis not consensual
PLEG
- Some HTAb will ask for PLEG, others not thus the topic is not always considered - PLEG could be requested for second round of clinical assessment or for confirmation of cost-effectiveness results - Need for comparative data not always agreed - Lack of detailed enough information to exchange between HTAb

d. Applicant changes

In 12 out of 21 (57%) EDs analyzed, changes were proposed by the Applicant during the procedure after receiving the EUnetHTA List of Issues. This includes major changes like the addition of a study (2/21), changes of comparator (3/21), design adaptation (8/21), primary endpoint choice (5/21) but also population criteria, intervention and other outcomes.

Recommendations

A formal quality assurance system to evaluate the quality of the final deliverable needs to be established and parameters of how to measure this need to be defined including a mitigation procedure in case the ED fails the QA.

- Room for improving the process; Based on the findings above, overall room for improvement and simplification of the ED process should be explored to propose a concept for further modification of the advice procedure. Recommendations for this include:
    - Some adaptation of the briefing book to ensure sufficient information on PLEG and PRO/HQol is provided by the company
    - While different approaches were observed to make recommendations on PRO/HQoL, subgroup, and statistical analyses, further exchanges are needed between EDWP

members to discuss the rationale for the differences. This discussion could help to achieve further consensus.
    - Statistical support by dedicated expert group (WP4 expert group for example) and maybe also closer exchange with EMA on stats could also improve alignment.
    - Systematic recommendations should be further communicated

- Monitor the ED impact. The impact of the ED process is observed but we should consider further monitoring it. Unfortunately, industry feedback questionnaire is often missing due to many companies never returning the completed document. Time is needed in order to see the effect of an ED on development. Perhaps this should be further discussed with industry.

4. Communication

The Work Done and Experiences

Throughout JA3, the ED Secretariat communicated extensively on Early Dialogues, patient involvement in EDs, and our quantitative and qualitative analysis of the work carried out. The table below provides an overview of that effort.

Table 9: Communication on EUnetHTA EDs

Conference/Meeting	Date	Location	Subject
EMSP workshop	18/05/2017	Athens	Patient-based evidence and its growing importance for HTA Agencies
EMA/EUnetHTA bilateral	08/06/2017	Diemen	Evidence Generation Interaction-new launch EMA and EUnetHTA process
EFPIA technical meeting	05/12/2017	HAS	WP5 – Evidence Generation
LEEM	27/06/2018	Paris	La coopération européenne pour l'évaluation des technologies de santé (HTA) Aujourd'hui et demain?
EUnetHTA-EMA bilateral	05/07/2018	London	
EUPATI Expert Patient Training	17-20 /09/2018	Madrid	Formation pour patients EU, participation à une session dédiée à l'implication patient dans l'EUnetHTA
CIRS	26-27 /09/2018	London	Experience of early advice models/pathways – How do these work in Practice - Agency Perspectives / Early Dialogues in the EU with HTA Agencies
PARADIGM ED meeting	19/10/2018	London	Feedback from HTA agencies on the involvement of patients and/or advocates in ED between agencies and the industry
ISPOR	10/11/2018	Barcelona	Panel: Can Patient Involvement in Early Dialogues (Early Scientific

			Advice) Increase the Value of the Advice Given?
ISPOR	10/11/2018	Barcelona	Poster: Experience with Early Dialogues in EUnetHTA JA3
EBE Annual regulatory conference on Advanced Therapies	04/12/2018	Canary Wharf, London	Session 1: Efficient approaches to evidence generation for regulatory approval and health technology assessment of ATMPs
EUnetHTA Assembly & forum	24-25/05/2018	Cologne	
EUnetHTA EMA Bilateral	07/12/2018	London	Real World Data and decision-making procedures
EFPIA technical meeting	01/12/2018	HAS	Evidence Generation (WP5)
DG SANTE Stakeholder Workshop	16/01/2019	Brussels	EUnetHTA Update on current and future stakeholder involvement
Eurordis Meeting - Multi-Stakeholder on improving Patients 'access to rare disease therapies	13/02/2019	Brussels	Improving Multi-Stakeholder Early Dialogues to Optimize Determination of Value / 1st day
HTA network Stakeholder Pool - Health providers meeting	21/03/2019	Brussels	EUNETHTA JOINT ACTION INVOLVEMENT OF HEALTH PROVIDERS – EXPERT LEVEL INVOLVEMENT EUnetHTA Secretariat /Methods of involvement in early dialogues
ISPOR Warsaw	27-28/03/2019	Warsaw	Panel: Presentation of EUnetHTA Early Dialogues
Assembly & Forum	10 - 11/04/2019	Amsterdam	
EUnetHTA Workshop on HTA Medical Devices	28/05/2019	Vienna	Scientific advice/post launch evidence generation
HTAi	17-19/06/2019	Cologne	Two Poster Sessions
Joint "INNO" Meeting of SAWP, EU-IN, CTFG and EUnetHTA	17-19/07/2019	Helsinki	Different perspectives on methodologies and alternative evidence generation plan: Real World Evidence /The use of RWD/RWE for HTA purposes
TOPRA	1-2/10/2019	Dublin	Experience of EUnetHTA with Early Dialogues for pharmaceutical products
EMA/EUnetHTA meeting	21/11/2019	Amsterdam	

EFPIA technical meeting	02/12/2019	HAS	Evidence Generation (WP5)
TOPRA (Scotland)	28/01/2020	online	Presentation of EDs
Assembly & Forum	01/04/2020	online	
Joint "INNO" Meeting of SAWP, EU-IN, CTFG and EUnetHTA	01-02/10/2020	online	Different perspectives on methodologies and alternative evidence generation plan: Real World Evidence /The use of RWD/RWE for HTA purposes
Assembly & Forum	2021	online	

In addition to the presentations made above at Conferences and different national and international meetings, an article was published jointly with EMA about PLEG early dialogues. Finally, we plan to submit additional articles about the EUnetHTA ED experience and qualitative analysis.

Recommendations

Together with the recommendations made above, particularly some of those for communicating with patients, we would recommend the creation of a MOOC on the ED process.

Hand in hand with managing the expectations of industry is how we communicate them. It may be necessary to review how this is done and develop more efficient means of communication, such as an email newsletter to which interested companies subscribe.