EUnetHTA Joint Action 3 - WP1: A Future Model Of HTA Cooperation

Final White Paper

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ABBREVIATIONS

AEG	Additional Evidence Generation
AI	Artificial Intelligence
ATMP	Advanced Therapeutic Medicinal Product
CA	Collaborative Assessment
CHMP	Committee for Human Medicinal Products
COI	Conflict of interest
DOI	Declaration of interest
EC	European Commission
ED	Early Dialogues
EDWP	Early Dialogues Working Party
EPAR	European Public Assessment Report
EU	European Union
EUnetHTA	European Network for Health Technology Assessment
EVIDENT	Evidence database on new technologies
GDPR	General Data Protection Regulation
HRQoL	Health Related Quality of Life
HTA	Health Technology Assessment
HTAi	Health Technology Assessment International
IHSI	International Horizon Scanning Initiative
INAHTA	International Network of Agencies for Health Technology Assessment
ISPOR	International Society of Pharmacoeconomics and Outcomes Research
IT	Information Technology
JA3	Joint Action 3
JA	Joint Assessment
JA/CA	Joint and/or Collaborative Assessments
MAH	Marketing Authorisation Holder
MD	Medical Device
NRS	Non-Randomised Study
OT	Other Technologies
PICO	Population, Intervention, Comparators and Outcomes
PLEG	Post Launch Evidence Generation
POP	Planned and Ongoing Projects database

PT	Pharmaceuticals
QMS	Quality Management System
RCT	Randomised Controlled Trial
REA	Relative Effectiveness Assessment
REQueST	Registry Evaluation and Quality Standards Tool
RWE/RWD	Real World Evidence / Real World Data
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
TISP	Topic Identification, Selection and Prioritisation
WB	World Bank
WHO	World Health Organisation
WP	Work Package

FOREWORD

EUnetHTA has become synonymous with HTA in Europe, a trademark, in fact, that stands for a community of professionals dedicated to continuously improve the standards and quality of their own work, to ultimately achieve ever better results for patients.

This dedication of more than 15 years has lead to the creation of a European legal and financial framework. Joint Action 3 was the proof of concept stage, finally paving the way towards a more harmonised European framework encompassing more than 80 HTA bodies. The contributions of countless HTA experts across Europe have created a voluntary framework for collaboration and trust amongst all relevant actors, an achievement nurtured and carried by their conviction and dedication.

EUnetHTA, representing a network of experts, had one final duty, which was to ensure that the most important lessons learned would be provided in an appropriate format to the next phase of HTA collaboration in the EU. For this very purpose, the HTA White Paper was created, a process that took three years, with input from all EUnetHTA members together with a wide variety of stakeholders. Invaluable input was provided by those active in the work of EUnetHTA and our thanks go to all those who contributed to this collaborative effort!

This white paper is, in fact, the best possible demonstration of joint work as it carries the contributions and approval of EUnetHTA members. It would not be possible to single out one above the others, with one exception. This work would not have been possible without the relentless effort of Zoe Garrett. She has been the calm and diplomatic genius behind this white paper, allowing it to become the great piece of work we can present today. When initiating this white paper in 2018, I could never have hoped to find such outstanding champion to lead to its success.

With all this in mind, and when reading this white paper, please be advised that it represents the most thorough of processes that I personally have ever witnessed. It is not an easy read, but it provides a tale of true European collaboration.

Marcus C. Guardian
COO, EUnetHTA

1 INTRODUCTION

Objective 1.2 of the European Network for Health Technology Assessment (EUnetHTA) Joint Action 3 (JA3) Grant Agreement is to support voluntary cooperation at the scientific and technical level between HTA agencies by providing the scientific and technical mechanism of a permanent cooperation on HTA.

To meet this objective EUnetHTA Work Package (WP) 1 initiated a piece of work to develop the underlying scientific and technical principles for a future model of Health Technology Assessment (HTA) cooperation. The focus of the work and related recommendations is primarily at the scientific and technical level, emphasising the principles of governance, participation, procedures and infrastructure required to produce joint HTA outputs and support ongoing HTA cooperation. This work takes into consideration achievements and challenges of the current and former Joint Actions.

This report assumes that there will be a future legislative basis for HTA. In January 2018, the European Commission (EC) published a proposal for an HTA Regulation[1], the European Parliament adopted its amendments at first reading in February 2019[2] and the European Council published its proposals in April 2021[3]. Discussions between the three groups to reach a final text are now ongoing. Once adopted, the Regulation will provide a legal framework for cooperation on HTA. Since discussions about the regulation are ongoing, it is not possible to define exactly the structures and processes applicable to a future model of HTA cooperation with a legislative basis. However, the recommendations in this report coming from the experiences of the EUnetHTA Joint Actions will be useful for informing discussions on a European Union (EU) Regulation for HTA cooperation.

In the absence of a legislative basis for cooperation on HTA, the scientific and technical principles in this document are likely to remain valid. However, the extent to which they can be implemented in a sustainable manner will depend on whether HTA cooperation participants can either identify a financing mechanism to cover additional costs or can implement the principles in a manner that is cost neutral.

The learnings and recommendations described in this report should be revisited at regular intervals as the future HTA cooperation develops. This is so that as learnings and recommendations become relevant, they can be used to guide next steps and ensure that HTA cooperation continues to follow a robust trajectory.

The report focuses on the principles of HTA cooperation, but it recognises that sustainable HTA cooperation will require changes from within HTA agencies and from stakeholders, as well as other agencies involved in or affected by the HTA process. While future HTA cooperation should respect existing HTA procedures within countries, the differences in healthcare systems across Europe mean that to maximise the efficiency of HTA cooperation changes at a country level will be required so that HTA cooperation becomes part of routine working practice replacing steps of HTA agency procedures.

[1] https://ec.europa.eu/health/sites/health/files/technology_assessment/docs/com2018_51final_en.pdf
[2] https://www.europarl.europa.eu/doceo/document/TA-8-2019-0120_EN.html
[3] https://www.eesc.europa.eu/sites/default/files/files/council_of_the_eu_text_st07310.en21.pdf

1.1 Aims

The overarching aim of the work is to develop a complete set of scientific and technical principles for a future model of HTA cooperation.

The work to reach this aim was divided into two principal stages:

- Production of a RoadMap to list the elements of a model of HTA cooperation that have already been defined within JA3, identify which elements of a model of HTA cooperation could be improved or are missing, and recommending next steps to improve or develop the identified elements;
- Production of a White Paper, defining the scientific and technical principles for a future model of HTA cooperation, and referring to the elements in the RoadMap.

This report is stage 2 of the work, the White Paper.

2 METHODS

This section describes the methods used to (1) produce the RoadMap and (2) transform the RoadMap into the White Paper.

2.1 Production of the RoadMap

The work to produce the RoadMap was supported by a 17-member task group set up in October 2018. It followed three overarching stages; (1) audit of the existing elements of HTA cooperation produced in JA3, (2) discussion of areas missing or needing improvement, and (3) consultation on the draft RoadMap.

2.1.1 Audit

A data collection template was developed in June 2019 to collect information from work package leads and co-leads about the elements of a model of HTA cooperation that had been, or will be put in place, by the end of EUnetHTA JA3. The templates included a structured set of headings to support work package leads and co-leads to identify existing elements of a model of HTA cooperation and to suggest which elements were missing from existing joint HTA activities. The audit is included in Annex 1 of this report.

2.1.2 Discussion

From the audit, a series of briefing papers were prepared with the task group in November 2019. These briefing papers were used to support discussions to develop a consensus on the most important areas that were missing or needing improvement and to prioritise these for work going forward. Discussion groups were held with the RoadMap task group, the Executive Board, and the Project Managers Group.

During each discussion group, participants were asked to:

1. Come to a consensus about the important emerging areas for developing a model of HTA cooperation;

2. Prioritise the areas identified;

3. Propose next steps for the priority areas.

The prioritisation exercise was carried out by participants individually. Participants were given points that they could allocate to up to six of the identified areas. Data were analysed according to the total number of points each area scored and the total number of participants identifying the area as a priority.

At the end of the discussion phase there was a final scrutiny exercise where the Executive Board reviewed the outcomes from each discussion group together to ensure that the outcomes were consistent and that next steps were identified coherently across the different areas of the model of HTA cooperation.

2.1.3 Consultation

A consultation with EUnetHTA partners was held in May 2020. Twenty-two responses from partners were received. The consultation was used to validate the priorities identified and

gather comments about the proposed next steps for addressing the priorities. Twenty-two responses from partners were received. The report was updated after consultation.

2.2 Production of the White paper

The final stage of the work was to produce the White Paper. This work was led by the Executive Board, and the RoadMap task group was stood down.

The data sources for the White Paper were (1) the RoadMap, (2) milestones and deliverables from the JA3, and (3) additional work carried out by the Executive Board in response to the priorities identified in the RoadMap.

A framework was used to organise the data and structure the model. The framework was the same as the structured set of headings used to organise the RoadMap and was based on work carried out by WP7. The framework started with six broad categories that were adjusted and updated as the White Paper was developed:

- Concept and strategy e.g. the vision, purpose and aim of HTA cooperation;
- Governance and decision-making e.g. the leadership, steering and decision-making processes to support HTA cooperation;
- Participation of individuals, groups or organisations e.g. to reflect both engagement of external participants such as experts and stakeholders, but also internal partners and related organisations;
- Science and procedures e.g. methodological guidance, procedures and templates that support HTA cooperation or development of joint outputs;
- Infrastructure e.g. services, tools and databases needed to coordinate and meet the aims of HTA cooperation;
- Evaluation e.g. feedback mechanisms to ensure HTA cooperation can respond to changes and remain relevant to those involved.

The production of the White Paper paid particular attention to compiling the experiences from across the different joint HTA activities carried out in JA3, identifying the lessons learned, and making recommendations for future working and further development.

The White Paper was subject to consultation with the Executive Board and the European Medicines Agency (EMA) in February 2021 (8 responses) and to a consultation with EUnetHTA partners (10 responses) and stakeholders (7 responses) in April 2021. The report was updated after consultation before it was signed off by the Executive Board.

The comments received from stakeholders are included in Annex 2 of this report along with a summary of the key areas that were identified from the comments as requiring further consideration in future work to develop a model of HTA cooperation.

3 REPORT STRUCTURE

The rest of this report is split into 16 sections.

Section 4 outlines the objectives of a future model of HTA cooperation, the JA3 joint HTA activities, areas of potential future expansion for joint HTA activities, and the underlying principles that should guide HTA cooperation.

The next group of sections 5-8 describe aspects of HTA cooperation that are “transversal”, that is, working across all joint HTA activities. The features included in the White Paper are 1. Governance, 2. Participation, 3. Support systems and 4. Information technology. Governance covers decision-making and corporate governance. Participation considers the individuals, groups and organisations that should be involved as members, experts, collaborators and stakeholders. Support systems and Information technology describe the infrastructure needed to manage cooperation and undertake joint HTA activities.

The next group of sections 9-19 describes different aspects of cooperation at the level of the each joint HTA activity that the White Paper recommends, that is, Early Dialogues (ED), Joint and Collaborative Assessments (JA/CA) and Post Launch Evidence Generation (PLEG). Nine elements are considered in the White Paper. These are shown in Figure 3-1. The elements are not independent, i.e. decisions made in the conduct of one element will affect others.

The final section 20 is the conclusion to the report bringing the transversal and project-specific sections together into a summary.

Figure 3-1: Activity specific elements considered in the White Paper

The White Paper is not an exhaustive review of all aspects related to a future model of HTA cooperation. Instead, it focuses on the scientific and technical areas where principles and recommendations can most usefully be provided by EUnetHTA.

A common section structure is used for all chapters describing transversal and activity-specific HTA cooperation. These are:

- A summary of JA3 ways of working and key documents produced;
- Lessons learned from JA3;
- Recommendations for a future model of HTA cooperation;
- Recommendations for future work;
- A summary of themes identified from stakeholder comments.

4 CONCEPT AND STRATEGY

This section outlines the objectives of HTA cooperation, describes the joint HTA activities currently being carried out, areas of potential expansion in the future, and a set of scientific and participatory principles that should form the basis of a future model of HTA cooperation. This section sets the scene for HTA cooperation and starts to define how elements of a model of HTA cooperation should be elaborated.

4.1 Objectives of a future model of HTA cooperation

The following overarching objectives reflect the desired characteristics of a future model of HTA cooperation.

1. HTA cooperation should inform decision needs to promote an equitable, efficient, and high-quality health system recognising the core principles of HTA (transparent, unbiased, ethical, inclusive and independent);

2. HTA cooperation should create scientific outputs that provide added value for decision-making, but which do not pre-judge the decisions made by a country;

3. The outputs of HTA cooperation should be of high-quality, relevant, informative, unbiased, independent, transparent, reproducible, valued and trusted;

4. HTA cooperation should act across health technologies along their whole lifecycle. However, it must recognise the unique characteristics and HTA requirements of different health technologies at different stages of their lifecycle and adjust for these in the implementation of the model;

5. The mechanism of HTA cooperation should be one that all participants understand clearly, want to and are able to engage in, and benefit from;

6. HTA cooperation processes should be efficient, that is reducing duplication, supporting best use of resources, and promoting information exchange within and outside of the cooperation network;

7. HTA cooperation should be predictable but have sufficient flexibility to adapt and be adapted to differing and changing healthcare systems, objectives, decision-making frameworks, and evolution in the HTA landscape.

4.2 Joint HTA activities in EUnetHTA JA3

Three principle joint HTA activities were carried out in EUnetHTA JA3 and are recommended for future HTA cooperation:

1. Early Dialogues (ED);

2. Joint and Collaborative Assessments (JA/CA);

3. Post Launch Evidence Generation (PLEG).

These joint HTA activities are a group of linked activities that support the decision needs of participants and their health systems along the lifecycle of a technology (Figure 4-1). Increasingly for pharmaceuticals there is complementarity between HTA and regulatory

timelines. HTA starts in parallel to regulatory processes to support decision-making close to marketing authorisation. For non-pharmaceutical technologies there is currently no such regulatory anchor and there is greater variation in when HTA is carried out in relation to regulatory and launch processes.

In addition to the 3 principle joint HTA activities described above, EUnetHTA has started work on processes to identify emerging health technologies for joint HTA activities as part of horizon scanning. It is recommended that this work started in EUnetHTA JA3 is continued.

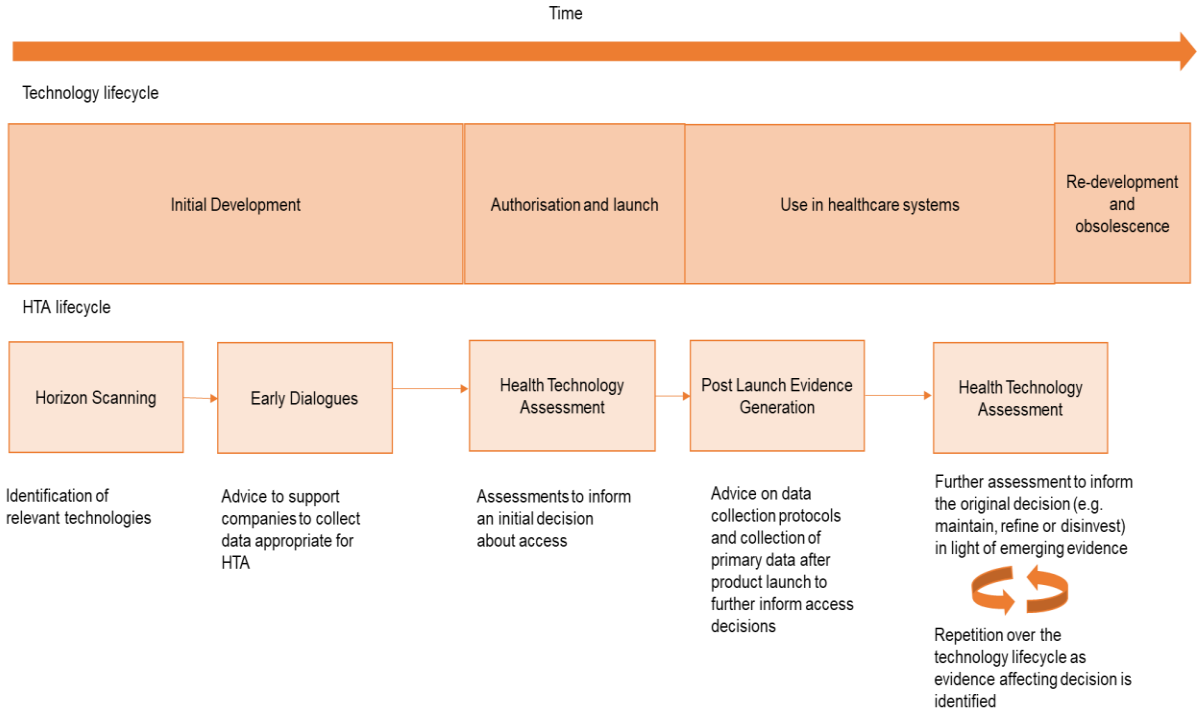


Figure 4-1: Position of joint HTA activities along the lifecycle of a health technology indication

4.2.1 Early Dialogues (ED)

An ED is a non-binding scientific advice, typically given before the start of pivotal clinical trials (after feasibility / proof of concept studies), to improve the quality and appropriateness of the data produced by developers for future HTA. The ED procedures are also used in exceptional cases for consultations taking place after a product is made available on the market in order to improve the quality and appropriateness of PLEG.

EDs enable an exchange between the applicant and HTA agencies at an early stage in the development process 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 and post-launch studies) and if requested the economic evidence generation plan. The main objective of EDs is to gather and provide common recommendations on how a drug or device could be developed to fulfil HTA requirements across multiple countries.

In JA3, three ED procedures were available:

1. Parallel consultations for pharmaceuticals involving multiple HTA agencies and the European Medicines Agency (EMA) (called in JA3 the parallel consultation procedure);

2. Procedures for pharmaceuticals involving multiple HTA agencies only (called in JA3 the multi-HTA procedure);

3. Procedures for medical devices involving multiple HTA agencies only (called in JA3 the medical device procedure).

The procedures are available in two formats; with or without a face-to-face meeting. Key documents are shown in Table 4-1.

Table 4-1: Key documents describing Early Dialogues

Key documents	Link
Guidance on the parallel consultation procedure	https://eunethta.eu/services/early-dialogues/parallel-consultations/
Guidance on the Multi-HTA procedure	https://eunethta.eu/services/early-dialogues/multi-hta/
Guidance on the medical device procedure	https://eunethta.eu/services/early-dialogues-for-medical-devices/
Early Dialogues financing mechanism framework	*Internal document only: limited circulation*

EUnetHTA and the EMA offer Parallel Consultations on evidence generation plans. Parallel Consultations allow technology developers to obtain feedback from regulators and HTA agencies on their development plans to support simultaneous decision-making on marketing authorisation and HTA of new medicines. These consultations normally take place before the product is made available on the market, but can also take place after the product is made available on the market. The aim of Parallel Consultations is to help generate optimal and robust evidence that satisfies the needs of both regulators and HTA agencies.

EUnetHTA also offers the multi-HTA ED procedure on evidence generation plans. These ED aim to allow technology developers to obtain simultaneous feedback on their development plans from multiple HTA agencies without the EMA being involved. The objective is to help generate optimal and strong evidence that satisfies the needs of HTA agencies, recognising that regulators and HTA agencies are operating in distinct remits.

Although the majority of the EUnetHTA EDs carried out in JA3 were done in parallel with EMA, some technology developers may choose to request a Multi-HTA ED. Therefore, both options should be available.

4.2.2 Joint and collaborative assessments (JA/CA)

Joint Assessments (JA) are HTAs jointly produced by HTA agencies in different countries. EUnetHTA processes, templates and guidelines support their production. JAs are carried out for pharmaceuticals (PT) and for other technologies (OT). JAs are centrally coordinated and include the use of an evidence submission and a scoping (e-) meeting with the prospective marketing authorisation holder. To facilitate the timely availability of the PT JA after marketing authorisation, direct exchanges are arranged with EMA on the regulatory assessment.

EUnetHTA Collaborative Assessments (CA) are only produced for OT. They differ from the EUnetHTA JAs regarding coordination, that is, the project management can be performed in a decentralised manner and the use of an evidence submission and scoping (e-)meeting with industry are optional.

Key JA/CA documents are shown in Table 4-2.

Table 4-2: Key documents for Joint and Collaborative Assessments

Key documents	Link
Recommendations for topic identification, selection and prioritisation	https://eunethta.eu/services/horizon-scanning/
Recommendations for future production processes	https://www.eunethta.eu/wp-content/uploads/2021/06/Recommendations-for-production-process-after-Joint-Action-3_WP4_May-2021.pdf
Companion Guide	https://www.eunethta.eu/eunethta-companion-guide/
Submission requirements – pharmaceutical joint assessments	https://eunethta.eu/wp-content/uploads/2019/09/EUnetHTA-submission-requirements-V2.pdf
Analysis of HTA and reimbursement procedures in EUnetHTA partner countries	https://eunethta.eu/national-implementation/analysis-hta-reimbursement-procedures-eunethta-partner-countries/

PT JA focus on relative effectiveness assessment (REA), including the health condition, description of the technology, clinical effectiveness and safety. They are single technology assessments (that is, they include one intervention) and are carried out as an initial assessment in parallel with marketing authorisation. They are designed to be used in agency-level HTA procedures. OT JA or OT CA are not usually single technology assessments and although they mainly focus on REA, they can include other HTA domains. They are not restricted to a specific time-point in a technology lifecycle and can also be reassessments.

4.2.3 Post Launch Evidence Generation (PLEG)

PLEG is a newer joint HTA activity for EUnetHTA as compared with ED and JA/CA. PLEG has an important role addressing uncertainties in the evidence at the time of initial assessment and adding to the evidence base that is then used to re-assess a health technology. As the pharmaceutical regulatory landscape changes and technologies are approved earlier in their lifecycle, PLEG activities are becoming ever more visible.

EUnetHTA has piloted two types of joint HTA activity that support evidence generation after the launch of a health technology:

1. Product-specific PLEG projects. This activity is technology-specific arising from HTA and identification of evidence gaps. Cooperation consists of defining a common data set to address evidence gaps for a specific health technology, and whenever possible, compiling and analysing corresponding evidence collected locally;

2. Registry PLEG projects. This activity is specific to a registry rather than a technology. Cooperation consists of assessing the suitability of an existing data source for PLEG purposes in terms of variables collected and the quality of data collection. The output is a report which contains non-binding recommendations to the registry holder from the participating agencies on the aspects discussed. This type of activity can be performed in collaboration with the EMA.

Key PLEG documents are shown in Table 4-3:

Table 4-3: Key documents for Post Launch Evidence Generation Activities

Key documents	Link
JA3 Final Deliverable "Recommendations and tools for PLEG"	https://www.eunethta.eu/pleg/
REQUEST tool and Vision paper on the sustainable availability of REQueST	https://eunethta.eu/request-tool-and-its-vision-paper/
PLEG practice among HTA agencies	*Formal EUnetHTA deliverable available via* ec.europa.eu

PLEG activities complement evidence generation already undertaken for HTA, addressing remaining uncertainties but also potentially covering wider questions of disease management and healthcare delivery.

4.3 Additional areas of cooperation

Health systems, populations and HTA processes differ across Europe. This means that the needs of the individuals, groups and agencies involved in HTA vary across countries and regions. HTA cooperation is ideally placed to address a wide range of needs. Additional activities that go beyond the JA3 joint HTA activities described above may provide added value to a broad range of participants and help guide and support the evolution of HTA cooperation, maintaining its relevance to participants.

Four areas are identified for joint HTA activities that go beyond those undertaken in JA3, either by expanding the remit of the activity or carrying out activity in an additional area.

- Information exchange;
- Advice/HTA guidance;
- Assessment;
- Expertise.

4.3.1 Information exchange

Systems that support agencies to share information help them to make best possible use of data available, understand whether others are facing the same issues, and promote joined-up problem solving and alignment of methods and processes. Sharing mechanisms need to be user-friendly so that providing information for others to use is not onerous and does not outweigh the benefits of access.

EUnetHTA has developed two databases that promote information sharing: POP [4] and EVIDENT[5]. POP is a database of planned and ongoing assessments that helps agencies identify potential overlap in work programmes and topics for collaboration. EVIDENT is part of PLEG and includes information about requests for evidence generation studies after HTA.

[4] https://eunethta.eu/pop-database/
[5] https://eunethta.eu/evident-database/

Systems to support information exchange like POP and EVIDENT could be expanded to cover additional areas not covered by these databases (Table 4-4).

Table 4-4: Areas of expansion – Examples of information exchange

	Additional area of cooperation
Context	• Changes to HTA and reimbursement processes • Monitoring activities and re-assessment • Exchange on new challenges (e.g., new health technologies)
Data and data sources	• Real world data (e.g., from registries) to inform re-assessment • Prices and pricing strategies • Epidemiological data (e.g., patient numbers, co-morbidities, disease progression) • Information about national registries (including information on the registries and registry holders)

4.3.2 Advice / HTA guidance

Ongoing HTA cooperation puts participants in a good position to provide a wide range of types of advice that is broader than current ED. EUnetHTA initiated some activity in this area, for example, exploring the potential for enlarging the scope of ED to include further methodological advice, but found that currently this can be constrained by national legislation. The confidential nature of ED means that a joint HTA activity that provides general advice or pre-formulated advice could provide a publicly available output, thereby improving transparency and benefiting a wider audience.

Table 4-5: Areas of expansion – Examples of advice

	Additional area of cooperation
General advice	• Advice in areas of HTA collaboration • Educational advice and/or guidelines on HTA • Advice on specific issues such as methods around biomarkers, selecting patients for Advanced Therapeutic Medicinal Products (ATMP), indirect comparisons.
“do your own advice”-toolbox	• Pre-formulated advice to generic and frequently asked questions

4.3.3 Assessments

JA3 JA/CA production processes have focussed mainly on REA. However, for both PT and OT, an HTA often includes assessment of information from HTA domains that are broader than REA. These other domains including organisational, ethical, legal and social issues, and in particular health economics, are related to REA and can be an important driver for implementation of REA.

EUnetHTA JA3 PT JA have focussed on single technologies close to launch that have a company evidence submission. While this type of assessment is produced by many HTA

agencies, there are other types of assessments also carried out including multiple technology assessments and assessments without company evidence submissions.

Multiple technology assessments and assessments that go broader than REA are often complex and resource intensive and HTA cooperation may provide value in certain cases. Expanding the remit of joint HTA activities will need to be balanced against time and resources required to develop supporting tools and procedures.

Table 4-6: Areas of expansion – Examples of assessments

	Additional area of cooperation
Breadth of work	• Voluntary collaboration in JA/CA in HTA domains broader than REA including health economics, organisational, ethical, legal and social issues • PT multiple technology assessments and assessments without a submission of evidence from the technology developer • Assessment of new types of health technologies e.g., artificial intelligence (AI), digital health and public health measures

4.3.4 Expertise

HTA is not equally established across all countries and some stakeholder and technical expertise, particularly when it is newly developing, is held by a small group of individuals. Pooling expertise to make the best use of resources can support development of HTA capacity across Europe and improve the scientific rigour of HTA.

Table 4-7: Areas of expansion – Examples of expertise

	Additional area of cooperation
Pooling of knowledge	• Pool of scientific and technical experts to be available for ad-hoc advice on challenging methodological issues • Information about the specialist knowledge held by HTA agencies, experts who can be consulted for specific questions, stakeholders from different fields, patient representatives and translation agencies/experts • Pooling of stakeholder or technical knowledge and sharing knowledge across regions in situations where knowledge is held by a small number of people
Training	• Supporting HTA training opportunities for participants to learn and develop • Methodology training sessions from scientific experts to develop each other's expertise
Scientific leadership	• Joint contribution to regulatory guideline consultations • A common framework / guidance on new and evolving methodologies and approaches • Opportunity to provide guidance on evidence requirements and methodology to encourage optimum evidence generation

4.4 Underlying principles of HTA cooperation

EUnetHTA has defined a set of shared principles that support the development of transversal and activity-specific HTA cooperation.

The first set of principles (Table 4-8) are scientific that should guide the procedures used in all joint HTA activities.

The second set of principles (Table 4-9) are specifically for joint HTA outputs that inform resource allocation decisions.

The third set of principles (Table 4-10) are participation principles that should support engagement of internal and external participants in HTA cooperation.

Table 4-8: Scientific principles guiding all joint HTA activities

	Principle	Importance in HTA cooperation
1	HTA should be an unbiased exercise free from financial and intellectual conflicts of interest.	• Independence of HTA expertise is key. Freedom from conflicts of interest is critical to ensuring national uptake. An agency must be able to assess whether an output could be subject to COI and know that the output is not affected by COI. • COI management must be implemented across joint HTA activities including in horizon scanning and the selection of products for joint assessment and in PLEG where COI can happen in methodology, data collection and data presentation. • It must be transparent in each product how COIs were handled and potential COIs were mediated.
2	Conflicts of interest (COI) management should be included in published reports and any potential sources of conflict documented.	
3	Methods and general procedures of HTA including rules for participation and decision-making should be transparent, reproducible and reliable.	• Transparency is a basic ethical requirement for research in humans and a prerequisite to ensure safe and efficient use of health technologies and therefore it is of strong public interest.
4	General Data Protection Regulation (GDPR) requirements and confidential information should be respected.	• While transparency is a basic ethical requirement for research in humans, it is recognised that in certain strict conditions confidentiality is required. • Personal data needs to be handled according to GDPR-requirements and confidential data needs to be protected against unauthorised access. • ED can only be pursued if confidentiality of the data submitted is ensured, a greater transparency should be possible closer to authorisation.
5	All steps of topic identification, selection and prioritisation (TISP) should be unbiased, inclusive, efficient and transparent.	• The success of HTA cooperation relies on the identification of topics that are relevant and timely for decision making. • HTA cooperation should focus on topics that are of most value to countries (for example, topics that have added value to multiple participants and topics for which the benefit of sharing expertise is highest) to meet the objective of reducing duplication and workload • The potential activities to benefit from TISP workflows include ED, JA/CA and PLEG
6	Joint HTA activities should be of broad value and be initiated in a timely manner.	
7	A common system of TISP for all joint HTA activities should be available.	

	Principle	Importance in HTA cooperation
8	A quality management system (QMS) should cover all areas of joint work.	• The relevance of HTA cooperation depends on the reliability of processes and outcomes. To ensure that the joint work is conducted to a reliably high standard and that the outcomes fulfil the predefined expectations (i.e., are of high quality), a systematic QMS needs to be in place that covers all areas of joint work. • Agencies can only build trust in the quality of joint work if there is a mechanism to ensure defined methods and procedures are followed.
9	Compliance to joint processes and methods should be ensured.	
10	Decision-makers should have timely access to HTA of prioritised topics.	• If an HTA is not timely, there can be an inefficient use of HTA resources (for example, because the HTA is not used by decision makers) and a detrimental effect on patient outcomes.
11	HTA methods, procedures and outputs should be up-to date and published in a manner that is unbiased and transparent.	• HTA methodology is an evolving science that should consider and respond to methodological change. To create a robust HTA the system must ensure that authors of the HTA have up-to-date scientific knowledge and appropriate up to date guidance for submissions and authoring teams. • HTA does not sit in isolation from the wider health technology environment. HTA must be able to respond to changes either upstream e.g. regulatory changes and/or downstream e.g. changes in decision-making frameworks and processes. • Robust decision making requires an HTA that uses an up-to-date evidence base and methodology. • Efficiencies at a national level are only maximised if joint HTA methods and reports are up-to-date so the HTA is fully informative.
12	HTA cooperation should be subject to a cycle of evaluation.	• HTA cooperation must remain relevant to its participants and provide benefits for those taking part and the wider health system.

Table 4-9: Additional scientific and technical principles for joint HTA activities informing resource allocation decisions

	Principle	Importance in HTA cooperation
1	The scope of HTA should be based on policy questions from the health care systems in which the report is going to be used. The policy questions should be reflected in research questions and should be pre-specified at the start of a given assessment.	• HTA cooperation relies on agencies using outputs in decision making that they have not been involved in producing. Therefore, agencies must be able to inform planning stages to help create outputs that are relevant for their national (or regional) policy question. • Early alignment on the concept of PICO (that is, population, intervention, comparator and outcomes) and its role in the assessment is needed to guide the development of European HTA. • Pre-specification of research questions is a fundamental foundation of HTA supporting production of robust outputs.
2	The scope of HTA should cover the needs of as many users' policy questions as possible to result in as less extra local assessment work as possible.	
3	Assessments should include the best available evidence at a specific time point to address the defined research questions.	• The preferred evidence for relative effectiveness assessment is randomised controlled trials. However, it is recognised that these are not always available. The use of best available evidence ensures a timely and adequate response to the HTA needs and avoids production of reviews where there are no studies eligible for inclusion due to strict inclusion criteria, thereby facilitating decision-making. At the same time, the strengths and weaknesses of the included data must be presented and discussed to allow conclusions to be drawn at national level.
4	The evidence submitted for HTA should be complete.	
5	The evidence included in the HTA should be transparent.	
6	Strengths and weaknesses of different study types must be considered and elucidated when assessing relative effectiveness and safety.	
7	The assessment of certainty of evidence needs to be done in a context independent manner.	• Joint HTA outputs are part of a process that informs resource allocation decisions. REA's should reduce as much as possible the workload of HTA agencies that use them. However, health technologies embody a variety of economic, organisational, social and political implications for individuals and society. Therefore, there is a need for independent contextualization, appraisal and decision making at the national level to comply with national legislation, policies, healthcare organisation and values.

	Principle	Importance in HTA cooperation
8	Reports to inform HTA decisions should be published without redaction with all the information and data required to perform the assessment.	• The relevance and reliability of reports intended for use in HTA decisions depends on the ability of HTA agencies and all other interested parties to follow the processes, methods and data used.
9	All evidence and data, including the submissions from technology developers and regulatory information, should be available to the participants in the HTA cooperation.	• Availability of data to all participants in the cooperation ensures reliability of the assessments and results and thus supports better implementation by ensuring that where needed there is sufficient accountability for decision-makers.

Table 4-10: Participation principles for all HTA activities

	Principle	Importance in HTA cooperation
External participation		
1	Systematically seek a variety of external stakeholder engagement with wide representation (for example, varying expertise and nationalities).	• There needs to be a mutual understanding between participants of HTA activities. This ensures that the input from external stakeholders is relevant for joint HTA activities and that their perspective is included. • Relevant external stakeholders, who are willing to contribute, should get the opportunity to participate, where feasible. This should enable joint HTA activities to collect a wide range of inputs, so that users of the outputs can be confident that relevant input was gathered. • Input from technology developers is necessary to ensure the joint production includes all relevant data and studies. • Independence of HTA is key. Freedom from conflicts of interest is critical to ensuring national uptake. An agency must be able to assess whether an output could be subject to COI and know that the output is not affected by COI.
2	Integration of external stakeholder input in joint HTA activities.	
3	Transparency, fairness, and independence throughout the identification, selection and engagement process of external stakeholders.	
4	Conflict of interest must be assessed and avoided where applicable.	
5	External communication should be based on clarity, openness and transparency.	• HTA relies on open communication, transparency and trust in a high-quality scientific methodology.

	Principle	Importance in HTA cooperation
6	Communication should focus on scientific and technical elements of HTA cooperation in simple, factual language that reaches the widest possible audience.	• While HTA is a scientific and technical exercise, it must be understood by a wide variety of stakeholders.
Internal participation		
8	Participants in the HTA cooperation should feel informed about and engaged in the cooperation and its activities	• Considering the large number of HTA agencies involved in HTA cooperation not all HTA agencies can take part in all joint HTA activities. Transparency of opportunity, procedure and decision-making is therefore essential for the creation of trust in the system.
9	Participants in the HTA cooperation should understand how decisions affecting them are made and have an opportunity to inform such decisions.	
10	Participant involvement in joint HTA activities should be guided by transparent selection procedures and criteria.	
11	HTA cooperation should be inclusive and support participants who wish to be involved through training and development opportunities.	
12	Communication should be timely, democratic (equal treatment and participation opportunities for all partners), and be based on two-way channels between the coordinating Secretariat and the wider network of participants in the HTA cooperation.	

5 TRANSVERSAL: PARTICIPATION

This section considers who should be participants in HTA cooperation, including:

1. Internal participation, that is the individuals, groups and organisations who are members or partners in the cooperation (for example, in JA3 internal participants were organisations producing or using HTA nominated as a partner in the action);

2. External participation, that is individuals, groups and organisations with an interest in the cooperation but who are not members (for example, in JA3 these were experts, stakeholders and related organisations who participated in joint HTA activities or were involved in the cooperation but did not have member status).

Differences in healthcare systems and agency roles and responsibilities means that for some countries the internal participant is a dedicated HTA agency whereas in other counties a payer or regulator could be an internal participant because the agency also has an HTA remit.

For internal and external participants this section considers who to involve and the methods for involving them in general transversal HTA cooperation. Participation associated with specific joint HTA activities are considered in sections 11, 14, 15 and 16.

5.1 Summary of JA3 approach

Table 5-1: Key JA3 documents about participation in HTA cooperation

Key documents	Link
Engaging stakeholders in EUnetHTA	https://www.eunethta.eu/wp-content/uploads/2021/05/Engaging-stakeholders-in-EUnetHTA-Joint-Action-3.pdf
Stakeholder analysis	*Formal EUnetHTA deliverable available via* ec.europa.eu
Declarations of interest and confidentiality agreement	https://eunethta.eu/doi/
EUnetHTA-EMA work plan	https://www.eunethta.eu/ema-eunethta-joint-work-plan-for-2017-2020/

The approach to participation in JA3 is shown in Figure 5-1 below.

Internal participants can be organisations that produce, contribute to, or use HTA nominated by their Member State representative. Participants include HTA agencies, as well as HTA programmes or departments in a larger organisation such as a payer organisation, regulator, Ministry of Health or academic institution. Participants choose which work packages and projects they are involved in and their involvement in tasks is voluntary. Participants can lead work packages or activities, be members of project teams, of advisory, expert and decision-making groups, as well as general participation though consultations and event attendance.

External participants in JA3 have been patient and consumer organisations, healthcare professionals and providers, payers, industry, regulators and the wider HTA community (including academic institutions, related networks, and other HTA agencies). The role of these participants has been as experts, stakeholders and/or collaborators. Patients and healthcare professionals have more usually acted in an expert role, while regulatory authorities have been collaborators.

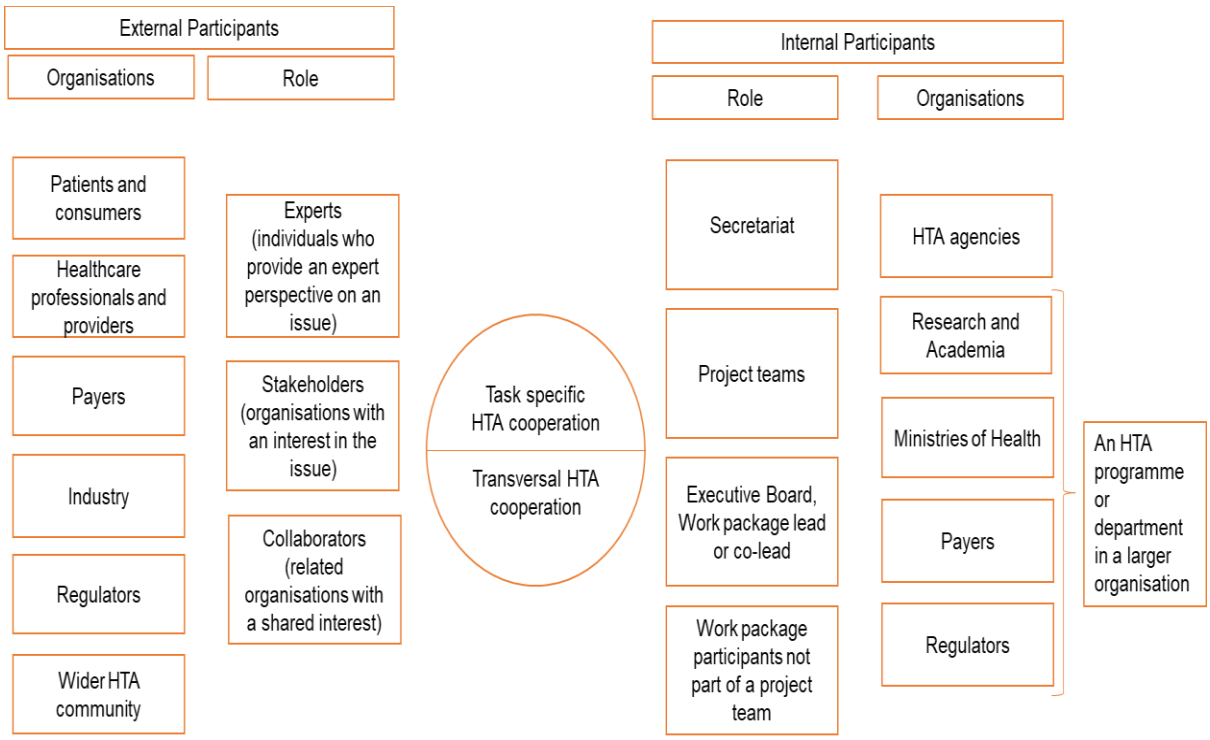


Figure 5-1: Internal and external participation in JA3

The main focus of stakeholder engagement has been through involvement in specific joint HTA activities. Opportunities for transversal participation in JA3 have included:

- Information exchange e.g., forum and regular stakeholder meetings;
- Consultation e.g., document consultations, revision of guidelines, reflection papers and documents for the public;
- Collaboration e.g., EUnetHTA-EMA workplan and Task Groups for specific topics.

The forum is an open meeting that any stakeholder group can attend. Stakeholder meetings are specific to a group and have been held for industry, patients and consumers, payers, regulators, and healthcare providers and professionals. A key collaborator in JA3 has been the EMA, who have worked collaboratively across the range of joint HTA activities as well as in a transversal work programme based on exchanging information and developing a shared understanding between HTA agencies and regulators.

5.2 Lessons learned

5.2.1 Internal participation

Participation in JA3 has been voluntary. Voluntary participation provides freedom for agencies to choose how they engage. However, for any specific joint HTA activity, agencies may decide not to be involved when projects do not align fully with national priorities, timeframes and resource availability. This can create management problems if it affects the ability to constitute project teams.

Agencies act at different levels (e.g., national, regional, hospital-level) and have different remits and responsibilities within the HTA process. More than one agency per country may

need to participate in HTA cooperation and different agencies have different participation needs.

HTA responsibilities in a country change, new agencies are set up, and existing agencies change and move organisations. Organisations that need to be involved in HTA cooperation are therefore not static.

While large networks support inclusiveness, they require significant resources to manage and coordinate to ensure ongoing engagement.

The structures for collaboration need to be as simple as possible. Complicated and burdensome structures can act to decrease the possibilities of cooperation because agencies have challenges engaging with them.

At the start of JA3 EUnetHTA relied primarily on the intranet as the means of communication. Feedback suggested that this was not sufficient. Communication infrastructure now includes additional modalities e.g., email newsletters.

5.2.2 External participation

HTA agencies differ in their understanding of the objective of external stakeholder involvement. Some HTA agencies have no experience of stakeholder engagement, especially patient engagement.

Some external stakeholders (for example small and medium-sized enterprises) may not always have a clear understanding of HTA, HTA agencies, or the role of HTA agencies versus the role of regulatory agencies. This can compromise their ability and willingness to engage and contribute to joint HTA activities. Collaboration with regulatory agencies, including joint presentations about joint HTA activities, has increased the understanding of external stakeholders. Furthermore, this work has enhanced the mutual understanding between HTA and regulatory agencies.

There are divergent opinions among HTA agencies about whether some stakeholder groups, and in particular industry and payer organisations, should be included in joint HTA activities and, if they are included, where in the process it is appropriate to include them. Some HTA agencies are distanced from these groups to maintain independence, while other HTA agencies have a more cooperative relationship.

5.3 Recommendations for a future model of HTA cooperation

Internal and external participation in HTA cooperation should be guided by transversal principles and a framework for engagement. Differences in approach to participation across activities should have a justified rationale.

Participation should be broad acting at the national, regional and hospital-level to ensure inclusivity and that all relevant perspectives are captured.

- Participation should be underpinned by transparent criteria about who needs to be engaged, based on their responsibilities and remit;
- A simple mechanism to add, remove, and change participants is necessary;
- Resources should be available to ensure the HTA cooperation is managed and coordinated effectively.

HTA cooperation should include appropriate stakeholder involvement, and especially involve patients and health care providers.

All participants who are part of a project team or act as an expert to a project team should make an annual declaration of their interests and update whenever necessary. The declaration of interest (DOI) of each participant should be assessed by an independent committee, before being involved in any joint HTA activity. Normally, any COI should be avoided.

To facilitate participation:

- All participants should have an overview of the role, responsibilities and expectations of participation;
- Cooperation structures, methods and tools across activities should be aligned where possible to make participation easier;
- Participant documents should be harmonised so that they are easier for participants to become familiar with, encouraging ease of use, understanding of activities, and avoidance of procedural errors;
- There should be publicly available guidance on involvement;
- Multiple modalities of communication should be used.

Internal and external participants should be engaged in general HTA cooperation activities through a programme of routine information exchange and consultation on decisions that will affect them, in addition to activity-specific involvement. HTA cooperation should include strategic collaborations with external participants in critical areas. For example, collaboration with regulators on a framework for sharing confidential information to facilitate efficient decision-making.

HTA cooperation works at a European level to support national decision-making. This means that some external participants will have a European remit and some will mainly have a national remit. Resources to support the promotion of HTA cooperation within a country need to be available, alongside guidance for when European engagement or national engagement may be more or less appropriate.

The HTA cooperation should be supported by a strategic engagement plan outlining how the cooperation will engage with other related organisations so that synergies can be identified, and formalised relationships and work programmes developed. Specific organisations and networks identified for formal collaborations are:

- Regional HTA initiatives e.g. the BENELUXA Initiative, the Nordic collaboration FINOSE, and The Valletta Declaration;
- Scientific societies or organisations e.g. INAHTA, WHO, WB, ISPOR, Euroscan, IHSI and HTAi;
- Non-participating HTA agencies and relevant academic groups;
- The clinical guidelines community and European Reference Networks.

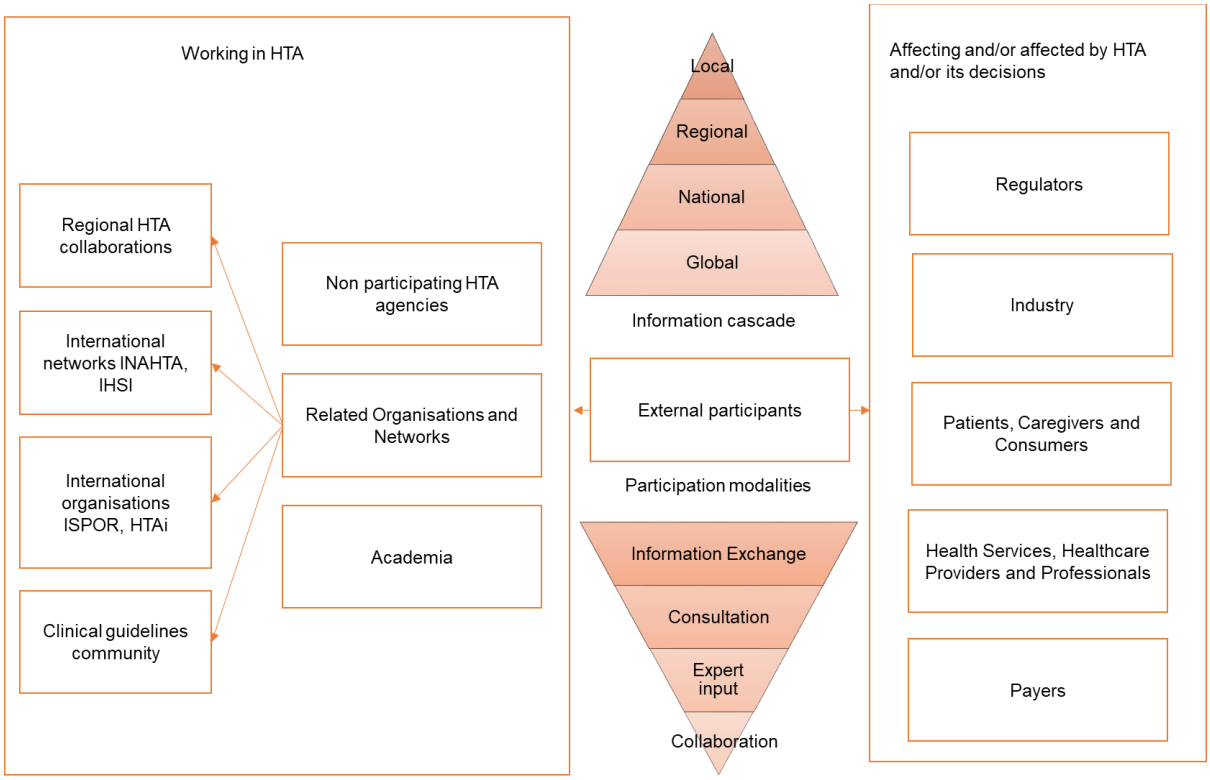


Figure 5-2: External participation in future HTA cooperation

5.4 Recommendations for future work

Further work to develop an agreement among HTA agencies of where in joint HTA activities different stakeholder groups should be engaged and in what capacity (e.g. as stakeholders, experts or collaborators). From this work, development of a participation framework and shared set of principles for stakeholder engagement to be applied transversally across all joint HTA activities.

Preparation of documents describing roles, responsibilities and participation in joint HTA activities of external participants. Consistent availability, specification and structure of these documents: SOPs, manuals, guides or overviews.

Creation of a strategic engagement plan to support relationships between the future HTA cooperation and other related organisations, and to position the future HTA cooperation with other EU organisations or initiatives, as well as with other international organisations and networks

Definition of the criteria that individual, groups and organisations should fulfil to be experts or internal participants in the HTA cooperation.

Discussions with stakeholder groups about how they wish to be involved in transversal HTA cooperation activities, for example the fora and mechanisms for routine information exchange and activity updates.

6 TRANSVERSAL: GOVERNANCE OF THE COOPERATION

This section discusses two areas of transversal governance:

1. Governance and decision-making structures e.g., leadership and steering of HTA cooperation;

2. Corporate governance e.g., rules, practices, and processes through which HTA cooperation is governed.

These areas are considered with a specific focus on the issues arising for HTA cooperation because of the scientific principles underlining it, its operation as a network, and the data it handles.

6.1 Summary of JA3 features

Table 6-1: Key documents relating to transversal governance procedures

Key documents	Link
EUnetHTA Governance Development (defines the principles and processes for setting up subgroups)	*Internal document only: limited circulation*
List of decisions and action points agreed upon during the Executive Board F2F in May 2018 (including Role of the EUnetHTA Executive Board and Role of the Chair of the EUnetHTA Executive Board)	*Internal document only: limited circulation*

Figure 6-1 shows the governance structure implemented in JA3. At the highest level exists (1) the Assembly, comprised of representatives of each consortium partner and (2) the Heads of Agency group, made up of the heads of the agencies of the countries of the Executive Board. These two groups meet annually and biannually respectively. At the next level is the Executive Board, which meets monthly and is made up of work package leads and co-leads, elected members from the Consortium, and the Assembly chair and vice-chair. Finally, at an operational level there are subgroups preparing work for Executive Board decision-making, Work Packages, the Secretariat, and the Project Managers Group. The approach adopted in JA3 has been primarily based on the project structure of JA3 and the division of activities into work packages.

The decision-making configuration changed part way through the JA3 with the introduction of the Heads of Agency group, subgroups to support Executive Board decision-making on strategic issues, and the chair and vice-chair roles. These changes created a more supportive structure that enhanced decision making.

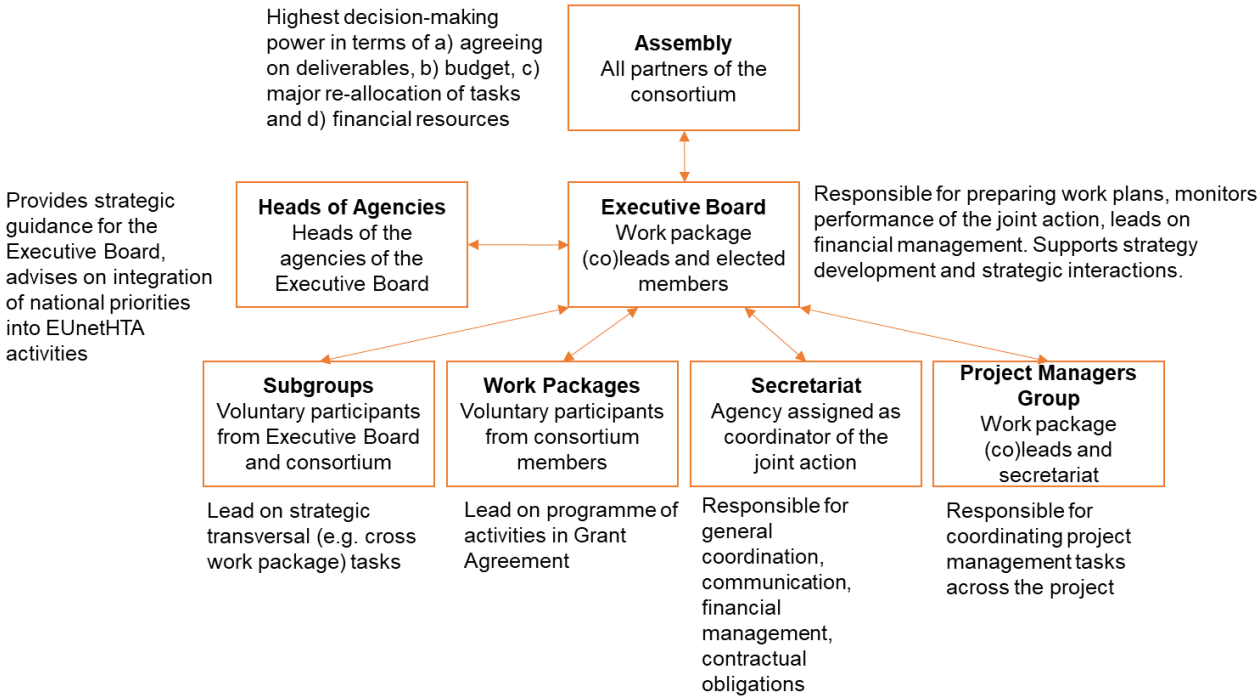


Figure 6-1: Transversal governance structures EUnetHTA JA3

In JA3, two key transversal corporate governance policies have been developed: declarations of interest and the confidentiality agreement. Declarations of interest are fundamental to the principle of independence in HTA, while the confidentiality agreement is fundamental to the nature of the work and access to data provided by technology developers and regulators. In addition, work in JA3 was undertaken to improve the standardisation of the authorship and copyrighting of the documents produced. These policies were developed for the context of JA3 but provide a suitable foundation for further development of policies for a future action.

Table 6-2: Key corporate governance documents

Key documents	Link
EUnetHTA Procedure Guidance for handling Declaration of Interest (DOI) and Confidentiality Agreement forms	https://eunethta.eu/doi/
Declaration of Interest (DOI) Form	https://eunethta.eu/doi/
EUnetHTA Confidentiality agreement	https://eunethta.eu/wp-content/uploads/2020/03/Confidentiality-Agreement.pdf
Declaration of Interest (DOI)/confidentiality agreement assessment template	https://eunethta.eu/doi/
Authorship rules and copyright issues	*Available to EUnetHTA partners*

6.2 Lessons learned

Decision-making groups need to be able to take into account the variations in healthcare systems across Europe. This includes differences in:

- National, regional and hospital-level HTA responsibilities;
- Responsibilities for the assessment of health technologies used in primary and secondary care;
- Responsibilities for pharmaceutical and other health technologies;
- Remit for HTA assessment, appraisal and decision-making.

Strategic decision-making and governance functions require access to expert knowledge to support the decision-making process. A system of expert support in a range of areas needs to be available for decision-makers to use.

Procedural flexibility is required to change governance and decision-making structures in response to feedback and the need for improvement.

HTA cooperation requires a framework that supports implementation of robust approval procedures. Some governance processes could not be fully implemented because of the JA3 framework.

Robust corporate governance needs to be in place to support the network. In JA3 some corporate governance policies and structures were put in place, for example, a standing COI committee and database. However, a comprehensive set of corporate governance policies and structures applied across all activities is still needed.

In JA3, access to DOI information was restricted to a standing COI committee. Some HTA agencies would like information to be available to all internal participants to ensure transparency and accountability of the process. This will require the appropriate GDPR and confidentiality arrangements.

6.3 Recommendations for a future model of HTA cooperation

The framework for HTA cooperation should ensure the cooperation can be responsible and is accountable for the outputs arising from joint HTA activities.

There should be a group that make decisions on behalf of the cooperation. This decision-making body should follow a set of shared and transparent principles and have a membership that can be configured differently for different types of health technologies, and that is representative of EU HTA approaches.

The process for assembling the decision-making body needs to be transparent and inclusive and open to all HTA bodies with clear communication structures.

The decision-making body will plan activities, monitor activities with respect to the work programme of joint HTA activities, and approve outputs arising from joint HTA activities.

The decision-making body should be able to access a range of personnel to support them to make decisions, including:

- A Secretariat to support the decision-making body and its activities;

- A range of other transversal support services (see section 7);
- Ad-hoc and standing expert groups to work and advise the decision-making body on scientific and procedural issues;
- A chair and vice chair to work with the Secretariat and to lead meetings;
- A comprehensive set of corporate governance policies with the rules and procedures guiding the cooperation (Table 6-3).

There should be a cycle of evaluation and sufficient flexibility to allow the governance and decision-making structures to change to ensure that the decision-making body continues to function optimally as the cooperation and its work evolves.

Table 6-3: Corporate Governance policies

Corporate Governance Area	Description of the policy
Declarations of interest	Management of interests, definition of interests and declaring these including a common procedure, templates and guidance for completion. Includes an independent committee that assesses the declarations of interest.
Confidentiality policy, framework and agreement	Definition of confidentiality and managing confidential information submitted for a project. Publication and citation policy regarding confidential data, taking into account core principles of HTA (transparent, unbiased, and independent).
Complaints	A procedure for addressing and responding to internal and external complaints to include conflict resolution.
Consultation	Procedure for internal and external consultations and involvement of participants in decisions.
Policy and strategy development	Procedure for developing transversal policy or strategy.
Information governance	Data protection, access to information and data sharing. Relevant precautions taken and/or relevant procedures in place should be made transparent.
Risk Management	Approach to risk management; defines risk and how it is assessed and escalated; and roles and responsibilities.
Decision-making bodies and advisory groups	Standing orders and terms of reference for decision-making and the expert advisory groups.
Financial reimbursement of external parties	Procedure and rules for when external parties may be reimbursed for expert contributions to joint work.
External speaking	Speaking about the network, participation in research projects investigating the network, and participation in external events and meetings.
Branding	When can a document or tool be called a 'EUnetHTA' policy, tool, etc.
Authoring and copyright	Defines how participants will be attributed in documents and document access.

Corporate Governance Area	Description of the policy
Decision-making process	Procedure for decision-making by the decision-making body, including how decisions are made, who is involved and how decisions are communicated.

6.4 Recommendations for future work

Further work to define the general rules of transparency/confidentiality/independence/quality system approach and COI approach. Once these general rules have been defined development of corporate governance policies that will guide the cooperation.

Definition of the roles and responsibilities of the decision-making body, the Secretariat and the centralised support services.

Definition of the needed expert groups, with specific consideration of the requirements for:

- Transversal, scientific and methodological expert groups;
- Activity-specific programme expert groups.

Definition of the management structure between the decision-making body, the transversal and activity specific expert groups, the Secretariat and the centralised support services.

Development of the mechanism of decision-making, including:

- Principles for involving HTA agencies in decisions that can affect them;
- How the decision-making body will be assembled, including how expert groups will be represented in the decision-making body;
- How the decision-making body will act and how it will take its decisions;
- Ensuring transparency of all (decision) rules, structures and procedures.

7 TRANSVERSAL: COOPERATION SUPPORT SERVICES

This section discusses the services required to support general HTA cooperation and specific joint HTA activities. These support services include participant management, communications, and IT support, but also elements specific to HTA establishment, e.g. training and implementation, and to the scientific and technical nature of HTA, e.g. information services and science development.

7.1 Summary of JA3 features

Table 7-1: Key documents about cooperation support functions

Key documents	Link
Deliverable 2.4. WP2 Dissemination Final Report.	*Formal EUnetHTA deliverable available via* ec.europa.eu
Update of the EUnetHTA Training Strategy (part of Deliverable 2.4)	*Formal EUnetHTA deliverable available via* ec.europa.eu
EUnetHTA WP7: Deliverable 7.2 - Final Report[6]	Final-Deliverable-7.2-report-after-consultation_FINAL.pdf (eunethta.eu)
Virtual classroom	Available to EUnetHTA partners
Information specialist collaboration in Europe: collaborative methods, processes, and infrastructure through EUnetHTA.	Waffenschmidt S, van Amsterdam-Lunze M, Gomez RI, Rehrmann M, Harboe I, Hausner E (2020). Information specialist collaboration in Europe: collaborative methods, processes, and infrastructure through EUnetHTA. International Journal of Technology Assessment in Health Care 1–6. https://doi.org/10.1017/S0266462320000732

In JA3 some services to support HTA cooperation and WP activities are contained within the coordinating Secretariat, some are managed by WPs and/or HTA agencies leading on a joint HTA activity, and some are managed by a combination of the Secretariat and WPs. For example, communications and IT are managed as part of the Secretariat, but some communications e.g., WP newsletters are circulated by the WP lead producing the newsletter.

Figure 7-1 overleaf illustrates the different support services in JA3 and who manages the different part of the service.

[6] This report includes recommendations for structures to support implementation in a future model of HTA cooperation based on the JA3 experience.

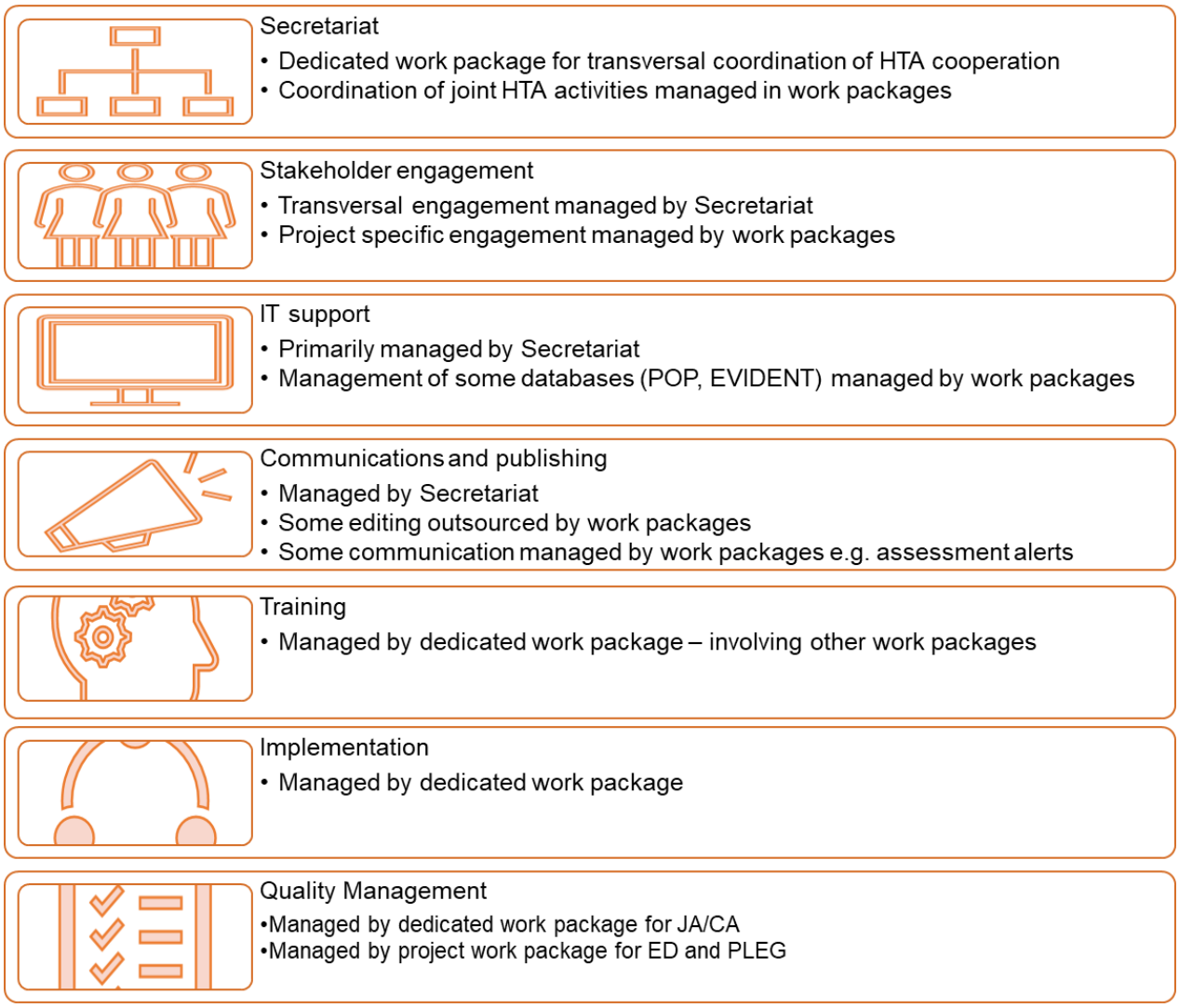


Figure 7-1: Support services in JA3

7.2 Lessons learned

Some services needed to support joint HTA activities have been handled by HTA agencies or WPs. However, these may be more effectively, efficiently and consistently delivered if centralised, because of the need for a harmonised approach and/or the specialised skills. Areas that could benefit from greater centralisation include:

- Stakeholder management and expert engagement: support to identify and engage experts. This support should have a particular focus on patient engagement;
- COI management: support to manage the declarations of interest made by project teams and experts involved in the joint HTA activity;
- Information services: the foundation of HTA is scientific literature, a centralised service to identify, procure and share literature in accordance with copyright law is needed to support scientific rigour;

- Editing and publishing: centralised editing and publishing supports a consistent 'house style' which is important for users of reports;
- Activity coordination: for example, organisation and planning of meetings, liaison with regulators, communication with technology developers, submission of documents for joint HTA activities, collection of input and exchange of documents with participants;
- Quality Management.

HTA is an establishing and evolving scientific field. This means that there is a need for ongoing support in two areas: (1) science development, and (2) capacity development, training and implementation support.

- Science development: to ensure that new areas requiring guidance are identified and guidance developed before they become an issue for joint HTA activities. Existing templates and guidance need to be kept up to date as methods change;
- Training and implementation: HTA is still establishing in some countries and these agencies require access to capacity development, training and implementation support to maximise the benefits from HTA cooperation.

Core services including IT, communications and evaluation should be single, dedicated functions supporting all activities to promote consistency of approach and engagement of participants.

Participants carrying out a joint HTA activity sometimes need hands-on support or advice on methodological aspects, such as information retrieval and statistics. In JA3, two networks, an Information Specialist Network and a Statistical Specialist Network, were set up to meet this need.

7.3 Recommendations for a future model of HTA cooperation

Joint HTA activities would benefit from centralised activity coordination to manage administratively important aspects of the activity (e.g. organisation and planning of meetings, liaison with regulators, communication with developers, submission of evidence, and document sharing).

In addition, HTA cooperation should be supported by a set of centralised, specialised scientific and technical services. These services should be available for all joint HTA activities, supporting consistency in approach and an efficient use of resources (Figure 7-2). For example, in figure 7-2, Information Services is one of the centralised support services. This service would work across all HTA cooperation activities, coordinating the Information Specialist (IS) Expert Network and being responsible for the management of information services (including management of databases/other data sources, reference management systems and screening tools, literature procurement, as well as advising on copyright issues e.g. to support full text sharing between participants working on a joint HTA activity).

Figure 7-2: Centralised support services

Internal participants taking part in decision-making bodies, expert groups and joint HTA activities will have access to information specialists, expert support for methodological issues, and a variety of cooperation support services (Figure 7-3).

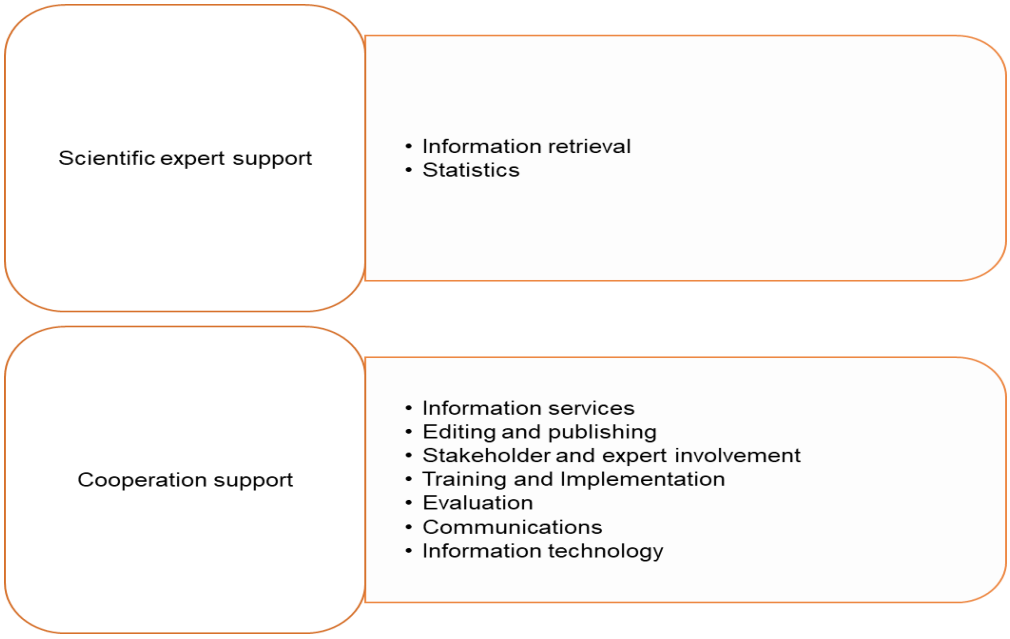


Figure 7-3: Centralised services available to internal participants

Some support services (e.g., capacity development, implementation and science development) need to be put in place early on, as these will primarily support setup of the HTA cooperation. These services may then be reduced in size once HTA cooperation is established and their role becomes one of ongoing maintenance and development. Other support services may start off smaller in size and be scaled up once joint HTA activities start and increase (e.g. expert engagement, information services, editing and publishing).

7.4 Recommendations for future work

Define the roles, remits and scope of each of the support services outlined in Figure 7-2.

Agree how support services will be managed in the cooperation and where they should sit within the management structures to be implemented.

Work with participants in the HTA cooperation to create a timeline for setting up each support service and identify which support services are needed with priority to help set up HTA cooperation.

Define the resources required to run the support services.

8 TRANSVERSAL: INFORMATION TECHNOLOGY

This section discusses the information technology (IT) required to support HTA cooperation and joint HTA activities. Since HTA cooperation operates as an international network, IT represents the main way in which cooperation and joint HTA activities are facilitated.

8.1 Summary of JA3 features

Table 8-1: Key documents about IT

Key documents	Link
Deliverable 6.9 Status report on tools management	*Formal EUnetHTA deliverable available via* ec.europa.eu
IT inventory	*Internal document only: limited circulation*

In JA3 the main IT tool has been the intranet based on Microsoft SharePoint. The SharePoint system supports communication and joint working by providing a:

- Partner contact directory;
- Conflicts of interest database;
- Secure data sharing platform;
- Intranet.

As JA3 has progressed, further functions have been incorporated into SharePoint. By the end of the JA3, the system will also contain databases used for scientific activities e.g. the POP database, EVIDENT, and REQueST.

In addition to the Intranet, EUnetHTA also maintains a website which is created using WordPress and is used to promote the network and its activities.

At the start of JA3, video conferencing used SABA. Difficulties with ensuring SABA worked across the different agency IT capacities meant that in the middle of JA3, SABA was replaced with ZOOM. However, not all participants are allowed to use ZOOM. This meant that by the end of JA3 a mixture of ZOOM and Microsoft Teams was used.

For the each joint HTA activity, the IT tools used are a mixture of:

- Centralised tools e.g. SharePoint is used across all joint HTA activities;
- Tools implemented at a WP level e.g. the quality management system used for JA/CA is contained in a DokuWiki-based online platform called the EUnetHTA Companion Guide;
- Tools implemented at an activity level e.g. tools that support scientific aspects of joint HTA activities (e.g. reference citation software, statistical analysis software) are those used by the HTA agencies involved in the activity.

The IT databases and tools currently managed by EUnetHTA are shown in Table 8-2.

Project management tools have also been developed in an activity specific manner. Work in JA3 to develop a SharePoint tool to manage ED was planned but not possible because of

human resource constraints and the setup of the initial SharePoint environment. This meant that the ED Secretariat had to create an Excel document used for planning each ED and standardised communication templates for use with internal and external participants. In the last year of JA3, the WP5 intranet area was used to assist development of the new SharePoint environment so that the platform will be better suited for creating and implementing the type of functionality needed for the ED Secretariat going forward.

Table 8-2: JA3 IT tools

Infrastructure item	Use in joint HTA activities			Aim of the tool
	ED	JA/CA	PLEG	
Companion Guide		Y		The EUnetHTA Companion Guide is a comprehensive repository that aims to provide ultimate support and guidance for the assessment teams. The tool comprises all components of the EUnetHTA QMS i.e. process flows, standard operating procedures (SOPs), templates, scientific guidance and tools, as well as QM-related training.
REQUEST			Y	A comprehensive resource that covers all important aspects relating to the quality of registries. The standards set out in the tool are universal and essential elements of good practice and evidence quality that are, therefore, relevant for different types of registries. Its purpose is to highlight areas of a registry that need improvement to maximise the quality of its data and ensure that those data can be used for HTA and regulatory purposes
EVIDENT			Y	Sharing and storage of information on requests or recommendations for PLEG made by EUnetHTA partners after the initial HTA. Its goal is to promote the generation of PLEG, reduce redundancy, and facilitate European collaboration.
POP		Y	Y	HTA agencies to share information with each other on planned, ongoing or recently published projects conducted at the individual agency. The aim of the database is to reduce duplication and facilitate collaboration among HTA agencies.
HTA Core model online				This tool has not been used in JA3. Online version of the HTA Core model that supports production of HTA using the HTA Core model framework. When HTA is produced online, it is stored in an HTA collection and the information is searchable by other HTA producers for their use.

8.2 Lessons Learned

To support efficient and sustainable maintenance and further development, databases need to be developed consistently using the same software, programming, and hosting. Having multiple databases that need to be maintained differently creates an administrative IT burden, because each database needs to be maintained by an IT specialist with a different skill set.

The use of multiple databases using different software with related but different functions also affects the usability of the tools. Ease of use is imperative. If tools are not easy to use, participants will be more reluctant to engage in activities and use the tools to provide data important to sustain HTA cooperation.

Different tools should ideally use the same access credentials so that participants do not need to maintain multiple user ID and passwords to access tools.

Between EUnetHTA joint actions there have been gaps when some tools were not maintained or in use. This meant that partners could not enter or access data, and the tools could not be relied on as part of routine work. This also created a catch-up period to bring the databases back up to date. IT tools and databases require ongoing and stable maintenance and hosting to maintain participant engagement and to be useful tools.

Tools used to manage joint HTA activities have not been fully integrated and have been developed separately for different joint HTA activities. There needs to be a robust management tool and database for all joint HTA activities.

In JA3, joint HTA activities have had to rely on participants using their own information retrieval, evidence synthesis, and statistical software and tools. This creates challenges when different participants use different tools and need to collaborate, as tools are not necessarily interoperable. An alignment of software and tools used to carry out joint HTA activities would support better collaboration.

IT infrastructure needs to be maintained and updated to retain its relevance and usability. There needs to be flexibility to change and disinvest in IT infrastructure if it becomes obsolete as collaboration changes, or other more appropriate tools become available.

8.3 Recommendations for a future model of HTA cooperation

IT infrastructure should be guided by the following principles:

- All IT should be managed centrally by an IT support team;
- All IT needs to be based on principles of data security and be legally compliant (for example GDPR);
- To promote efficient maintenance and ease of use, where possible:
    - The approach to IT tool development (for example, software, programming, access) should be aligned;
    - Different IT tools should be integrated to support the smallest number of different tools required for necessary functions;
    - IT tools should be the same across different joint HTA activities.

At an activity level, all joint HTA activities require:

- An activity management tool (or function within a tool) should be implemented across all joint HTA activities to support project management;
- A QMS i.e. the procedural steps, SOPs, checklists, methodological guidance and tools and templates;
- Software, tools and databases that support the scientific aspects of the activity, for example:
    - Bibliographic databases (e.g. Embase, Medline and CENTRAL);
    - Literature screening (e.g. Covidence or EPPI- Reviewer);
    - Reference software (e.g. Endnote, Citavi or Zotero);
    - Data extraction and evidence synthesis (e.g. RevMan or EPPI-Reviewer);
    - Assessment of the evidence (e.g. GRADEPro);
    - Statistical data analysis (e.g., R, SAS, Stata or SPSS);
    - Bayesian analysis (e.g. WinBUGS or OpenBUGS).

Required features of the activity management tool include:

- A workflow solution to monitor each step of the process;
- Secure system for exchange of documents with internal participants in the cooperation and external participants outside of the cooperation;
- Automated process to calculate timelines;
- Database to keep track of project specifics (e.g. acceptance/rejecting teams, time/duration of the different phases, minutes of meetings) to help analyse the process and define future improvements;
- A feature to track, for any technology, the joint HTA activities in which it has been included (to support a joined-up approach to joint HTA activities).

IT tools are also needed for the following transversal aspects:

- Corporate governance:
    - Database to record and manage declarations of interest of internal and external participants.
- Cooperation support:
    - Manage stakeholders, recording involvement, contacts, etc.

IT tools and infrastructure must be subject to a regular review and evaluation to help ensure that they continue to meet HTA needs.

8.4 Recommendations for future work

Assess the feasibility of developing a single integrated IT platform that houses all the needed IT functions. This can build on work started in JA3 using the SharePoint platform, with further integration of other applications e.g. Microsoft Teams.

Development work on the following:

- Feasibility of developing the POP and EVIDENT databases into a single database of HTA topics that can follow the lifecycle of the technology from topic identification and initial HTA, to PLEG;
- Feasibility of integrating the Companion Guide into SharePoint and extension of it to other joint HTA activities (e.g. ED, PLEG) and to transversal HTA cooperation e.g. evaluation and feedback;
- Feasibility of making the information contained in IT databases publicly available to increase transparency of information.
- Feasibility of integrating tools that must be accessed by external participants into the IT platform used by internal participants. For example, the REQueST IT tool is used by internal participants and must also be accessed by external registry holders because they complete the information needed for registry evaluation;
- Feasibility of implementing an authoring and publication tool/platform for JA/CA. The HTA Core model online was developed as an authoring and publishing tool for JA/CA. However, it was not used in JA3 because it was not sufficiently easy to use. Currently, Word templates are used to prepare JA/CA and JA/CA are published as PDFs. There have been difficulties with authors using old versions of the templates and PDFs are not always ideal for readers and users.

Analysis of the software, tools and databases HTA agencies currently use and have expertise in using. This work will show where the software, tools and databases used by HTA agencies are largely in common and where there is significant variation that may require investment in IT tools to harmonise tool use and support efficient working practices.

Development of a transversal activity management tool.

9 ACTIVITY SPECIFIC: TOPIC IDENTIFICATION AND SELECTION

A joint HTA activity starts with the identification of a suitable topic where the joint work will provide value. This section covers topic identification and selection and scheduling of joint HTA activities into a work programme.

9.1 Summary of JA3 features

Table 9-1: Key JA3 topic identification and selection documents

Key documents	Link
Recommendations for Horizon Scanning, Topic Identification, Selection and Prioritisation for European Cooperation on Health Technology Assessment	https://eunethta.eu/wp-content/uploads/2020/04/200305-EUnetHTA-WP4-Deliverable-4.10-TISP-recommendations-final-version-1.pdf
Criteria to select and prioritise health technologies for additional evidence generation	https://eunethta.eu/wp-content/uploads/2019/10/Selection-prioritisation-criteria-1.pdf
ED procedures and guidelines	https://eunethta.eu/services/early-dialogues/

In JA3 topics for joint HTA activities have normally been identified by one of two routes:

- Product owner identified. This route is used for ED, PT JA and PLEG registry projects. A topic is considered if requested by the product owner (e.g. the technology developer or registry holder). These joint HTA activities only go ahead with owner involvement. In PT JA the identification process is supported by a list of prioritised topics (the EUnetHTA prioritisation list) based on HTA agency interest in a compound;
- HTA agency identified. This route is used for OT JA/CA and PLEG product-specific pilots. These joint HTA activities are normally based on proposals received from HTA agencies. These joint HTA activities can go ahead without involvement of the technology developer.

There are also other identification routes for some activities, for example in OT JA/CA, topics can be identified by anyone including patient groups, professional groups, and technology developers. However, these have not been a main source of topics in JA3.

Once a topic has been proposed the approach to topic selection differs between activities, with ED and PLEG using technology criteria for selecting topics and PT and OT JA/CA selecting topics based on agency interest. The final decision on whether a topic is appropriate for joint HTA activity also varies between activities. The decision is sometimes made by working groups, work packages, or work package leads.

In JA3, the only joint HTA activity which has needed an extensive prioritisation process has been ED, where the demand for pharmaceutical ED was greater than the capacity to supply. From the beginning of JA3 selection criteria were applied to restrict ED to innovative technologies. Then, with the increase of the demand, ED prioritisation of topics included defining the maximum capacity and maximum number that could run at any one time, and

additional selection based on whether there are other products recently developed for a similar indication, and whether there has already been an evaluation of a product for a similar indication.

In JA3, the only joint HTA activity that has defined timelines for topic identification has been ED. At the beginning of JA3 the ED topics were identified in batches every month. Later in JA3 this switched to a less frequent open call system. For other joint HTA activities, topic proposers are advised to propose a topic for a JA on a timely basis, e.g. for PT JA topic proposals should be aligned to regulatory timelines so that an assessment can be finalised at publication of the European public assessment report (EPAR) by the EMA.

Table 9-2: JA3 approach to topic identification and selection

	ED	JA PT	JA/CA OT	PLEG (product)	PLEG (registry)
Identification					
Who	Industry	Industry[7]	Normally partners but topics can also be proposed by industry, patient organisations, clinicians, and or other organisations.	Partners in the PLEG task force (designated as leads and activity centres in the work package).	Registry holder[8]
How	Application for ED following a call for applications	EUnetHTA prioritisation list Letter of intent to submit	Topic proposal	Topic proposal	Application
When	Open call (2 x per year)	Ad-hoc	Ad-hoc	Ad-hoc	Ad-hoc
Selection					
Actor making the decision to proceed	Early Dialogues Working Party (EDWP). The decision is taken with a simple majority of the votes cast by the members of the EDWP.	WP Co-Lead partner based on sufficient interest from partners, sometimes in discussion with the Lead partner and Executive Board.		Primary selection by partners in the PLEG task force. Final selection by WP5 partners at their annual meeting.	Partners in the PLEG task force
How	Against criteria	Call for collaboration		Against criteria and partner interest in call for collaboration	

[7] Topics could be proposed by other organisations, but acting upon topic suggestions from other organisations was contingent on technology developers then agreeing to submit for the PT JA.
[8] In JA3 PLEG registry pilots were identified by registry holders, but in a future model of HTA cooperation, proposals could come from a variety of sources including industry and patient organisations

	ED	JA PT	JA/CA OT	PLEG (product)	PLEG (registry)
Technology related selection criteria	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).	None – based on topic interest		Secondary criteria (applied after research applicability eligibility criteria) 1. Burden of target disease. 2. Expected benefit of the technology (on the burden of disease/on the management of 3. Disease/economic benefit/organisational/social benefit). 4. Potential of the technology to cover unmet health care needs or to substantially improve 5. The health care compared to existing alternatives. 6. Importance of additional evidence generation for confirming expected benefit and for monitoring/optimising conditions of use.	

9.2 Lessons learned

Some HTA agencies respond to requests from decision-makers or applications for HTA rather than proactively identifying topics. This means that joint HTA activities should not rely only on topic proposals from participants in the HTA cooperation, and participants will not always be able to indicate the importance of a particular topic.

Topic selection and scheduling ideally needs to link to the launch plans for the health technology. If a health technology will only be launched in a small number of countries or launch will be staggered over a long time period, this can affect the number of countries that can benefit from the joint HTA activity and for JA/CA whether it will still be up to date when an HTA agency needs it.

For OT, there are few lists of relevant topics for sharing voluntarily and these are not comprehensive. For OT, timeliness of technology readiness for JA/CA is difficult to predict because there is no regulatory anchor and variable routes to market.

For PT JA, it is necessary to align assessments with timelines for marketing authorisation and HTA decision-making. This is often not possible if relying on published information or information from participants in the cooperation. Early and timely identification and sharing of relevant topics by regulators has been limited by the framework governing EUnetHTA JA3, and information being considered commercially sensitive or shared with participants in the cooperation confidentially.

Although topics for ED are identified by the technology developer, the timing of ED is very sensitive. EDs on pivotal trials can only take place before the clinical evaluation for reimbursement, and only if the pivotal clinical trial has not yet begun. Additionally, an ED could also be considered if changes in the study protocol are foreseen which could affect HTA needs. Therefore, EDs would also benefit from proactive early (relative to technology readiness) identification so that, for topics likely to be of importance to HTA, there can be proactive outreach if necessary.

PLEG pilots are identified after HTA has been carried out. This was too late for many participants in the cooperation to be involved, but also too late to allow for exchanges with external stakeholders. Ideally, the identification of potential PLEG topics should be more proactive and start prior to marketing approval. Proactive identification of topics would focus on identifying products where there are likely to be evidence gaps requiring evidence generation, so that joint PLEG activities can be put in place early on.

There need to be clear eligibility and prioritisation criteria for joint HTA activities. Technology developers need to be able to predict which topics will be eligible for joint HTA activities so that joint HTA activities can be scheduled into product development. Users of the outputs of joint HTA activities need to know the topics that will be subject to a joint HTA activity so they can plan to use the output.

For ED, an open call system for topic identification is recommended because it allows for better resource allocation. However, this system requires additional preparation up front, and requires a clear understanding in advance of the resources in participating HTA agencies to calculate how many EDs can be accepted for a given call period.

Initially, PT JA relied on voluntary initiation by technology developers. Voluntary initiation did not lead to sufficient topics for PT JA. As the JA3 progressed an active acquisition process was implemented. This process resulted in a list of priority topics (the EUnetHTA prioritisation list). There was then proactive reaching out to technology developers to ask for their submission of compounds on the priority list.

For MD ED, there has been less demand than expected. Strategies to reach out to technology developers and communicate the service may be needed to increase uptake.

9.3 Recommendations for a future model of HTA cooperation

A topic identification system is required to identify in advance which topics are coming and will benefit from joint HTA activities.

One aim of the topic identification system should be to identify health technologies or technological advances where joint HTA activity along the life cycle is likely to be relevant, so that there is early identification of topics that are likely to be important to joint HTA activity (e.g. topics where it is likely to be appropriate to undertake ED, JA and PLEG). For this reason, all topics proposed for joint HTA activities should be triaged into a single identification system so that they can be followed up for joint HTA activities along their lifecycle.

The exact nature of the topic identification system will depend on the features of a future model of HTA cooperation, in particular:

- Whether all or only a selection of health technologies of a particular type is assessed – if only a selection is assessed, prioritisation becomes a very important process;

- The nature of the health technologies to be assessed – different approaches are needed for PT and for OT because of the differences in regulatory processes and access pathways;
- How far in advance the system needs to operate – very early identification can require a different identification strategy.

The topic identification system should use both proactive (e.g. a range of predefined sources are searched for information) and reactive (e.g. open to proposals from HTA agencies and stakeholders) approaches for topic identification. For any type of joint HTA activity, topic proposals can come via either proactive or reactive approaches. However, for different joint HTA activities topics may be more likely to come via a certain route.

Topic identification should be guided by a transparent set of criteria that define the types of topics suitable for joint HTA activities.

There are existing horizon scanning initiatives and organisations that undertake horizon scanning. Collaborations with these initiatives and organisations are recommended rather than developing a new function. For example, PT topics may be efficiently identified via collaboration with the EMA.

The topic identification system needs to include a communication plan so that stakeholders less familiar with HTA cooperation know how topics are identified, how topics can be proposed and when topic identification will be timely for joint HTA activities.

Criteria should be used to select and prioritise the topics for joint HTA activities from the identified topics. Where possible, criteria should be aligned across activities to promote a lifecycle approach to technology assessment. Criteria should be as objective as possible to allow companies to predict which products are likely to be eligible for joint HTA activities and plan accordingly.

Decisions to select topics should be overseen by a decision-making group as part of the planning cycle for the work programme of joint HTA activities.

Scheduling of topics needs to support planning by technology developers and use by HTA agencies and decision-makers. The schedule of topics needs to be transparent and communicated in advance of work starting to the technology developer and expected users. There needs to be sufficient flexibility in the scheduling and work allocation to be able to manage regulatory delays and short notice emergencies that may arise.

Where there is selection and prioritisation of topics from those identified, positive and negative selection decisions with reasons should be communicated in a timely manner to stakeholders and participants to ensure that products are able to move back to national or single agency processes in a smooth and timely manner.

The overarching topic selection process is described below in Figure 9-1.

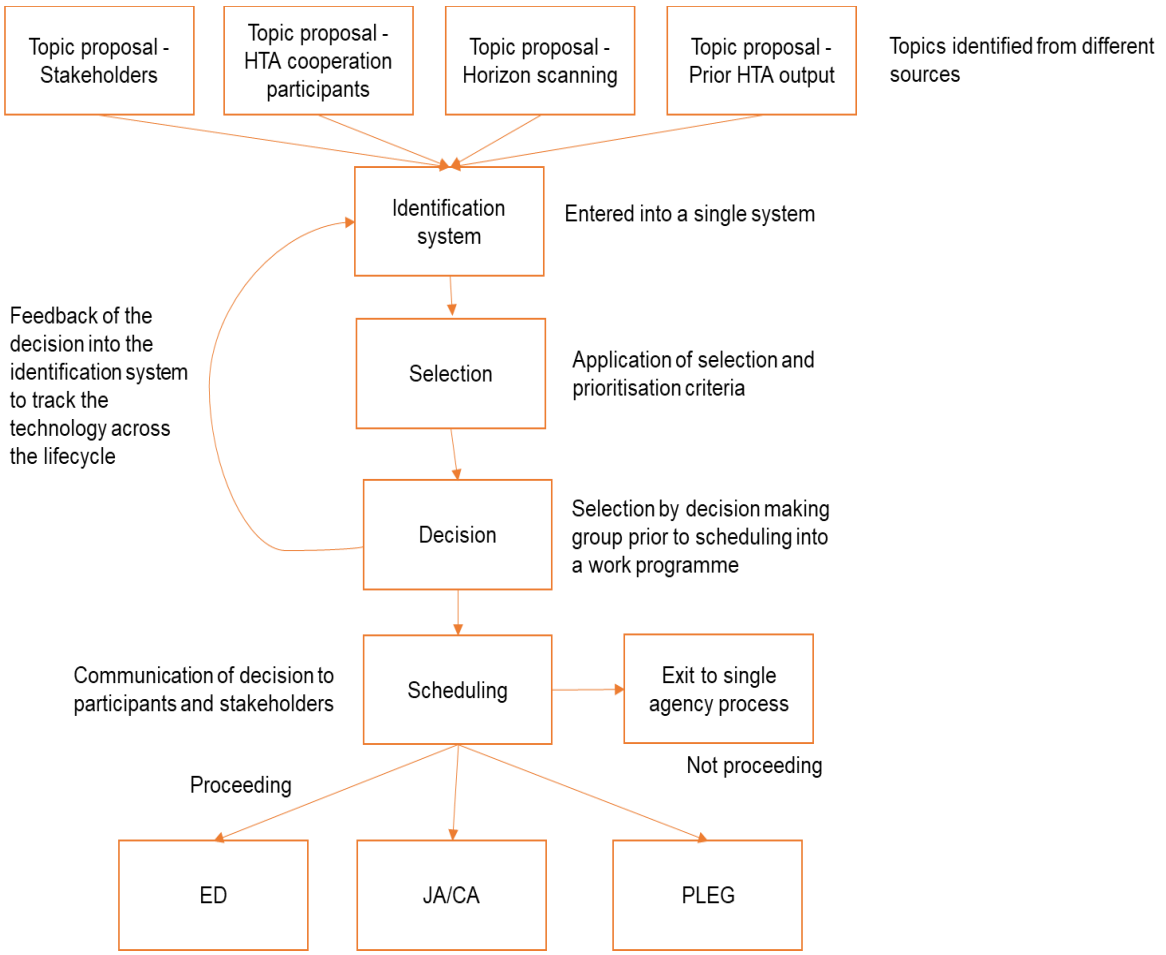


Figure 9-1: Proposal for a topic selection process

9.4 Recommendations for future work

Develop a transversal topic identification procedure and infrastructure to support the procedure. The following elements are noted as requiring specific development work:

- Legal framework to ensure that appropriate confidentiality frameworks can be put in place to facilitate data exchange;
- Establishing formal relationships with organisations undertaking horizon scanning (such as the IHSI) in order to support proactive identification of topics;
- Further collaboration with medical device (MD) regulators to identify mechanisms that allow for timely identification of MD topics for joint HTA activities;
- Further collaboration with the EMA to support timely pharmaceutical identification;
- Development of the appropriate IT platform to manage the identification and selection process and support timely communication about the decision to select;
- Criteria for selection, prioritisation, and resource allocation;
- Rules and procedures for managing reactive and emergency topic requests.

10 ACTIVITY SPECIFIC: OUTPUTS AND CONTENTS

This section discusses the nature of the joint HTA outputs and their contents.

10.1 Summary of JA3 features

Table 10-1: Key JA3 documents describing the outputs of HTA activities

Key documents	Link
Output of the PICO subgroup	Available to EUnetHTA partners in the Companion Guide and now also a FAQ is published: http://eunethta.eu/pico
Output from common phrases and GRADE group	https://www.eunethta.eu/grade/
JA/CA Assessment report templates, submission dossier templates and Plain Language Summary	Available in the Companion Guide - for pharma: https://companionguide.eunethta.be/doku.php?id=pharma:templates - for OT: https://companionguide.eunethta.be/doku.php?id=ot:templates
PLEG templates	*Limited circulation: PLEG templates are in development following the pilots and currently available for WP5 partners on the Intranet*
ED templates	https://eunethta.eu/services/early-dialogues/parallel-consultations/ https://eunethta.eu/services/early-dialogues/multi-hta/
Outputs from submission dossier and assessment report subgroup	https://www.eunethta.eu/services/submission-guidelines/submission-template-pharmaceuticals-submission-template-medical-devices/
Evidence gaps report used in JA/CA to inform PLEG	Available to EUnetHTA partners in the Companion Guide

In JA3 the output of each joint HTA activity is a document, the content and target audience of which varies depending on the activity. For ED and PLEG registry pilots the document is a set of recommendations and the target audience of the output is the product owner e.g. the technology developer or the registry holder. For JA/CA the document is an assessment report, and the target audience of the output are HTA agencies carrying out work in the topic area. In addition, JA/CA have piloted the use of plain language summaries for their assessment reports to make the reports more accessible to a broader audience. For PLEG product pilots the document is a data analysis, and the target audience is the group of HTA agencies who have agreed to collaborate in the evidence generation exercise.

The publication status of the documents varies between activities. ED recommendations are confidential because they are carried out at a time in product development when information is commercially sensitive. For PLEG registry pilots carried out with the EMA, EUnetHTA applies the same document publication status as the EMA. All other outputs are publicly available, including for PT JA the core company evidence submission.

JA3 has started to create links between the joint HTA activities. A JA/CA explicitly describes the evidence gaps identified to inform PLEG. There is no reciprocal link between ED and JA/CA because of challenges with the confidentiality status of the ED recommendations and there are no dedicated procedures for updating outputs from JA/CA in light of any further evidence generated.

Table 10-2: Output characteristics of JA3 HTA activities

	ED	PT JA	OT JA/CA	PLEG (product)	PLEG (registry)
Key stages of the preparation process	Discussion of issues by the HTA agencies. Development of HTA positions and recommendations Reviewing and editing.	Creation of the assessment (scoping, information retrieval, data extraction, risk of bias, data analysis), expert input, reviewing, editing.		Jointly defined requirements from PLEG pilots serve as the basis for the national data collection. Common data (from different jurisdictions) are shared, compiled and analysed.	Discussion of issues by the HTA agencies. Development of HTA positions and recommendations.
Nature of the output	Report	Project Plan (including PICO) Assessment Report Plain Language Summary		Evidence gaps report Common data set Final report	Report
Content of the output	Consolidated recommendations	An assessment aligned to PICO in the project plan, covering aspects of REA, Health condition, Technology, Clinical effectiveness and Safety.		Compilation of common (aggregate) data from pilot participants (whenever possible). Analysis of common (aggregate) data (whenever possible).	Recommendations from participating agencies on the discussed aspects (variables collected, data quality).
Supporting documents made available	-	Company evidence submission (without appendices). Fact check comments and responses. Expert comments received and responses.		-	-
Status of the output	Non-binding	Non-binding		Non-binding	Non-binding
Main audience of the final output	The product owner (usually a company/manufacturer)	HTA agencies and decision makers		HTA agencies	The product owner (the registry owner)

	ED	PT JA	OT JA/CA	PLEG (product)	PLEG (registry)
Availability	Confidential	Public		Public	For PLEG pilots carried out with the EMA a summary of the recommendations is made public For PLEG pilots with HTA bodies only – recommendations are publicly accessible

10.2 Lessons learned

The outputs of joint HTA activities can present a consensus position. However, it is necessary to allow for flexibility in the output to present individual HTA agency perspectives where there are nuanced positions or disagreements.

There are different perspectives among HTA agencies on principles of confidentiality and whether the outputs of joint HTA activities can be kept confidential. EDs can only proceed if they are kept confidential, because they are carried out at a time that is commercially sensitive to technology developers. However, this absence of transparency and accountability is not acceptable to all HTA agencies and stakeholder groups.

Currently, there is neither sufficient experience of EDs nor sufficient alignment in the methodological approach to JA to produce a generic advice output for specific therapeutic areas that represent common scientific advice from HTA agencies. However, such generic advice may be possible in the future as experience and alignment grows.

For outputs of joint HTA activities expected to inform decision making, the documents that support the development of the output (e.g. the evidence submission from the technology developer) need to be made available to users in full without removing any information. This is required for transparency and to support accountability for decisions made using the output.

For outputs of joint HTA activities expected to inform decision making, the appropriate content must be negotiated between the expected users of the output. What is considered appropriate content depends on a variety of factors including:

- The remit of the user and where the user draws the boundary between assessment and appraisal;
- Whether the user wants to use the joint HTA output to replace their report or to use the content of the joint HTA output to develop their own report (that is, adoption versus adaptation);
- Whether the user is responsible for producing a written detailed technical analysis or a summarising document based on their analysis;
- The legal status of the decision and the documentation.

Some aspects of HTA are context-dependent and must be presented objectively to allow for local contextualisation. Areas less dependent on context include risk of bias, inconsistency of evidence, and indirectness where this relates to the assessment of an indirect comparison.

For PLEG product pilots there were issues encountered during the pilots associated with differing infrastructure, data access, and ability to share data that affected the ability to produce outputs from the pilot. Further work is needed to promote good practices in databases to allow PLEG activities to be undertaken in a fully efficient and informative manner.

HTA agencies make use of reports over a number of years depending on when technology developers choose to launch their products and HTA agencies start assessments. The ongoing accrual of evidence over this time means that a JA/CA can be out of date by the time an HTA agency wishes to use it. Procedures for ensuring reports are up to date are needed so that reports are fully informative. However, if not put in place carefully, review procedures can become overwhelming and consume significant resources.

10.3 Recommendations for a future model of HTA cooperation

The outputs developed in JA3 provide a basis for a future model of HTA cooperation.

Whilst REA forms a basis for JA/CA, HTA is a broader activity than just REA encompassing economic, organisational, social, legal and ethical aspects. HTA cooperation in these aspects should be supported where these will add value to participants.

Joint HTA activities should always work towards a consensus position rather than a per agency perspective. However, procedures and templates should ensure enough flexibility of approach to allow for individual agency perspectives to be added.

Recognising the different perspectives from HTA agencies on the confidentiality status of EDs, JA3 has reached a position between HTA agencies that to improve the transparency of the ED recommendations, ED recommendations should be shared with the JA/CA team and be part of the evidence submission for JA/CA. Likewise, JA/CA should include an analysis of identified evidence gaps to be used in PLEG (Figure 10-1).

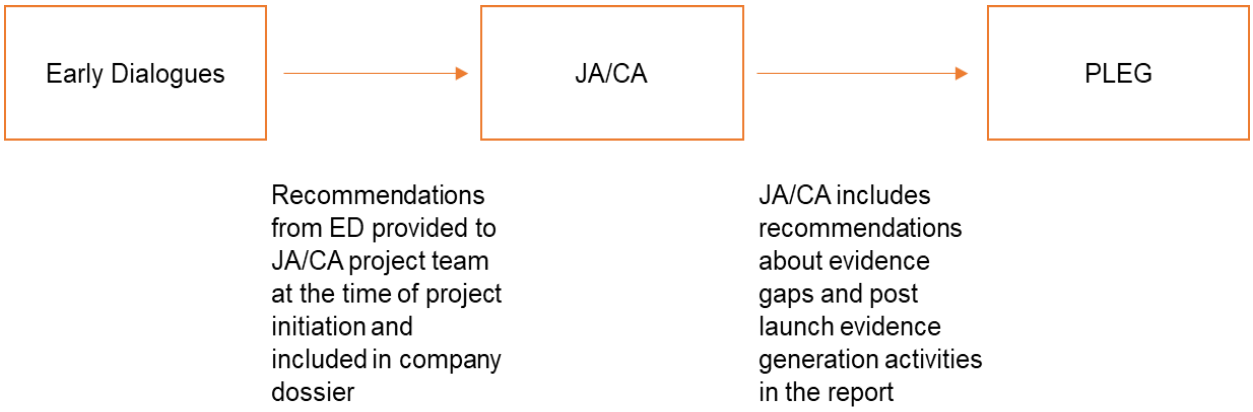


Figure 10-1: Links between the outputs of joint HTA activities

For JA/CA there needs to be guidance available for users on the role that local contextualisation is expected to play when interpreting the output, and where local contextualisation may be needed (Figure 10-2).

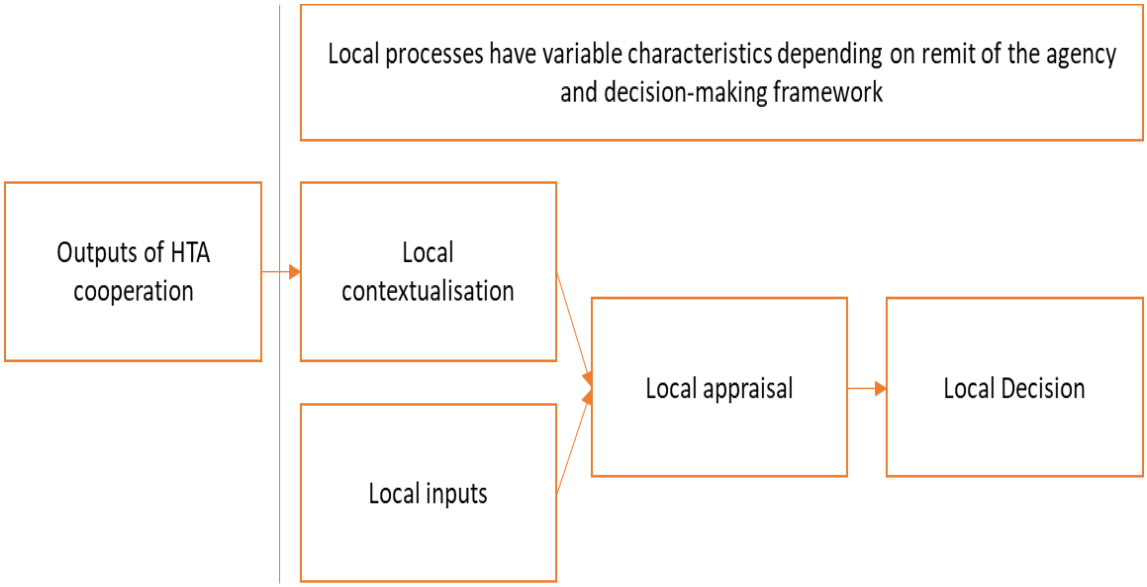


Figure 10-2: Role of the outputs from joint HTA activities in decision-making processes

The JA/CA should be made available to the public. An open repository should be used to store all JA/CA.

Documents that support the assessment (e.g. the evidence submission from the technology developer) should be published and all data available to users of the report.

There needs to be a procedure to monitor whether assessments might need updating. Such a procedure is necessary to manage the risks of assessments with out-of-date content being used to inform decision making.

Updating of JA/CA should not be automatic, as the need to update is influenced by a number of factors and is not always of value to decision-makers. Instead:

- The authors of the JA/CA should indicate, based on the evidence available, if there is likely to be a need to review the JA/CA, and if so, when the JA/CA should be considered for review;
- Users should also have the option of being able to request that a JA/CA is considered for review;
- Requests to consider a JA/CA for review should be graded against a set of criteria and be subject to review with other potential users;
- The grading and review should inform a decision about whether an update as a joint HTA activity will be a good use of resources, or if the update should be prepared in a single HTA agency process with sharing to other interested HTA agencies;
- The update process should link to the topic identification and selection process and annual work planning.

10.4 Recommendations for future work

Using the recommendations from the EUnetHTA JA3 subgroups (1) PICO subgroup, (2) the common phrase subgroup and (3) the submission dossier and assessment report template

subgroup continue the process of reaching a consensus agreement on the appropriate level of depth and content for JA/CA.

For outputs of joint HTA activities to be used by HTA agencies, consider whether a procedure can be implemented that allows for HTA agency input into the draft output in a way that supports timeliness and resourcing of the production process.

JA3 started work to develop plain language summaries to improve the accessibility of the outputs from JA/CA. Work to develop these summaries should continue.

Develop the procedural steps for a monitoring and reassessment process for JA/CA.

For PLEG, further develop national and international good practices for databases to promote and help establish joint PLEG activities. Including:

- Data sharing arrangements: competencies, methods and legal basis;
- Participation and collaboration between regulators and HTA agencies in existing or new EU database projects.

For PLEG, further work to consider the recommended outputs from joint PLEG activities and appropriate timing for topic identification, including whether possible PLEG topics can be identified at the stage of ED to set up PLEG strategies for topics that are likely to become targets for PLEG.

11 ACTIVITY-SPECIFIC: PROJECT TEAMS

Once a topic has been identified a group of people (that is a project team) must be constituted to carry out the work involved in the joint HTA activity. This section summarises how internal participants are selected and included in joint HTA activities.

11.1 Summary of JA3 approach

Table 11-1: Key JA3 documents about internal participation

Key documents	Link
SOP: Call for Collaboration and Formation of Assessment Team	Available for EUnetHTA partners in the Companion Guide Separate versions for PT and OT
Early Dialogues financing mechanism framework	*Internal document only: limited circulation*
Recommendations for future production processes	https://www.eunethta.eu/wp-content/uploads/2021/06/Recommendations-for-production-process-after-Joint-Action-3_WP4_May-2021.pdf

The vocabulary used to describe internal participation differs between joint HTA activities, but there is a broadly consistent structure and characteristics of the project team carrying out the scientific and technical work of a joint HTA activity including:

- 2-3 HTA agencies who lead and take on the authoring role;
- A wider group of HTA agencies who provide input and review documents.

There are two major differences:

- PLEG product pilots have been led by a single HTA agency;
- ED includes an oversight group (the EDWP) which does not exist in the other activities.

ED was initially launched using a procedure where all participants in the project team wrote responses and a scientific coordinator and rapporteur consolidated them into a single document. This approach was very resource intensive. The procedure was revised so that the scientific coordinator and rapporteur provide the responses and other participants in the project team act as reviewers. The project team made up of the scientific coordinator, rapporteur, and other participants is called the Early Dialogues Committee (EDC). This created a similar internal participation structure to that used in JA/CA and also facilitated the interface with EMA reviewers in ED Parallel Consultations.

The criteria for participation vary across activities. Criteria are most comprehensive for JA/CA. Both JA/CA and ED include criteria about the experience of the authors.

Internal participants outside of the project team are involved in the early stages of a joint HTA activity to identify if a topic is of interest, and in PT JA to support the process of scoping to identify the PICO elements that meet the needs of multiple HTA agencies. The differences in participation at this stage reflects that PT JA aims to meet the needs of multiple HTA agencies, not all of whom are involved in the project team, whereas ED and PLEG activities have a different and smaller audience.

The resources required for each joint HTA activity vary:

- The workload for PT JA is about 60 person days for authors, 40 person days for co-authors, and 3-5 person days for dedicated reviewer;
- The workload for OT JA/CA, is about 80 person days for authors, 25 person days for co-authors, and 5 person days for dedicated reviewers;
- The workload for ED is about 16 person days for scientific coordinator, 12 person days for rapporteur, and 7 person days for reviewers.

Table 11-2: Internal participation in JA3 activities

	ED	JA PT	JA/CA OT	PLEG (product)	PLEG (registry)
Project team	1 scientific coordinator 1 rapporteur EDWP EDC (EDWP + other HTA agencies participating)	1 author 1-2 co-author(s) 2-4 dedicated reviewers observer(s) (optional)		1 HTA agency acting as activity lead or coordinator. Other HTA agencies providing input and review observer(s) (optional).	
Recruitment	Scientific coordinator and rapporteur selected from the EDWP (voluntary). Voluntary involvement of HTA agencies outside of the EDWP – via call for collaboration.	Call for collaboration – voluntary involvement		Call for collaboration – voluntary involvement	
Key Criteria	Scientific coordinator and rapporteur are members of the EDWP with experience of ED. • Availability in timelines • No conflict of interest	• Availability in timelines • No conflict of interest • Knowledge of the disease area • Knowledge, understanding and experience of procedures • One author and reviewer must be an information specialist • One author and reviewer must have statistical skills • Commitment to use report in national setting • Geographical representation across Europe		• HTA agencies • Able to use any data collected by the pilot in reassessment	Members of WP5B willing to participate

	ED	JA PT	JA/CA OT	PLEG (product)	PLEG (registry)
Other internal participation	Additionally, and until the prolongation period, when an ED was accepted all WP5A partners were informed and invited to respond to a call for participation.	WP partners indicate interest and relevance of topic during the call for collaboration. For PT, partners are surveyed as part of project planning to gather feedback on the appropriate PICO to meet partner needs. Expert input in projects via the statistical and information specialists' networks Partner consultation in some guideline documents e.g., TISP, recommendations for production processes		WP5B working group who were regularly informed on PLEG pilots and were systematically invited to review PLEG procedures and guidelines and to participate in pilots.	

11.2 Lessons learned

Between JA2 and JA3 the participation in JA/CA was refined to include smaller project teams. The reduction in the number of participants supports a more efficient and timely production approach without loss of input. Significant concerns about this change have not been raised by internal participants in JA3.

For ED, it is possible for reports to be prepared using an author and co-author approach like in JA/CA. Alignment between the project team is generally achieved. However, it is important to maintain the possibility for each member of the project team to add their own nuances to the final report based on national requirements.

There have been difficulties in recruiting project teams in both PT JA, ED, and PLEG. This has meant that recruitment procedures have in some cases been drawn out and/or joint HTA activities not carried out because of staffing challenges rather than because of a lack of financial resources or interest. The main reasons for this are:

- Lack of human resources and staff capacity in HTA agencies;
- HTA agencies unable to allocate staff a long time in advance or if insufficient notice is given or timelines change;
- Some HTA agencies are only able to commit to joint HTA activities where these are aligned to national regulations and requests from decision-makers;
- Joint HTA activities can require more work than the same national activity.

For JA/CA several other exacerbating factors were also identified:

- Lack of methodological clarity (e.g. missing methodological guidance or standpoint on defining the PICO and advanced statistical methods);
- Complex procedures with many different steps.

It is necessary to have clear criteria to select members of a project team. However, experience has shown that not all HTA agencies have full access to the specialist statistical and information retrieval skills required for joint HTA activities. Instead of rejecting participants from these agencies, it is better to be able to support them with expert groups that can be consulted by project teams when they do not have access to the methodological expertise required for a joint HTA activity. Areas where experts may be needed to support project teams are information retrieval and statistics. The JA3 experience is that these expert groups can be constituted from the pool of internal participants in the HTA cooperation.

There are differing opinions about whether the same person can work on multiple joint HTA activities of the same health technology, notably EDs and JA/CAs. In some HTA agencies the same person cannot work on both, while in other HTA agencies the opposite is true. Within JA3 there was no agreement on this issue. If the person working on different joint HTA activities of the same health technology needs to be different then this will need to be taken into account when considering capacity for joint HTA activities.

The demand from PT technology developers for ED has been greater than the available capacity within HTA agencies. Although, HTA agencies consider ED to be a very important joint HTA activity, they are not always able to take part. Additional financial resources may

help create additional capacity for ED in some cases, but only if the limiting factor is not governed by the ability of HTA agencies to recruit and retain staff.

JA3 established that a fee-for-service system is viable for ED and a framework was developed. However, it could not be piloted during JA3 due to the lack of a participant to perform the role of the Secretariat for the financing mechanism. If a fee-for-service mechanism is required to create a sustainable model, then a legal framework (i.e. a joint action, or a contract such as was used to create SEED or a European Regulation) is required.

11.3 Recommendations for a future model of HTA cooperation

HTA cooperation relies on internal participants to carry out joint work.

- There should be a formal commitment from HTA agencies taking part in the HTA cooperation to undertake activities as part of work programme planning.

In return, HTA agencies must be able to rely on:

- Funding at a level commensurate with the resources required;
- Timelines that take into account the amount work required;
- Planning processes that allow HTA agencies to know in advance when work is required.

The JA3 experience using small project teams has worked well. For joint HTA activities a common structure of a project lead (who authors the output), co-lead (who supports the authoring), and wider project team (who take a smaller role providing input, discussion and review) can be applied (Figure 11-1).

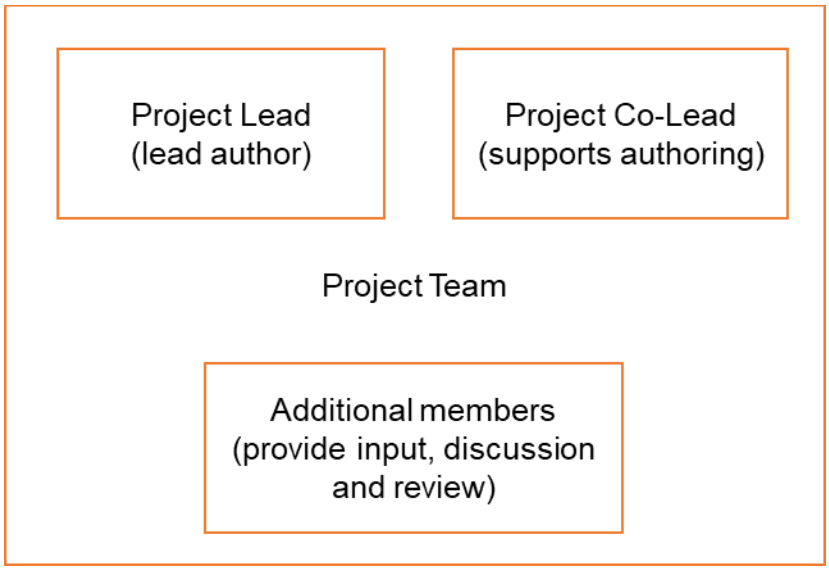


Figure 11-1: Proposed scientific project team

Each project team must have relevant skills and experience to carry out the joint HTA activity. For all activities, selection criteria in terms of skills and experience should be available. The procedure for selecting participants should be transparent, so it is understood how the skills of team members are evaluated and by whom.

To be sustainable, HTA cooperation must always ensure that the pool of HTA agencies available for joint HTA activities is sufficiently large. To support sustainability there should be:

- A programme of ongoing training on methodology and procedure across all joint HTA activities to ensure that pools of expertise are expanded and maintained.
- Participation in joint HTA activities as observers and on advisory bodies to support up-skilling of participants to take on greater responsibilities.

11.4 Recommendations for future work

A piece of work to gather insight into existing HTA agency capacity and scientific and technical skills. Analysis of the staff available to support HTA cooperation and major gaps in human resources and scientific knowledge.

Training and capacity development programme that fills the gaps identified.

Definition of a model for commissioning and allocating joint HTA activities that ensures that project teams are available when required.

If required to ensure a sustainable model of HTA cooperation, implementation of the Early Dialogue fee-for-service mechanism.

A guideline outlining the criteria and procedure for establishing project teams and the distribution of roles and levels of responsibility. These should be guided by accredited scientific capabilities; in such a way that it is skills, rather than belonging to a certain agency or country, that would guide the formation of project teams and project leads.

12 ACTIVITY-SPECIFIC: ACTIVITY MANAGEMENT

A joint HTA activity must be managed appropriately to ensure a robust and timely output. This section considers how specific activities of the cooperation should be managed.

12.1 Summary of JA3 approach

Table 12-1: Key JA3 documents describing activity management

Key documents	Link
Consensus Procedure	Available to EUnetHTA partners in the Companion Guide
The Concept Paper for Quality Management (Deliverable D6.1)	https://ec.europa.eu/research/participants/documents/downloadPublic?documentIds=080166e5b81d509e&appId=PPGMS
Recommendations for future production processes	https://www.eunethta.eu/wp-content/uploads/2021/06/Recommendations-for-production-process-after-Joint-Action-3_WP4_May-2021.pdf
Internal procedure manuals for project managers	*Internal document only: limited circulation*
SOPs for project managers	Multiple SOPs available to EUnetHTA partners in the Companion Guide

In JA3, all joint HTA activities have had dedicated project management support. Two approaches to project management have been used:

- Centralised project management used for PT and OT JA, ED and PLEG registry pilots;
- Decentralised project management with oversight from a coordinating HTA agency used for OT CA and PLEG product pilots.

Project managers use activity specific SOPs and have dedicated project management materials.

Scientific oversight is provided differently across joint HTA activities. For ED, it is provided by a standing group, the EDWP and the ED Secretariat. For JA/CA, scientific oversight is primarily provided by the quality management system and the procedures, templates and methods guidelines. For ED, the EDWP also approves the final output for each ED.

Conflict resolution (both conflicts between internal participants and between internal and external participants) is managed differently across joint HTA activities. All project teams work towards consensus agreement. However, where consensus cannot be reached, JA/CA use support for conflict resolution from a senior scientific officer within the Secretariat and the WP lead. ED and PLEG instead rely on resources within the WP to manage conflict using the EDWP and the ED and PLEG Secretariats to negotiate through the conflict. For all joint HTA activities conflicts can be escalated to the Executive Board if considered necessary by the WP lead.

Within the framework of EUnetHTA JA3, the final accountability for the output from the joint HTA activity has rested with the authors, without any centralised approval processes.

Table 12-2: Activity management of JA3 outputs

	ED	JA PT/OT	CA OT	PLEG (product)	PLEG (registry)
Project coordination	Centralised ED Secretariat	Centralised project management	Centralised global coordination Decentralised activity management	Centralised global coordination Decentralised activity management	Centralised project management
Transparency of project participants	Public list of members of the EDWP	Public list of HTA agencies involved		Public list of HTA agencies involved	
Decision-making approach	Consensus joint position of participating HTA agencies, when applicable, or individual positions of each HTA agency, when a joint position cannot be reached.	Consensus Where consensus is reached, a final consensus opinion is presented. Where consensus cannot be reached individual positions can be presented.		Consensus Where consensus is reached a final consensus opinion is presented. Where necessary, individual positions will be presented.	
Conflict resolution	Escalation to EDWP	Escalation to senior scientific officer. Final decision by the senior scientific officer if agreement cannot be reached. If the senior scientific officer is not available, then the WP lead partner will be involved.		Project Lead agency	Scientific Coordinator
Accountability of output	Scientific Coordinator	Authoring agency		Project lead agency	Participating HTA agencies

12.2 Lessons learned

Each joint HTA activity requires a single point of contact for activity management. This promotes best possible engagement of internal and external participants. A secondary contact is needed to oversee the activity when the main point of contact is away or unavailable.

Project management should be predictable and guarantee fairness of procedure. Therefore, it needs to be conducted according to standardised processes and requires procedures, manuals, templates and tools. There needs to be frequent communication between project managers.

Activity management includes not only project management but also tasks requiring scientific skills and judgement. For ED, the ED Secretariat identified that they needed to carry out the following scientific tasks:

- Assess eligibility of requests for ED based on EDWP feedback;
- Checking the quality of the output (at each step of the ED process);
- Coordination with EMA in the case of parallel consultations;
- Evaluating the areas with final consensus and identifying areas of divergence to establish rules to apply to the situation(s);
- Training of new participants in the ED process.

HTA involves making scientific judgements and decisions. Judgements have subjective elements and different participants can make judgements differently. Transparent procedures need to be in place for managing conflicts and when to escalate these.

Where accountability rests with the final authors of the output, this can mean that the authors need to follow guidance from their own HTA agency, which differs across HTA agencies. A framework that enables the HTA cooperation to approve and to be accountable for its outputs is required to ensure robust outputs and to maximise output consistency.

12.3 Recommendations for a future model of HTA cooperation

As part of activity management, each joint HTA activity (Figure 12-1) should have:

- Dedicated project management that is responsible for managing the activity using standardised tools and procedures;
- Oversight from a standing group of programme experts to ensure that scientific judgements made by project teams are made consistently;
- Access to an independent conflict resolution service that can manage disagreements between project teams;
- Guidance from a service outside of the project team that manages conflicts of interest and other corporate governance aspects;
- Approval of the final output from a decision-making group.

It is important that experts and services providing guidance and approval are involved early in the process from the planning stages so that issues that could affect approval are identified in a timely manner and can be resolved without creating process delays.

The exact configuration of activity management structures is sensitive to the number of outputs to be produced and the nature of the people involved in each HTA cooperation structure. For example, scientific oversight requires technical experts who may or may not be the same group of people who can also approve the output from the joint HTA activity. In addition, people may perform more than one function when the number of outputs to be produced is low, but the workload from having to perform multiple functions becomes unmanageable as the number of outputs increases.

Procedures used to manage different joint HTA activities should be consistent with a rationale for any differences. Principles of activity management that need to be defined include:

- How decisions affecting a broad group of participants should be made, including when internal and external participants should be consulted on a decision.
- Monitoring procedures to ensure joint HTA activities keep to remit, budget and timelines. Monitoring procedures need to be proportional to take account of the strategic value of the joint HTA activity and degree of risk. Procedures need to include actions to be taken where joint HTA activities do not keep to remit, budget or timelines.
- Risk management to support project teams and decision-making bodies to know when to escalate and steps to be taken to manage risk.
- Procedures for resolving conflicts between internal and external participants in the HTA cooperation. These need to be transparent and independent so that procedures are not perceived to be influenced in a particular direction.
- A mitigation procedure to be applied when the output of a joint HTA activity fails the necessary quality standards.
- Procedures that define interactions between participants (e.g. between Industry and authors, or with regulators) during a joint HTA activity.

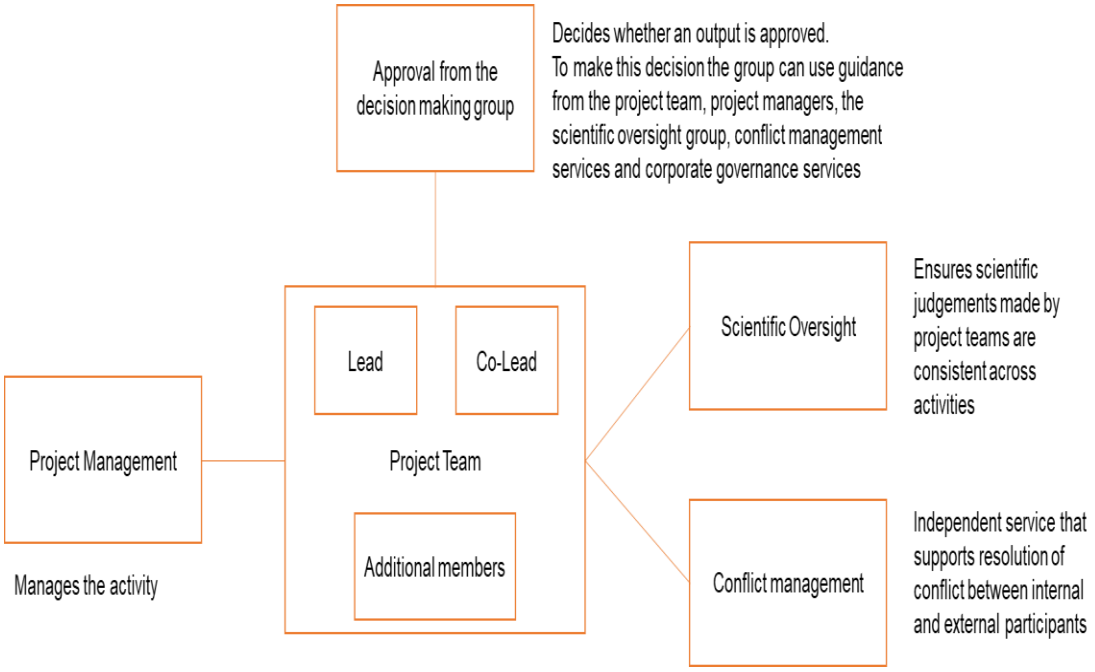


Figure 12-1: Proposals for activity management

12.4 Recommendations for future work

Definition of the centralised procedures for activity management.

Definition of the roles, responsibility and procedures for the provision of corporate governance, conflict management, scientific oversight and approval for joint HTA activities.

Development of a publicly accessible manual to describe activity management processes.

13 ACTIVITY-SPECIFIC: PROJECT PLANNING

The stage of planning is a fundamental component of a joint HTA activity to ensure that the issues and questions addressed are relevant to users. This section addresses the planning stage after the topic has been identified and a decision made to proceed, but before the output from the joint HTA activity starts to be prepared.

13.1 Summary of JA3 features

Table 13-1: Key JA3 project planning documents

Key documents	Link
SOPs: Developing a project plan	Available to EUnetHTA partners in the Companion Guide
SOPs: Review of submission dossier	Available to EUnetHTA partners in the Companion Guide
SOPs: Review of project plan	Available to EUnetHTA partners in the Companion Guide
Output of the PICO subgroup	Available to EUnetHTA partners in the Companion Guide and now also a FAQ is published: http://eunethta.eu/pico
ED procedures and guidelines	https://eunethta.eu/services/early-dialogues/

The project planning phase of joint HTA activities aims to reach an agreement in advance of the activity starting about how the activity should progress and the issues to be addressed. The specific steps of project planning are necessarily different for different types of joint HTA activity, reflecting the different purposes of the activities and end users. Broad elements of project planning in JA3 activities include:

- Decision on the format (for ED) or procedure (for OT JA/CA) to be used in the activity;
- Internal and external input into the issues to be addressed (all activities);
- Agreement among the project team on the issues (ED, PLEG) or research question (JA/CA) to be addressed in the activity.

A decision about the format or procedure is only required for ED and OT JA/CA, because for other activities there is only one procedure or format available. For ED, a decision is made between a face-to-face discussion and a written-only format. For OT, a decision is made about whether the topic should be a JA or a CA.

Input into issues to be addressed in the joint HTA activity varies between activities. In JA3 this element of project planning has involved the whole project team and has also included expert input from patients and healthcare professionals to understand the issues. For PT JA there are additional steps not used in other joint HTA activities:

- A survey (PICO survey) about the scope of the project to gather opinions from agencies who are users of the PT JA, but not involved as the project team;

- A meeting with the prospective MAH to discuss the evidence requirements because PT JA are based on an evidence submission from the technology developer[9]

For all joint HTA activities at the end of project planning phase there is a document produced that describes what is to be addressed in the activity. This document is published for those activities where the target user is an HTA agency and kept confidential for activities where the target user is the product owner (e.g. technology developer or registry holder).

[9] In JA3 it was an option for patients to be part of this meeting, but there was no experience from JA3 of patients being part of this meeting

Table 13-2: Planning processes used in JA3 HTA activities

	ED	PT JA	OT JA/CA	PLEG (product)	PLEG (registry)
Key stages of the process	Decision by EDWP on the format of the ED. Check and clarification of issues in the company briefing book. Circulation of the briefing book to participating HTA agencies. Agreeing on the issues for discussion.	Development of the scope and project plan. PICO survey. Scoping meeting with the prospective MAH. Request and check for a submission of evidence from technology developer. Publication of the project plan.	Development of the scope and project plan. Optional PICO survey. Scoping meeting with the technology developer (optional in CA). Optional request and check for a submission of evidence from technology developer. Publication of the project.	Agreeing, among participating HTA agencies, on the common requirements for PLEG (common evidence gaps, minimum data set and quality requirements).	Agreeing on the issues/question for discussion (quality aspects and variables collected).
Output of planning	List of issues for discussion.	Project plan.	Project plan.	Evidence gaps report - Presentation of common evidence gaps and subsequent research recommendations (in the PICO format). Minimum data set report - Definition of the minimum data set (outcomes and variables) to be collected.	List of issues for discussion.
Status	Confidential.	Public.	Public.	Public.	Confidential (publication of final report only).

	ED	PT JA	OT JA/CA	PLEG (product)	PLEG (registry)
Process documentation	Guidance document Available on the website. EMA/EUnetHTA guidance for Parallel Consultation.	SOPs and process flows are available in an online Companion Guide. Available to all JA3 internal participants. Separate manual available for Industry.	SOPs and process flows are available in an online Companion Guide. Available to all JA3 internal participants.	Scientific guidance available on the website. Procedure checklist available to project team. Procedures with the EMA: follows the EMA publicly available process for registry qualification.	

13.2 Lessons learned

For all joint HTA activities, it has proven feasible to identify and agree on the data and issues to be addressed in the joint HTA activity. The experience of JA3 highlighted that it is important to have documents and frameworks (e.g., PICO framework for JA/CA, REQUEST for PLEG) and meetings among internal and external participants to support the process of getting to a shared understanding.

For PT JA, taking part in the PICO survey is challenging for some HTA agencies because assessment scopes are not always pre-planned before their HTA starts and are not always defined by the HTA agency. In general, HTA agencies can take part in the PICO survey and provide feedback that supports PT JA.

For PT JA, the timing of the project planning phase is crucial. At the start of JA3 project planning occurred very early on in the regulatory process. It now starts six months before CHMP opinion is expected. This start date provides more certainty about authorisation dates, wording of the likely indication, and more reliably secures authors.

The timeframe for gathering input into the issues to be addressed in a joint HTA activity needs to be sufficiently long to allow HTA agencies to gather meaningful input from relevant external groups e.g., decision-makers and/or healthcare professionals.

For OT JA/CA, a PICO survey was not possible because either the PICO was considered very straightforward from the beginning (e.g. requested by the authoring HTA agency) or it was already very broad, or timing pressures meant that the scoping process could not be extended further to incorporate a survey of HTA agencies.

For PT JA, the final PICO for the assessment is derived from national policy questions. However, the technology developer is the main provider of the evidence used for the JA. To ensure the best possible submission, the technology developer should have the option to discuss with the project team the PICO to be addressed in the JA and the methodological requirements for the JA.

For some topics it can be challenging to balance the need for a broad European PICO with the scientific documentation to support all comparisons and with the timelines and availability of human resources to conduct the JA.

13.3 Recommendations for a future model of HTA cooperation

Joint HTA activities should involve the following groups in defining the issues or questions to be addressed in the activity:

- The target user(s) of the output from the activity;
- Patients and clinical experts.

In JA the final scope for the JA should be discussed with the technology developer that is expected to submit evidence so that the technology developer can understand the evidence requirements for the JA and the technology developer can provide the project team with insights into aspects of the JA such as patient population, regulatory label, endpoints and outcomes, potential areas of uncertainty, clinical trial design and analysis. However, the PICO to be addressed in the JA should be defined by the policy questions of the target users, technology developers should not define the scope.

The principle of involving the target user in project planning is particularly important for JA/CA where the target users of the report are a group of HTA agencies, not all of whom can be part of the protect team, and the questions to the addressed in the activity should be based on national policy questions.

For PT JA, JA3 has demonstrated that input for project planning can be obtained through a survey of HTA agencies asking for input on the population, intervention, comparators and outcomes. This should be standard practice in PT JA.

The planning process for a joint HTA activities should follow a standardised set of procedures depending on whether it is an advice activity where the target user of the output is the owner of the health technology or registry or an assessment activity where HTA agencies are the target user of the output (Figure 13-1).

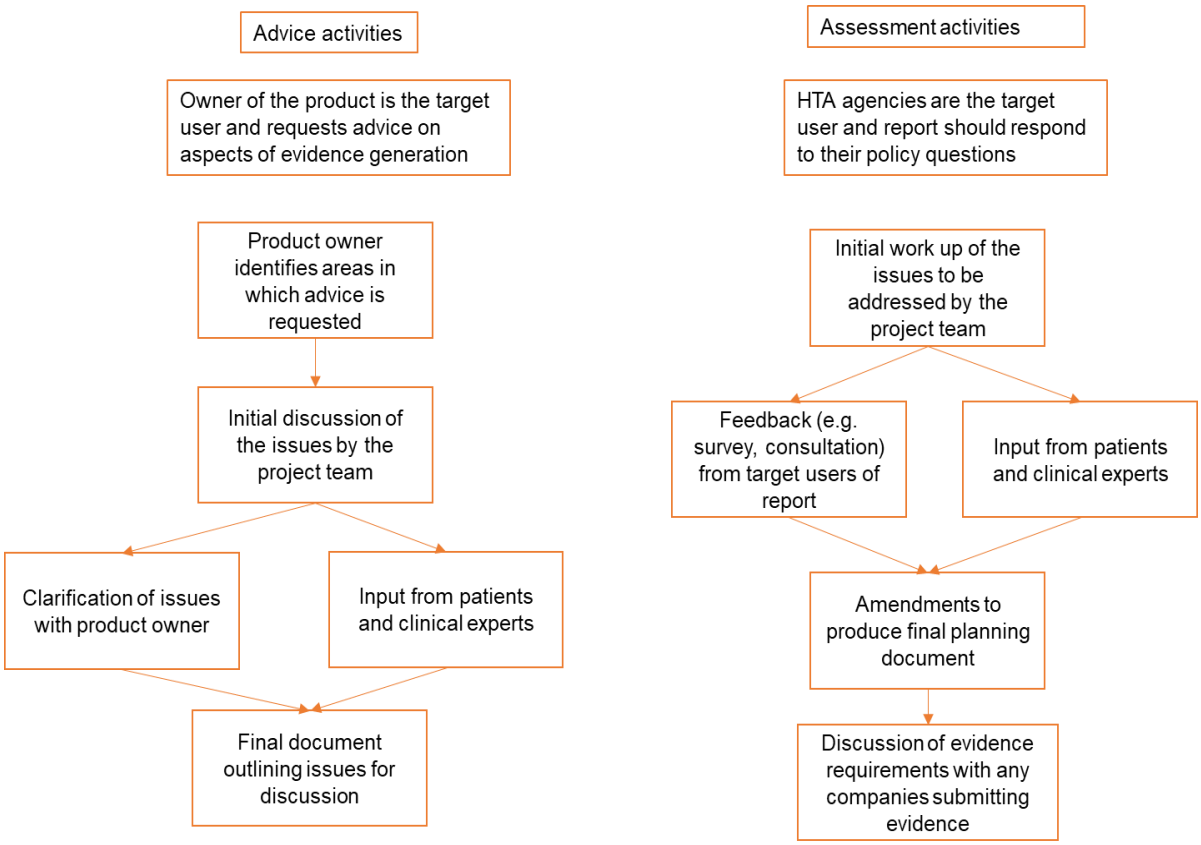


Figure 13-1: Proposed project planning process

13.4 Recommendations for future work

An OT process for getting target user input into the PICO.

Guidelines for project teams and participants on the scoping process e.g. principles for choosing comparators, dealing with one PICO vs. multiple PICO.

14 ACTIVITY-SPECIFIC: EXPERT INVOLVEMENT

The quality and transparency of HTA project procedures can be enhanced by the involvement of patients or patient experts, and healthcare professionals. This section discusses involvement of experts (that is, people external to the HTA cooperation who provide an individual and/or expert perspective on an issue) in joint HTA activities.

14.1 Summary of JA3 approach

Table 14-1: Key JA3 documents about expert involvement

Key documents	Link
SOP: compensation of external parties in JA3	Available for EUnetHTA partners in the Companion Guide
SOP: outlining external review processes for project plans and assessments	Available for EUnetHTA partners in the Companion Guide
Patient involvement leaflet	https://eunethta.eu/wp-content/uploads/2020/01/Electronic-Flyer-Patients.pdf
Patient Involvement in REA	https://www.eunethta.eu/wp-content/uploads/2019/06/Final_290519_Patient-Input-in-REAs.pdf
Patient input template	https://eunethta.eu/eunethta-patient-input-template/
Healthcare Professional Involvement in REA	https://www.eunethta.eu/wp-content/uploads/2020/04/Final_HCP-Involvement-in-EUnetHTA-assessments.pdf
ED Framework for patient involvement	*High level information is currently available on the website.* https://eunethta.eu/services/early-dialogues/ *A link to more detailed guidance will be published when available*
SOP: Identification of Stakeholders	Available for EUnetHTA partners in the Companion Guide

In JA3, work was carried out to improve patient and healthcare professional engagement in joint HTA activities. There is now an expectation that input from these groups is routinely sought. Involvement of patients most often occurs early in the process to help understand the issues that need to be addressed in the joint HTA activity. Healthcare professionals have been additionally engaged during the review phase of the draft output from the joint HTA activity.

The procedure for PLEG has differed from that used for ED and JA/CA. In JA3 PLEG activities were pilots with more reliance on HTA agency processes for engaging experts rather than a centralised 'joint' approach. Greater harmonisation and centralisation of expert involvement is expected as PLEG becomes more established.

In JA3, the approach to identifying experts varies across activities and between expert groups. For JA/CA an open call is published on the website for patient organisations to respond to. This approach cannot be used for ED because of the confidentiality status of the activity. For healthcare professionals a different approach is used. For ED, healthcare professionals are

identified via HTA agencies and for JA/CA via a combination of approaches including centralised contact via stakeholder organisations involved in JA3 and direct approaches at either an EU level or a national level.

The JA/CA open call for patient input is open to all patient organisations to answer and organisations only have to declare their interests. For more in-depth involvement in JA/CA and involvement of healthcare professionals there cannot be conflicts of interest.

The approach to gathering the input from experts has also varied across activities and within activities. These differences in approach have tended to arise initially from different approaches used across individual HTA agencies. However, a flexible approach also allows best possible expert engagement.

Table 14-2: Expert participation in JA3 joint HTA activities

	ED	JA PT	JA/CA OT	PLEG (product)	PLEG (registry)
Who	Patients or patient representatives Healthcare professionals	Patients Healthcare professionals		Patients Healthcare professionals	None
Identification and Recruitment	Patients via ED Secretariat and patient organisations. Healthcare professionals via HTA agencies.	For both patients and healthcare professionals: • Via email at EU or agency level. • Through the HTA network stakeholder pool. • Direct contact via EUnetHTA stakeholder list. Additionally, for PTJA: Through EMA patient, consumer and healthcare provider, stakeholder department. Additionally, for patient input only: Open call on website for patient input through patient organisations.		Involvement when part of national PLEG processes – using national processes	NA
Criteria	Declaration of conflicts of interest – participants should be free from conflicts of interest.	For the open call for patient input funding and interests only need to be declared. Other expert involvement in JA/CA should be free from conflicts of interest.		Involvement when part of national PLEG processes – using national processes.	NA
Numbers participating	1-2 patients per ED	2 x healthcare professional. Patient input – depends on response to open call.	2x healthcare professional. Patient input - depends on feasibility (e.g. topic/timelines) and/or response received.	Variable	NA

	ED	JA PT	JA/CA OT	PLEG (product)	PLEG (registry)
Methods of involvement	Approach 1: Expert interviewed regarding the disease and their experience. Approach 2: Approach 1 + discussion with local HTA agency regarding submission file (without applicant). Approach 3: Approach 2 + discussion with all participating HTA agencies regarding the submission file and participation in the F2F meeting with the applicant.	Healthcare professional: Feedback via virtual meeting about PICO. Review of drafts – project plan and assessments. Response to questions during the planning and production phase. Approach varies depending on needs and timeframe for assessment. Patient experts: Through patient organisations using a modified version of the HTAi patient input questionnaire Individual conversations. Group discussions. Scoping meeting.		Involvement when part of HTA agency PLEG processes – using agency own processes.	NA
Engagement support	ED Secretariat (patient engagement) HTA agencies (healthcare professional engagement)	PT project managers Compensation as per SOP.	OT project managers Compensation as per SOP.	HTA agencies – using their own processes.	NA
Mandatory/ Voluntary	Patient – expected on a routine basis. Healthcare professional – if considered necessary.	PT mandatory to seek input from patients and healthcare professionals, expected on a routine basis.	Patient – OT mandatory to discuss seeking input, sound rationale required for not including. healthcare professionals mandatory to seek input, expected on a routine basis.	Involvement when part of agency PLEG processes – using HTA agency own processes.	NA

14.2 Lessons learned

Managing expert involvement in joint HTA activities is resource intensive. There can be duplication in efforts and activities if carried out at an activity-specific manner.

There are varying levels of expertise among HTA agencies about how to involve experts and, in particular, patients. Involvement is most effective when done by HTA agencies who have experience of involving that group. Procedures need to be available to support HTA agencies to gain relevant experience where necessary.

In JA3, different mechanisms of identifying experts were used. Direct approaches to national or European condition-specific organisations were sometimes more successful and timelier than going via networks of organisations.

The following challenges were encountered when involving patient organisations:

- For some topics and conditions, patient groups are less established than for other conditions;
- Longer timelines are needed to identify individual patients and small populations than other groups;
- Where conditions are associated with severe burden of disease, identifying patients to be involved may not be possible;
- For ED, an open call system of expert identification is not possible because of confidentiality of ED;
- Information and/or training on HTA and joint HTA activities is needed;
- A system for renumeration was required in JA3 and needed to be set up.

The following challenges were encountered when involving healthcare professionals:

- In ED, most HTA agencies include their own healthcare professionals in an informal manner. This expert input can be directly related to the local standard of care and the national situation. It was difficult to involve a common expert;
- In PT JA, healthcare professionals were sometimes reluctant to take part in reviewing the outputs of the joint HTA activities because of resource constraints (most healthcare professionals are practicing medical doctors) and the low remuneration;
- Healthcare professionals that have expressed interest to participate were often rejected due to a conflict of interest. Often these experts had participated as Principal Investigator in the pharmaceutical under assessment or a comparator.

For rare disease areas and specialised technologies, knowledge may be held by a small group of experts.

- COI policies that are very stringent can act against the involvement of the most knowledgeable experts;
- It may not be possible to identify experts without COI; potential conflicts need to be documented consistently and transparently – a question and answer approach (in

which no information on the specific health technology is provided to the expert) can be used to gather input from experts where there is a potential COI. However, strong COI situations still need to be avoided.

14.3 Recommendations for a future model of HTA cooperation

External expert involvement (including both patients and healthcare professionals) in joint HTA activities:

- Should be systematic, transparent and, where appropriate, consistent across activities with a rationale for differences;
- Should be meaningful and relevant;
- Should be guided by a clear and structured framework for engagement
- Should have some procedural flexibility to allow for the best possible contribution.

In terms of where in the process experts should be involved:

- Joint HTA activities should normally include a contribution from experts early in the process to inform project planning (e.g. to inform the issues to be addressed in the joint HTA activity);
- Joint HTA activities should normally include experts during the preparation process (e.g. during production of the output of the joint HTA activity) to discuss and clarify any issues arising.

Where there are no COI, experts should have access to all relevant documents supporting the joint HTA activity, e.g. briefing books, submissions.

The expert contribution should be described in the joint HTA output.

Identification and management of experts should be supported centrally with outreach to HTA agencies where required. The following should also be provided:

- Information and training for experts to help them understand the role, expectations, and what they should provide. This should be developed in a variety of formats suitable for the intended group, e.g. manuals, guidance, information sheets and videos;
- Guidance to project teams on how to conduct interviews;
- Guidance to project teams on how to use the contribution in joint HTA activities;
- Additional support to allow patients to provide the best possible contribution, including:
    - A contact who can provide additional support for them to complete documents and raise queries;
    - Guidance documents and templates translated into national languages;
    - Training and information sheets;
    - A platform to explain the principles of HTA and European HTA, the engagement methods and how their input is being used.

14.4 Recommendations for future work

Creation of a centralised engagement service including a platform and materials for experts with a particular focus on engagement of patients.

Further development of expert recruitment processes and, in particular, healthcare professional involvement. Recruitment processes for joint HTA activities should include consideration of when it is appropriate to include:

- European expertise and national expertise;
- direct contact and open call;
- centralised identification processes and decentralised identification via HTA agencies.

Training tools and materials to support collection and inclusion of expert contributions in joint HTA activities.

Development of a COI policy that supports participation of experts, but which maintains an acceptable level of independence that allows HTA agencies to use the output from the joint HTA activity.

A procedure and guidance for project teams describing how to incorporate patient input into the output from the joint HTA activity.

15 ACTIVITY-SPECIFIC: STAKEHOLDER INVOLVEMENT

In addition to the expert contribution, joint HTA activities can also include a stakeholder contribution (that is inclusion of groups and organisations with an interest in a topic usually through opportunities for evidence submission and/or opportunities for consultation). In the context of JA3, the focus of this section is on the involvement of Industry and registry holders. However, in the context of a future model of HTA cooperation, stakeholder contributions could include the involvement of a range of groups and organisations with an interest in a topic.

15.1 Summary of JA3 approach

Table 15-1: Key JA3 documents about involvement of product owners

Key documents	Link
Industry procedure manual - PT	https://eunethta.eu/wp-content/uploads/2020/07/EUnetHTA-pMAH-procedure-manual-PTJA-generic-v1.0.pdf
Industry procedure manual - OT	https://eunethta.eu/wp-content/uploads/2020/10/Procedure-manual-JA-or-CA-for-manufacturers-OT.pdf
Fact check guidance documents (2 for OT, 1 for PT)	Available for EUnetHTA partners in the Companion Guide
Fact check evaluation	Available for EUnetHTA partners in the Companion Guide
Submission guidelines	https://eunethta.eu/services/submission-guidelines/
SOP: Identification of Stakeholders	Available for EUnetHTA partners in the Companion Guide

Once a decision to initiate an ED, JA/CA and PLEG has been made, the involvement of stakeholders in JA3 is limited to product owners. This is usually the technology developer. In JA3, involvement has tended to be in the early stages of the process before the output of the joint HTA activity is drafted. Some joint methods work has included a stakeholder consultation on the draft report, but not the core outputs from ED, JA/CA or PLEG.

ED and PT JA are initiated by the technology developer and an evidence submission from the technology developer is the main source of evidence used to develop the output from the activity. The technology developer is not obliged to initiate and ED or a PT JA, but once an activity has been initiated their involvement is required. The technology developer is therefore a key stakeholder in these joint HTA activities.

For OT JA/CA and product specific PLEGs, the technology developer can choose to be involved and/or be informed. However, these activities can go ahead regardless of their involvement, because the evidence informing the output from the activity is generated by the project team rather than provided by the technology developer.

In both PT and OT JA/CA, there are procedures for optional fact checks by the technology developer of the assessment (PT and OT) and/or the project plan (OT).

Interactions between stakeholders and project groups are mediated through project managers and secretariats rather than through direct contact with project teams.

This approach to engagement of stakeholders was adopted in JA3 to ensure independence of the HTA output and to improve the timeliness of the outputs.

Table 15-2: Participation of stakeholders (industry and registry holders) in JA3 HTA activities

	ED	JA PT	JA/CA OT	PLEG (product)	PLEG (registry)
Who	Health technology developer	Health technology developer	Health technology developer	Marketing authorisation holder	Registry Holder[10]
Identification and Recruitment	Self-selection by applying for process	Voluntary participation with active outreach to support submissions of priority topics.	Once a topic is selected technology developers will be identified and contacted.	Once a topic is selected, the marketing authorisation holder will be identified and contacted.	Self-selection by applying for process
Numbers participating	1	1	1 or more	1	1
Methods of involvement	Initiation of the process Provision of an evidence submission. Responding to clarifications. Meeting to discuss issues.	Initiation of the process. Provision of an evidence submission. Responding to clarifications. Scoping meeting. Optional fact check of output.	Topic proposals. Optional submission of information. Scoping meeting (optional in CA). Optional fact check of project plan and output.	Contacted and when they respond, kept informed about different pilot steps and outputs.	Initiation of the process. Provision of a registry details. Responding to clarifications. Meeting to discuss issues.
Engagement support	ED Secretariat HTA agencies are discouraged from having individual contact with the company.	Project Manager The authoring team does not have direct contact with the company to avoid conflicts.	Project Manager	Project Lead	Scientific Coordinator

[10] In JA3 PLEG registry pilots were initiated by registry holders, but in a future model of HTA cooperation PLEG registry pilots could be initiated by a variety of groups including industry and patient organisations

	ED	JA PT	JA/CA OT	PLEG (product)	PLEG (registry)
Mandatory/Voluntary	Voluntary to apply, but if a technology developer applies then further involvement is required.	Voluntary to apply, but if a technology developer applies then further involvement is required.	Voluntary	Voluntary	Voluntary to apply, but if a registry holder applies then further involvement is required.

15.2 Lessons learned

HTA agencies differ in the extent to which they consider it appropriate to include a stakeholder contribution in joint HTA activities. This tension is particularly apparent for involvement of industry and payer organisations. In JA3, concerns have been raised about the extent to which stakeholder groups have had opportunities to be involved in joint HTA activities. However, there are divergent opinions among HTA agencies about the extent to which this is appropriate and desirable, because of the perceived threat to independence. In general, there is less disagreement about stakeholder involvement:

- In earlier phases of joint HTA activities e.g. to inform the project plan and the issues to be addressed rather than in later stages once the output from the joint HTA activity has been developed, e.g. consultation on reports and issue resolution meetings;
- Where the output from the joint HTA activity is informing a non-binding rather than a mandatory resource allocation decision.

The involvement of the technology developer in factual accuracy checks is not acceptable to all HTA agencies. However, an evaluation of the factual accuracy check process in JA3 by WP4 and WP6 demonstrated that a process for identifying factual errors and inaccuracies in draft project plans/assessment reports is needed before publication.

Stakeholder involvement needs to be subject to standardised processes that are consistent across projects. Involvement needs to be appropriately supported with manuals and guidance to help stakeholders understand their role, the expectations, and what they should provide.

Not all stakeholders have a good familiarity with HTA. Some stakeholders may need additional support and training besides manuals and guidance to make the best possible contribution.

15.3 Recommendations for a future model of HTA cooperation

Stakeholder involvement should distinguish between the different types and function of joint HTA activities as the approach required may need to be different:

- Advice activities such as ED and PLEG registries where the target user is the product owner, and the output is non-binding recommendations;
- Assessment activities such as JA/CA where the target user is an HTA agency and the output is published and expected to inform a decision-making process about resource allocation.

For all joint HTA activities with input from stakeholders, there should be:

- Manuals and guides to describe the role and responsibilities;
- Guidance on the contribution.

Involvement of stakeholders should be mediated through secretariats and project managers rather than being handled directly by the project team.

Stakeholder engagement in joint HTA activities needs to be given adequate time for stakeholder groups to engage, and for project teams to consider and respond to comments received.

15.4 Recommendations for future work

Agreement on procedures for involving stakeholders in later stages of the HTA process including fact checking.

16 ACTIVITY SPECIFIC: COLLABORATION WITH REGULATORS

Regulators and HTA agencies have different remits and responsibilities, but regulators are important collaborators in HTA cooperation because a joined-up approach to regulation and HTA supports access to health technologies. This section describes collaborative activities with the pharmaceutical regulator, EMA, and opportunities for future collaboration with medical device regulators.

16.1 Summary of JA3 approach

Table 16-1: Key JA3 documents describing collaboration with regulators

Key documents	Link
A Vision Map describing the plan for coordinated activities on HTA and medical device authorities.	*Formal EUnetHTA deliverable available via* ec.europa.eu
EUnetHTA-EMA work plan	https://www.eunethta.eu/ema-eunethta-joint-work-plan-for-2017-2020/

In JA3 work was carried out to improve collaborations with regulators. Work with regulators is underpinned by a joint EUnetHTA-EMA work plan, regular bilateral meetings and a Vision Map to support engagement with MD regulators.

For ED and PLEG registry pilots, procedures have been developed so that there are joint regulatory and HTA advice procedures.

With the EMA there is now a framework and a procedure to ensure alignment of the JA process with EMA processes. This includes:

- Exchange on parts of the final CHMP assessment report (once adopted) and the relevant Summary of Product Characteristics (SmPC);
- Discussions between the authors of the JA and the CHMP rapporteurs to facilitate a mutual understanding of the outcomes of each process.

Exchanges have dedicated confidentiality arrangements, and the different remits of regulatory assessment and HTA are respected.

Other types of information exchange have also taken place, including exchanges of information about relevant experts and stakeholders to engage in patient involvement and involvement in topic identification pilots. Furthermore, the joint EUnetHTA-EMA workplan allows progression of methodological topics of mutual interest, such as extrapolation/evidence transfer and the identification of therapeutic indications.

For OT JA/CA a series of workshops have been held to identify the synergies and areas for potential collaboration going forward.

Table 16-2: Collaboration with regulations in JA3 joint HTA activities

	ED PT	JA PT	JA/CA OT	PLEG (product)	PLEG (registry)
Who	EMA	EMA	None	None	EMA
How	Joint parallel consultation procedure that includes HTA agencies, the EMA and the company.	Information sharing between PT JA authors and CHMP (Co)-rapporteurs using a formal confidentiality framework	NA	NA	Follows EMA procedure for the qualification of novel methodologies.

16.2 Lessons learned

The framework for Parallel Consultation was continuously improved based on experience, leading to significant updates in the framework by developers.

The framework within which EUnetHTA operates limited the ability to develop confidentiality agreements with the EMA. This meant that collaboration and learning opportunities could not be maximised. In the context of PT JA, agreements could only be put in place between the authors and co-authors of the JA and not the whole project team. This meant that some members of the project team had less access to information used in the JA than others, which impacts on the ability to review documents.

When sharing information from the EMA for PT JA:

- Regulatory information of interest for project teams in the EPAR include: Section 2.1 (problem statement), 2.4 (clinical aspects), 2.5 (clinical efficacy), 2.6 (clinical safety), 3 (benefit-risk balance), 4 (recommendations);
- Project teams need to be able to cite the information from the EMA;
- Processes need to be in place to highlight and manage any changes to the EPAR that occur after it has been shared and before publication.

Collaboration with regulators around topic identification was identified as an area for joint work. However, taking this work forward was hindered by the need for confidentiality and challenges with setting up an appropriate confidentiality framework.

Methodological discussions with regulators enhanced mutual understanding and progression of relevant topics, e.g. on combination products/companion diagnostics.

For PT ED, the parallel process with the EMA is a preferred option for providing advice, but some technology developers will choose to obtain separate advice and there remains a need to be able to undertake an advice process that includes only HTA agencies.

Open channels for communication with regulators to develop a shared understanding are critical. Successful communication between the EMA and the EUnetHTA ED Secretariat allowed the adoption of PICO as an organisational framework for the list of issues for discussion and the F2F meeting in parallel consultations.

For the PLEG registry qualifications in parallel with EMA, timelines should be pre-defined to ensure a common deadline for a final recommendation from regulators and participating HTA agencies.

16.3 Recommendations for a future model of HTA cooperation

HTA cooperation should build on the synergies between regulatory and HTA processes. There should be formal collaboration with regulators based on a work programme of activities covering methods, concepts, information exchange and consultation, and linked to all joint HTA activities: ED, JA/CA and PLEG.

Existing joint HTA and regulatory activities (ED and PLEG) should continue. HTA and regulatory agencies should work together to promote joint regulatory and HTA activities to technology developers less familiar with HTA.

Both parallel scientific advice with the EMA and separate advice (only involving HTA agencies) should be offered. Where a technology developer chooses to have separate HTA and regulatory advice, the technology developer should be encouraged to seek advice from the HTA and regulatory agencies within a similar timeframe (dependent on availability). In addition, the benefits of allowing HTA agencies and regulators to exchange scientific advice documents, as for Parallel Consultation, should be highlighted.

The information exchanges described in 16.1 and 16.2 for PT JA should continue. This collaboration should be strengthened by implementing a framework for HTA cooperation that allows:

- The creation of a confidentiality framework that allows optimal data sharing and usage to include timeline information;
- The entire project team to have access to the CHMP Assessment Report and SmPC, and be involved in information exchange with regulators.

Building on the Vision Map elaborated in JA3, a joint work plan between HTA agencies and MD regulators should be built into HTA cooperation. The joint work plan between HTA agencies and MD regulators should aim towards a mutual understanding of requirements, processes and products, and build up to activity-specific collaborations. The learnings from developing and implementing the EUnetHTA EMA joint work plan can inform the development of a work plan between HTA agencies and MD regulators, but the different nature of MD and PT regulation and HTA means that joint exchanges and activities will be necessarily different.

16.4 Recommendations for future work

Once the framework for HTA cooperation has been defined, a confidentiality framework should be set up that allows for optimal data sharing for PT JA. This will also strengthen other joint HTA activities such as ED and PLEG.

Further develop the opportunities for collaboration between HTA agencies and regulators in the context of the European Health Dataspace and DARWIN EU (Data Analytics and Real World Interrogation Network).

Building on the work started in JA3, further develop collaboration with MD regulators and establish a joint work programme

17 ACTIVITY-SPECIFIC: TEMPLATES AND PROCEDURES

Templates and procedures support project teams to undertake the joint HTA activity. Templates and procedures help standardise the identification, planning and production processes of a joint HTA activity and are critical to producing a robust and trusted outputs from joint HTA activities.

17.1 Summary of JA3 approach

Table 17-1: Key JA3 documents describing templates and procedures

Key documents	Link
ED procedures and guidelines	https://eunethta.eu/services/early-dialogues/
Companion Guide	https://eunethta.eu/eunethta-companion-guide/
Deliverable D6.5 status report on revised quality management system for joint work.	Once uploaded by the Commission, the document will be publicly available here: https://webgate.ec.europa.eu/chafea_pdb/health/projects/724130/outputs
JA3 Final Deliverable "Recommendations and tools for PLEG"	https://www.eunethta.eu/pleg/
Output of the subgroup of assessment report and submission dossier.	https://www.eunethta.eu/services/submission-guidelines/submission-template-pharmaceuticals-submission-template-medical-devices/

Templates and procedures have been developed in an activity-specific manner, and their presentation and availability varies across joint HTA activities.

The individual templates and procedures developed in JA3 are listed in Appendix 1.

For JA/CA all templates and procedures are contained in the online Companion Guide, providing a single resource repository for project teams. Procedures are articulated as process flows and SOPs that cover each stage of the JA/CA process. Where needed, separate procedures are available for pharmaceuticals and other technologies. The procedures cover aspects of developing the JA/CA, as well as management of the system (e.g. creating and maintaining operating procedures) and administration (e.g. financial reimbursement of external participants). The Companion Guide can be accessed through the EUnetHTA website by any internal participant but is not available to external participants, for whom separate manuals are available.

For ED, procedures are contained in a single document covering each stage of the process, available on the EUnetHTA website. This difference in approach was adopted at the start of JA3 due to resource constraints and an agreement to focus the implementation of the Companion Guide in JA/CA.

For PLEG activities, JA3 has piloted different types of joint HTA activity and started the development work for the templates and procedures to support the activity. These procedures are currently available in less detail than for other activities, and will need further development if PLEG is established in HTA cooperation.

Table 17-2: JA3 templates and procedures

	ED	PT JA	OT JA/CA	PLEG (product)	PLEG (registry)
Templates	Standardised templates covering each stage of the process from topic identification to final output.	Standardised templates covering each stage of the process from topic identification to final output.		Standardised templates covering each stage of the process from topic identification to final output.	
Internal participation procedures	Guidance document available on the website.	Process flows. SOPs. Process-related guidance. Available in an online Companion Guide.		Scientific guidance available on the website. Procedure checklist available to project team.	Scientific guidance available on the website. Procedures with the EMA: follows the EMA publicly available process for registry qualification.
External participation procedures	Manual available for experts and stakeholders.	Separate manuals for participating technology developers and recommendations for engagement of experts (patients and healthcare providers).		Currently not defined in a procedure.	
Availability	Public	Public – Manuals, some templates. All partners – the Companion Guide.		Public – scientific guidance. Participants – checklist of procedural stages.	

17.2 Lessons Learned

Not all HTA agencies are used to having individual procedural tasks defined or following detailed SOPs. There may not always be compliance with the SOPs, therefore their availability does not, in of itself, create good quality products.

For JA/CA some of the challenges of creating project teams have been exacerbated by perceived complex and lengthy procedures that require more resources than a single-agency process. It is necessary to balance the differing needs of HTA agencies (e.g. content needs, quality and timeliness requirements), and what HTA agencies perceive is acceptable, against resources available.

Templates and procedures act at an operational level, but the decisions taken when developing the template or procedure can have strategic implications. For example, the process used to define the PICO can affect the number of HTA agencies that can use the JA/CA and how they can use it.

The experience of responding to the COVID-19 pandemic has shown that procedures need to have a certain level of flexibility so they can be adapted to respond to urgent and short notice requests in justified cases.

The acceptability of templates and procedures and the ability to implement them is sensitive to the framework and setting in which they are to be used. Some aspects of the templates and procedures developed in JA3 reflect a compromise to support their implementation in the JA3 voluntary framework.

Project teams require sufficient time to follow procedures and undertake a high-quality piece of work. Timelines need to reflect that the HTA cooperation is working internationally to inform policy decisions within a country. Information may need to be cascaded from a European or global level to a range of within-country individuals, groups and organisations, which increases the time needed for engagement and consultation.

Templates and procedures need to be regularly updated. Updating should be carried out in a predictable manner. For example, changes to templates and procedures should not be implemented part way through a joint HTA activity, and participants that will be affected by the updates should be advised in advance that changes are planned.

17.3 Recommendations for a future model of HTA cooperation

The templates and procedures developed in JA3 provide a foundation for future HTA cooperation. However, these documents have been developed and implemented in the context of the JA3 voluntary framework and will have to reviewed, adjusted, and balanced to fit any future legislative framework, the level of resourcing made available, and any timelines defined in the legislation.

Where procedural steps are added to a process, the impact on timelines and resources also needs to be considered.

To support ease of use, templates and procedures should be harmonised in their content, detail, structure, presentation and access, and be available in a single repository such as the Companion Guide.

Procedures and templates need to have a certain amount of flexibility to make it possible to work under new conditions, e.g. pandemics, or with new types of health technology, e.g. digital health.

To ensure transparency, there should be a publicly available guide about the procedure for all joint HTA activities. If necessary, more detailed SOPs could be available to project teams.

There should be a system in place to maintain templates and procedures. The system used in JA3 to maintain the Companion Guide provides an appropriate foundation for a future HTA cooperation. Updating should have the following features:

- Applied transversally to all methods, procedures and tools;
- Follows an explicit review cycle;
- No implementation of updates part way through a joint HTA activity;
- Sufficient resourcing to implement feedback received;
- Managed with centralised support and with expert input;
- A final approval process.

17.4 Recommendations for future work

The procedures used for joint HTA activities developed in EUnetHTA JA3 need to be adapted to fit the requirements of any EU HTA regulation.

The templates for the PT company evidence submission and assessment report template need to be updated to take into account the recommendations made in EUnetHTA JA3 by the PT templates subgroup, and to fit the requirements of any EU HTA regulation.

There is need to develop a system to maintain procedures. The JA3 update procedures provide an appropriate foundation for this work.

The work to develop the optimum procedures and templates to support ED should be continued e.g. inclusion of additional details in the ED Request Form, in particular patient reported outcomes (validity of the tool included in proposed development with minimal clinically important difference).

The work to develop procedures and templates to support ongoing collaboration in PLEG should be continued.

The following procedural aspects of JA/CA could not be addressed within the voluntary framework of EUnetHTA. Further work to reach an agreement between participants on the appropriate process for HTA cooperation is required:

- Non-submission by technology developers;
- The process of handling incomplete data;
- Provision of new data during the JA/CA;
- Consensus resolution;
- Study selection processes;

- Incorporation and presentation of patient input;
- Handling incomplete draft assessments sent to dedicated reviewers.

18 ACTIVITY-SPECIFIC: METHODOLOGY

HTA is a scientific exercise that should follow a transparent methodology.

18.1 Summary of JA3 features

Table 18-1: Key JA3 methodological documents

Key documents	Link
EUnetHTA website – methodology page	https://eunethta.eu/methodology-guidelines/
Deliverable D6.5 – Status report on revised quality management system for joint work.	https://webgate.ec.europa.eu/chafea_pdb/health/projects/724130/outputs
Milestone 6.5 - New Guidelines and tools	https://webgate.ec.europa.eu/chafea_pdb/health/projects/724130/outputs
Output of the JA3 common phrases subgroup.	https://www.eunethta.eu/grade/

EUnetHTA across the different joint actions has produced a suite of methodological and science documents. The individual documents available, the aim of the document, its use and update status are included in Table 18-2.

The methodological guidelines are primarily used in JA/CA, but can also be used in ED and PLEG. There are formal processes for developing, obtaining feedback, and reviewing methodological guidelines. However, in JA3 the ability to implement these processes have been limited by resource constraints.

There is a separate set of science documents that specifically support PLEG. These documents were developed in previous joint actions but will be reviewed in JA3.

Other science tools (that is, HTA Core model and evidence submission template) provide a foundation for the JA/CA templates used in JA3. Further development work in JA3 has been carried out to adapt the tools for use in joint HTA activities.

Table 18-2: Available methodology documents

Science item	Stated aim	Applicability to the existing work programme	Update required
Methodological Guidelines			
Process of information retrieval for systematic reviews and health technology assessments on clinical effectiveness (updated 2020)	To provide an up-to-date and transparent overview of the whole information retrieval process. To provide orientation for systematic searches on clinical effectiveness conducted within the framework of EUnetHTA.	Primarily support to HTA agencies and use in JA/CA	Update carried out in JA3
Endpoints used for Relative Effectiveness Assessment: Clinical Endpoints (updated 2015)	To describe the common characteristics of clinical endpoints, issues relating to their measurement and presentation, and to briefly outline some of the problems arising when comparing or pooling clinical endpoint data. To provide recommendations for the selection and the interpretation of clinical endpoints in the context of REA.	Transversal	Yes (feedback from partners) This needs to be updated to reflect guidance from the PICO subgroup. Further guidance is required for authors of JA/CA about the selection of relevant endpoints.
Endpoints used for Relative Effectiveness Assessment Composite endpoints (updated 2015)	To describe the advantages and disadvantages of the use of composite endpoints as opposed to single endpoints and offer guidance for assessors about construction, reporting, and interpretation of the results of composite endpoints in the context of REA.	Transversal	Further guidance is required for authors of JA/CA about the selection of relevant endpoints.
Endpoints used in Relative Effectiveness Assessment: Surrogate Endpoints (updated 2015)	To provide guidance on when and how surrogate endpoints can be used for REA.	Transversal	Further guidance is required for authors of JA/CA about the selection of relevant endpoints.

Science item	Stated aim	Applicability to the existing work programme	Update required
Endpoints used in Relative Effectiveness Assessment: Safety (updated 2015)	This guideline focuses on the relative safety assessment performed by the HTA assessors when conducting Relative Effectiveness Assessment (REA) and deals with the following methodological issues: - Objectives of HTA assessors - Terminology - Identification of adverse reactions: sources of information - Evaluation of sources of information - Synthesis and reporting of results compared to other interventions	Transversal	Yes (feedback from partners) Further guidance is required for authors of JA/CA about the selection of relevant endpoints.
Endpoints used for Relative Effectiveness Assessment Health: related quality of life and utility measures (updated 2015)	(1) Support assessors in identifying the strengths and weaknesses in the evidence provided and (2) inform researchers about the requirements regarding HRQoL assessment to allow them to anticipate the collection of the required data for REA when developing trial protocols.	Transversal	No feedback from JA3 about the need to update.
Comparators & Comparisons: Criteria for the choice of the most appropriate comparator(s) (updated 2015)	To summarise the available literature, the advice provided by existing national guidelines, and the information from current national practice on the choice of comparator, and to outline some of the challenges arising when establishing what the comparator for a specific assessment should be. Best practice recommendations for the selection of the most appropriate comparator when completing a REA.	Transversal	Yes (feedback from partners) This needs to be updated to reflect guidance from the PICO subgroup. Further guidance is required for selecting appropriate comparators in the context of JA/CA and for dealing with off-label comparators.

Science item	Stated aim	Applicability to the existing work programme	Update required
Comparators & Comparisons: Direct and indirect comparisons (updated 2015)	To describe the main methods of direct, indirect, and mixed treatment comparison available in terms of the types of relationship they can model and the assumptions inherent in them. Recommendations regarding the use of direct and indirect comparisons in a relative effectiveness assessment (REA).	Transversal	Yes (feedback from partners) A concept for reviewing this guideline was developed in JA3 but the update work was not carried out.
Levels of Evidence - Applicability of evidence for the context of a relative effectiveness assessment (updated 2015)	How to assess whether there is a relevant modification of the effect of the results in the clinical studies (e.g. an RCT) if the intervention is applied to the population of interest in clinical setting?	Transversal	Yes (feedback from partners)
Internal validity of randomised controlled trials (updated 2015)	To provide recommendations for the assessment of the internal validity of RCTs whose purpose is the determination of the relative effectiveness of health care interventions.	Transversal	Yes (feedback from partners)
Internal validity of non-randomised studies (NRS) on interventions (updated 2015)	To provide recommendations on the assessment of the internal validity of NRS used for the evaluation of effects of interventions.	Transversal	Yes (feedback from partners)
Meta-analysis of diagnostic test accuracy studies (updated 2014)	A review of the available methods for the meta-analysis of diagnostic test accuracy studies. The aim of the guideline is to highlight the circumstances in which it is appropriate to use each of the approaches.	Transversal	No feedback from JA3 about the need to update.
Therapeutic medical devices (updated 2015)	To provide systematic review methodology advice for evaluating the clinical effectiveness of therapeutic medical devices. The focus is on: 1. Aspects deriving from the incremental development of MD. 2. The greater importance of context and user dependence in the evaluation of MD compared to drugs.	Transversal	No feedback from JA3 about the need to update.

Science item	Stated aim	Applicability to the existing work programme	Update required
Personalised Medicine and Co-Dependent Technologies (updated 2015)	To contribute to the ongoing discussion, both within EUnetHTA and with external stakeholders, about appropriate methods for the evaluation of PM technologies.	Transversal	This is a reflection paper and was developed with a view to producing a future methodological guideline
Methods for health economic evaluations - A guideline based on current practices in Europe (updated 2015)	To set a general framework for EUnetHTA on how to conduct economic evaluations and increase the transferability of economic evaluations between EUnetHTA partners.	Primarily General support	No feedback from JA3 about the need to update.
Practical considerations when critically assessing economic evaluations. Guidance document (published 2020)	To aid in the critical assessment of relevant elements of an economic evaluation.	Primarily General support	No feedback from JA3 about the need to update.
PLEG science documents			
Position Paper on research recommendations for Additional Evidence Generation (AEG)	The position paper is aimed at improving presentation of research recommendations by providing a structured approach to identify research gaps and to formulate research recommendations.	PLEG and general support	To be further developed as part of the JA3 final deliverable PLEG recommendations.
Position Paper on study design for AEG	This paper discusses the role of the reviewer in specifying the design of subsequent primary research by considering current practice in Europe and beyond. It is not a guideline, but a position paper that presents a view of EUnetHTA members as to the best approaches to specifying primary research methods to follow from systematic review type HTA reports.	PLEG and general support	
Core Protocol Template for AEG	To define the “core elements” of a study protocol for Additional Evidence Generation, and develop a template, based on these core elements, that could be used in different countries.	PLEG and general support	

Science item	Stated aim	Applicability to the existing work programme	Update required
Selection Prioritisation Criteria for AEG	A set of selection/prioritisation criteria that should help HTA doers, funders, and other stakeholders to select technologies for which complementary studies are really worth performing.	PLEG and general support	
REQueST (published 2020)	The Registry Evaluation and Quality Standards Tool (REQueST®) aims to support HTA organisations and other actors in guiding and evaluating registries for effective usage in HTA.	PLEG and general support	
Other science documents and tools			
HTA Core model	The HTA Core Model is a methodological framework for production and sharing of HTA information, including: A standardised set of HTA questions (the ontology) allow users to define their specific research questions within a hierarchical structure. Methodological guidance to assist in answering the research questions. A common reporting structure for presenting findings in a standardised “question-answer pair” format.	Primarily support to HTA agencies and use in JA/CA.	Updating work in JA3, specifically focused on the reporting structure for other technologies.
Evidence submission template (published 2015)	A tool that agencies can use to request evidence from companies to support their HTA and reimbursement processes. The tool covers relative effectiveness assessment including a description of the health condition and health technology, as well as clinical effectiveness and safety information.	Primarily support to HTA agencies and use in JA/CA.	Updating work in JA3 specifically focusses on the template to be used for JA/CA.

18.2 Lessons learned

Methodological and scientific documents have accumulated over the course of the three joint actions. At the start of the joint actions, the aim of these documents tended to be to promote better understanding of methods used in HTA agencies, support capacity development, and support better alignment in methods across HTA agencies. The focus of HTA cooperation has changed over the joint actions so there is now a greater need for methodological guidance for project teams to support joint HTA activities and, in particular, production of JA/CA.

The value of scientific guidance is contingent on it being comprehensive, relevant, up-to-date and promoted. In JA3, there have been relatively low levels of updating work because of project resource allocation. This means that many of the methodological guidelines have not been updated since JA2 and have been identified by HTA agencies as no longer fully meeting the requirements of HTA cooperation (shown in the last column of Table 18-2).

Scientific and methodological development is an ongoing process. As the scientific field moves on, procedures need to be put in place to identify and work on topics that require scientific guidance or a shared position before these become issues for HTA, for example, as in digital health technologies and gene therapies.

In JA3 reviewing or establishing methodological guidelines with regulators on topics of mutual interest was originally envisaged, but eventually not considered feasible for resource reasons. Mutual commenting during public consultation was pursued.

18.3 Recommendations for a future model of HTA cooperation

There should be a suite of methodological documents that support all joint HTA activities, are applied across activities, and are tailored to the objectives and production requirements of HTA cooperation. The areas covered in the existing methodological guidelines provide a foundation for HTA cooperation. However, updates as shown in Table 18-2 are required in some instances and there are gaps where methodological guidance is not yet available as shown in Table 18-3.

Methodological documents need to be accompanied with guidance for project teams and for technology developers preparing evidence submissions about the preferred methodological approach to be taken in a joint HTA activity.

The methodological documents should take learnings from across joint HTA activities to ensure that recommendations made in advice activities, such as ED and PLEG, are consistent with the approach subsequently taken in assessment activities such as JA/CA.

There are a number of organisations producing methodological guidance for HTA. To avoid duplication of work, guidance developed outside of HTA cooperation should be drawn on to support joint HTA activities where appropriate and methodological guidance prepared in collaboration with other related organisations or projects.

To ensure that HTA cooperation remains up to date there needs to be:

- A procedure for identifying new science areas where methodological guidance will be required, prior to it becoming a problem for HTA;
- A regular cycle of identifying whether existing methodological guidance needs to be reviewed, with resourcing to then implement the changes.

The procedure for reviewing methodological and science documents should include stakeholder involvement.

Table 18-3: Areas requiring additional methodological guidance

Science area
A common framework / guidance for indirect comparisons (including Matching Adjusted Indirect Comparisons (MAIC) and network meta-analysis) and innovative trial designs.
Guidelines for incorporating RWD/RWE into HTA.
Position papers on specific issues such as methods around biomarkers, selecting patients for ATMPs, histology independent cancer drugs, personalised medicines.
A framework for minimum evidence requirements and minimal important differences (MID) in changes of endpoints.
Development of procedures to assess a wider range of health technologies, such as digital therapeutics, eHealth, artificial intelligence, complex interventions, etc.
Expansion of the frameworks of assessment to include new domains such as environmental impact and organisational analyses.
Guideline for the critical assessment of clinical evidence.
Guidance on the partial use of GRADE – outcome of the JA3 common phrases subgroup.
Guideline on study types to include in REAs.
Guidance for authors on detecting and handling selective reporting bias.

18.4 Recommendations for future work

Incorporate into methodological guidelines' relevant learnings and guidance from the qualitative analyses of ED experience to help align ED and JA/CA approaches.

Identify topics of mutual interest with regulators to jointly develop methodological guidelines for evidence generation (e.g. on clinical trial methodology or on evidence transfer).

Review of methodological guidelines identified in JA3 as being out of date (Table 18-2).

Develop science documents in the areas identified in Table 18-3.

Develop a procedure for identifying new science areas requiring methodological guidance for HTA in the future.

Adapt the existing JA3 development and update procedure for methodological guidelines to fit with any EU HTA regulation requirements.

Collaborate with regulators on access to and analysis of real-world data, e.g. data quality framework, data standards, meta-data, and a public catalogue of real-world data set

19 ACTIVITY SPECIFIC: FEEDBACK AND EVALUATION

Evaluation ensures that the process and outputs of HTA cooperation remain relevant and valued by participants in the HTA cooperation. Evaluation should exist across elements of HTA cooperation to include outputs of cooperation, cooperation structures and processes, and the people, groups and organisations involved. This section considers the cycle of feedback and evaluation needed.

19.1 Summary of JA3 features

Table 19-1: Key JA3 feedback and evaluation documents

Key documents	Link
SOP Procedure for Evaluation of Collaboration and QM-System	Available to EUnetHTA partners in the Companion Guide.
Feedback templates	*Internal documents only: limited circulation*

The project-based nature of JA3 means that formal evaluation activities tend to be targeted to evaluation of JA3.

Feedback and evaluation of joint HTA activities has tended to be put in place in an activity-specific manner by the HTA agency leading on the activity. This means that a variety of formal and informal feedback and evaluation approaches have been used across ED, JA/CA and PLEG.

In general, each joint HTA activity has sought feedback from internal and external participants. Feedback from external participants has been obtained through surveys. Feedback from internal participants has been collected through a mixture of informal feedback at meetings and surveys. In JA/CA feedback has also been obtained via interviews and workshops involving project teams, industry, and users.

Table 19-2: JA3 activity-specific feedback procedures

	ED	JA/CA	PLEG
Who	Technology Developers Patients/experts HTA agencies	Project teams and Project Manager. Users Industry	Project teams External participants
How	Questionnaires (applicants and patient/experts). HTA agency feedback via TC during EDWP meetings. Quantitative and qualitative analyses of the ED recommendations.	Online survey (project managers, project teams and users). Questionnaires (Industry (PT) and Patients/experts). Interviews (users). Feedback workshops (Industry (PT) and authoring teams).	Feedback from external participants collected informally. HTA agency feedback via teleconferences during WP5B meetings.

19.2 Lessons learned

Evaluation needs to have a mechanism by which the outcomes of evaluation fed back into the HTA cooperation to bring about change. In JA3, an explicit feedback loop has not been visible for all evaluation processes.

Collection of feedback needs to be accompanied with sufficient resourcing to implement feedback received. There have been situations in JA3 where participants have identified that updates were needed, but the resourcing has not been available to make the changes identified.

There needs to be clear objectives that HTA cooperation is working towards so that tools and indicators can be developed to measure progress towards achievement of the objectives. This also provides participants with a clear goal and insight into the changes that might need to be made at an HTA agency level.

In addition to surveys, workshops and interviews are useful to obtain in-depth feedback from internal and external participants.

19.3 Recommendations for a future model of HTA cooperation

HTA cooperation should have a regular cycle of evaluation and updating to ensure that there is an iterative learning process and that HTA cooperation remains relevant as the environment in which it functions changes. The evaluation process should cover not only the outputs and processes, but also the structures and the people, groups and organisations participating.

There should be a consistent and formal feedback procedure applied across joint HTA activities and across the cooperation. This process should be supported centrally. If possible, the evaluation procedure should be linked to and embedded in any IT system managing the templates and procedures of HTA cooperation.

As part of evaluation, the impact of the cooperation should be monitored. The benefits of cooperation are multiple and can be different for individual HTA agencies engaged in cooperation. Agreed objectives of HTA cooperation and indicators to measure these can support impact assessment.

19.4 Recommendations for future work

Identification of the variables that define the success of HTA cooperation. Agreement on how these variables should be measured (e.g. the parameters that define a high-quality JA/CA). Formulation of the variables into indicators that can be used to measure achievement of the objectives.

Having defined the variables and indicators formalisation and development of feedback tools.

Development of an evaluation procedure that links the desired objectives expected of HTA cooperation to the outputs of joint HTA activities and transversal cooperation processes and includes an explicit change process where activities and processes can be changed in light of feedback in order to meet the objectives of HTA cooperation.

A system to collect feedback about the impact of HTA cooperation to ensure that it continues to meet the needs of participants and health systems.

Ongoing monitoring of the resources needed for ED, JA/CA and PLEG.

Analysis to inform ED about whether advice provided in ED is seen to have improved the appropriateness of evidence submitted for HTA.

20 CONCLUSION: MODEL OF COOPERATION

The final section of the White Paper brings together the previous sections to present the progress in JA3 towards defining the principles of a model of HTA cooperation and the most important next steps to take the model forward.

20.1 The framework of HTA cooperation

The framework used for HTA cooperation is important. Four weaknesses were identified with the framework used in the JA3:

Inability to act as an entity in its own right: The nature of the JA3 HTA cooperation framework has limited the extent to which the cooperation can approve its products, be liable for its outcomes, be the owner of its infrastructure, and create official arrangements with other organisations (e.g. confidentiality agreements).

The voluntary nature of the cooperation: Voluntary participation allows HTA agencies to choose how they take part, but in JA3 has affected the ability to constitute project teams, affected clarity about uptake of outputs of joint HTA activities, and affected the ability to implement templates and procedures. Voluntary participation of industry has affected the ability to plan and implement prioritised work in JA3.

The work package structure: The project structure of JA3 provides flexibility in how joint HTA activities are undertaken but has also allowed differences in approach to joint HTA activities to grow. These differences have not always been underpinned with a clear rationale for those differences. This has affected the ease of engagement for participants and perceptions of the level of coherence of the cooperation. The project structure has also led in some cases to conflicting goals and lack of clarity of responsibility for certain tasks.

The absence of continuity: The project nature of the cooperation means that each joint action has a start and end date, and often a gap in between projects without resourcing. This has created staffing issues since staff leave towards the end of each joint action when their contracts expire. It has also created issues with stability of infrastructure hosting and maintenance when project responsibilities end and influenced planning and usability of outputs as all joint HTA activities must be finished at the end of the project.

The framework for HTA cooperation needs to provide stability and continuity, allow the cooperation to act as an entity, and have a commissioning and resourcing structure that can guarantee project teams for joint HTA activities.

Table 20-1: Priority areas for further development

Priority areas for further development
A resourcing and commissioning model for joint HTA activities that supports identification and maintenance of project teams.
If required, to ensure a sustainable model of HTA cooperation the implementation of the Early Dialogue fee-for-service mechanism.
A mechanism to ensure stable IT hosting of infrastructure.

20.2 The outputs of HTA cooperation

The value of HTA cooperation is contingent on the added value and relevance of its outputs to users. JA3 has identified three areas of importance.

HTA activities along the technology lifecycle: JA3 had three key joint HTA activities: ED, JA/CA and PLEG undertaken for both PT and OT. The experience of JA3 is that these activities and the health technologies covered must be retained in HTA cooperation. Two further recommendations are made:

- Joint HTA activities should be expanded to include other parts of the health technology lifecycle, to start with horizon scanning and following through the HTA process to include formal re-assessment procedures.
- There should be explicit and transparent links between joint HTA activities on the same topic, so that activities can inform each other and capitalise on the joint HTA activities already undertaken.

The implication from this first recommendation is that procedures for horizon scanning and reassessment need to be developed, including importantly when a reassessment will be of value. In addition, when considering reassessment, in order to reflect how HTA agencies carry out reassessments in 'real-life', it may be important to allow joint HTA activities to go beyond the framework of single technology assessment and REA and include multiple technology assessment and a consideration of additional HTA domains.

System preparedness: HTA cooperation is ideally positioned to identify and provide guidance on future scientific and methodological challenges before they become an issue for joint and agency-level HTA activities. HTA cooperation through joint horizon scanning activities should support the wider HTA environment to understand the technological and methodological challenges that HTA will face in the future.

Flexibility to evolve: Within the timeframe of JA3, changes needed to be made to the participants in the cooperation, the transversal cooperation processes, and the specific joint HTA activity procedures. JA3 also needed to make changes to its working practices to respond to external demands arising from the COVID-19 pandemic. HTA cooperation must have the flexibility to respond to internal feedback from participants engaging in the cooperation and changes in the external environment that affect the outputs and activities that will be valued by users.

Table 20-2: Priority areas for further development

Priority areas for further development
HTA activities along the technology lifecycle: • Develop a system to support proactive and timely identification and selection of topics that will provide most value to participants for each joint HTA activity (EDs, JA/CA, PLEG). • Develop a system to maintain and update JA/CA when needed. • For PLEG, further work to consider the recommended outputs from joint PLEG activities and to develop national and international good practices for databases to promote and help establish joint PLEG activities. • With the introduction of reassessment processes agree with cooperation participants whether the HTA assessment framework should also be expanded to include multiple technology assessment and additional domains of HTA.
System Preparedness: • A procedure to identify, in a timely manner, areas where further scientific guidance is needed and how that guidance can be sourced and/or developed.
Flexibility to evolve: • A feedback cycle that ensures that the nature and remit of activities continue to meet the needs of HTA agencies and healthcare systems to optimise outcomes for patients. • Evaluation processes for the cooperation including evaluation of outputs and transversal processes that link to the desired outcomes and achievements expected of HTA cooperation and explicit change processes.

20.3 The wider context

HTA cooperation sits alongside a regulatory environment and within a broader country-level HTA process. HTA cooperation must be able to link to the environments it interacts with in a way that adds value for participants. Two important learnings have been highlighted in JA3.

Collaboration with regulators and other HTA-related organisations: JA3 has demonstrated the value of collaboration with regulators across a range of joint HTA activities (ED, PT JA, PLEG). These collaborations build on the synergies between the organisations and add value to the joint HTA activities, while also respecting the differences in the remits and responsibilities of HTA and the regulators.

The MD regulatory environment is currently changing. Although the nature of the collaboration between HTA and PT regulators and HTA and MD regulators will be different, the changes to the MD regulatory environment provide an opportunity to use the experiences gathered from the PT collaboration with EMA to establish a collaborative relationship between MD regulators and HTA.

Alongside the regulators are HTA-related organisations and networks as well as regional collaborative HTA initiatives. A strategic approach to engaging with the entities will help support HTA cooperation to position itself relative to these other entities operating in HTA.

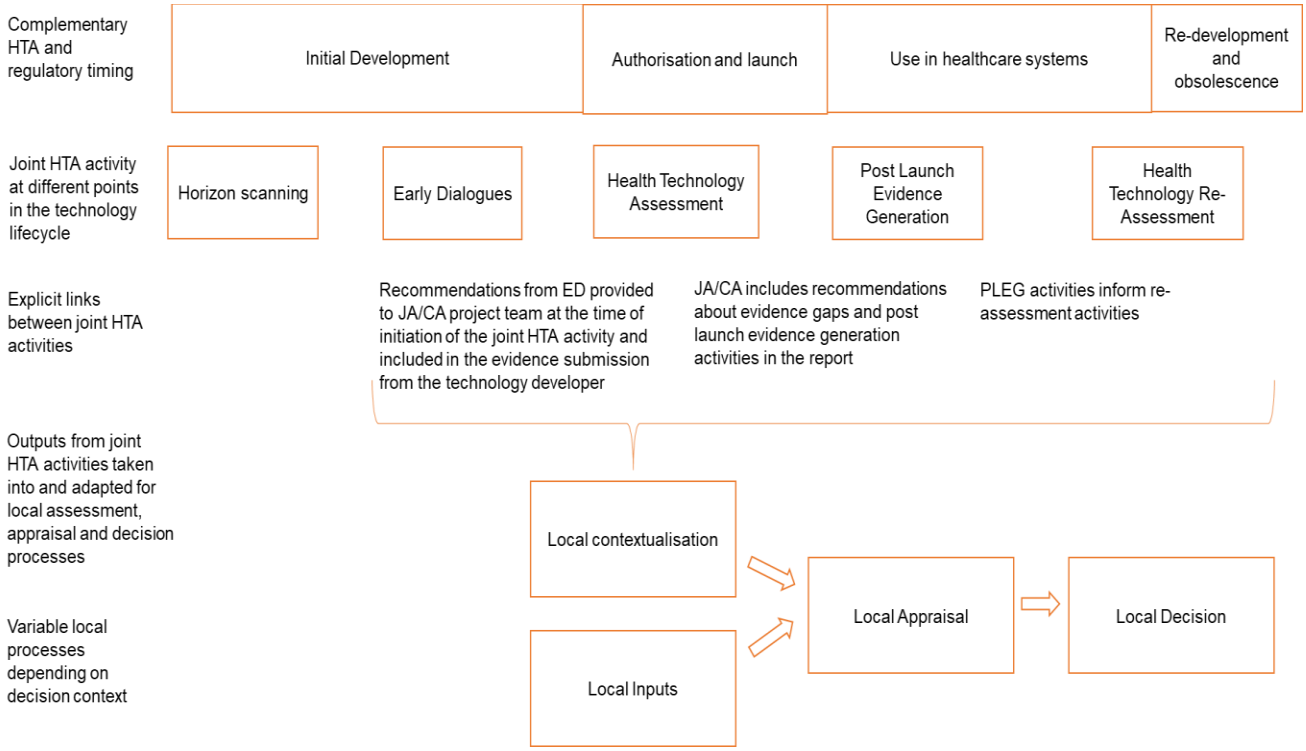
Responsive to varied decision contexts: JA3 has shown that the outputs of joint HTA activities can and will be taken into and adapted for local assessment, appraisal and decision-making processes. However, the outputs of joint HTA activities will be used in varied decision contexts. To be maximally informative, joint HTA activities should

- Collect as part of project planning, information and decision needs of its users and respond to these in the output from the joint HTA output;
- Present context-dependent information factually to allow for subsequent agency-level contextualization.

There remain divergent views about the extent to which HTA agencies should be involved in joint HTA activities that they are expected to use. There is consensus that HTA agency involvement during project planning is feasible and valuable. Some HTA agencies would also like to have an opportunity to review draft reports. However, there is also an acknowledgement that this could affect timeliness and resource requirements.

Table 20-3: Priority areas for further development

Priority areas for further development
Collaboration with regulators and other HTA-related organisations: • Following implementation of a framework for HTA cooperation, setting up a formal collaboration agreement with the EMA. • Building on the work undertaken in JA3, further development of collaboration with MD regulators building on lessons learned with the EMA. • Creation of a formal strategic engagement plan to support relationships between EU HTA cooperation and other organisations, and to position EU HTA cooperation with other EU organisations and initiatives, as well as with other international organisations and networks.
Decision context: • Continue the process of reaching a consensus among participants on the appropriate level of depth and content for JA/CA. • Develop guidelines for project teams and participants on the scoping process e.g. principles for choosing comparators or dealing with one PICO vs. multiple PICO. • Develop an OT JA/CA process for getting target user input into the PICO. • For the outputs of joint HTA activities to be used by HTA agencies, consider whether a procedure can be implemented that allows for HTA agency input into the draft joint output in a way that supports timeliness and resources.



Note: A health technology will not necessarily be subject to every joint HTA activity.
Figure 20-1: The context in which HTA cooperation is situated

20.4 Organisational structures

JA3 has identified the structural elements that need to be in place to support transversal HTA cooperation and specific joint HTA activities. The recommendations in JA3 are shown in Figure 20-2. The organisational structure is characterised by having:

- An inclusive network of internal participants that can include more than one HTA agency per country;
- External participants from a broad group of stakeholders to inform joint HTA activities. External participants should be involved in specific joint HTA activities, but also be given opportunities to engage in transversal HTA cooperation;
- A decision-making body, led by a Chair and Vice Chair, composed from the network of internal participants;
- A Secretariat to support the network and the decision-making body;
- Project teams constituted from the network that undertake a specific joint HTA activity;
- Technical advice and support for the decision-making body from standing and ad-hoc expert groups and centralised technical support services;
- A comprehensive and robust set of corporate governance policies that provide the rules and procedures guiding the cooperation.

A detailed work-up to define the roles and responsibilities, rules of procedure, decision-making processes and management structures is required when the framework for HTA cooperation is in place.

Table 20-4: Priority areas for further development

Priority areas for further development
Definition of the roles and responsibilities of the decision-making body, the Secretariat and the centralised support functions.
Agreement on the standing expert groups needed and their role in joint HTA activities. This should include specific consideration of the need for: • Transversal scientific and methodological expert advisory groups such as the information specialists' network and statistical specialists' network convened in JA3. • Activity-specific expert groups such as ED, JA/CA and PLEG programme experts.
Agreement on the management structure between the different governance elements.
Development of the mechanism of decision-making, including principles for involving participants in decisions that can affect them.
Development of corporate governance policies, to include: • Definition of general rules of transparency/confidentiality/independence/ quality system approach and COI approach. • Strengthening information governance and IT policy, including data security and legal issues. • Development of a COI policy that supports participation of experts, but which maintains an acceptable level of independence that allows agencies to use the outputs of joint HTA activities.
Define the roles, remits and resources needed for each of the required centralised support services.

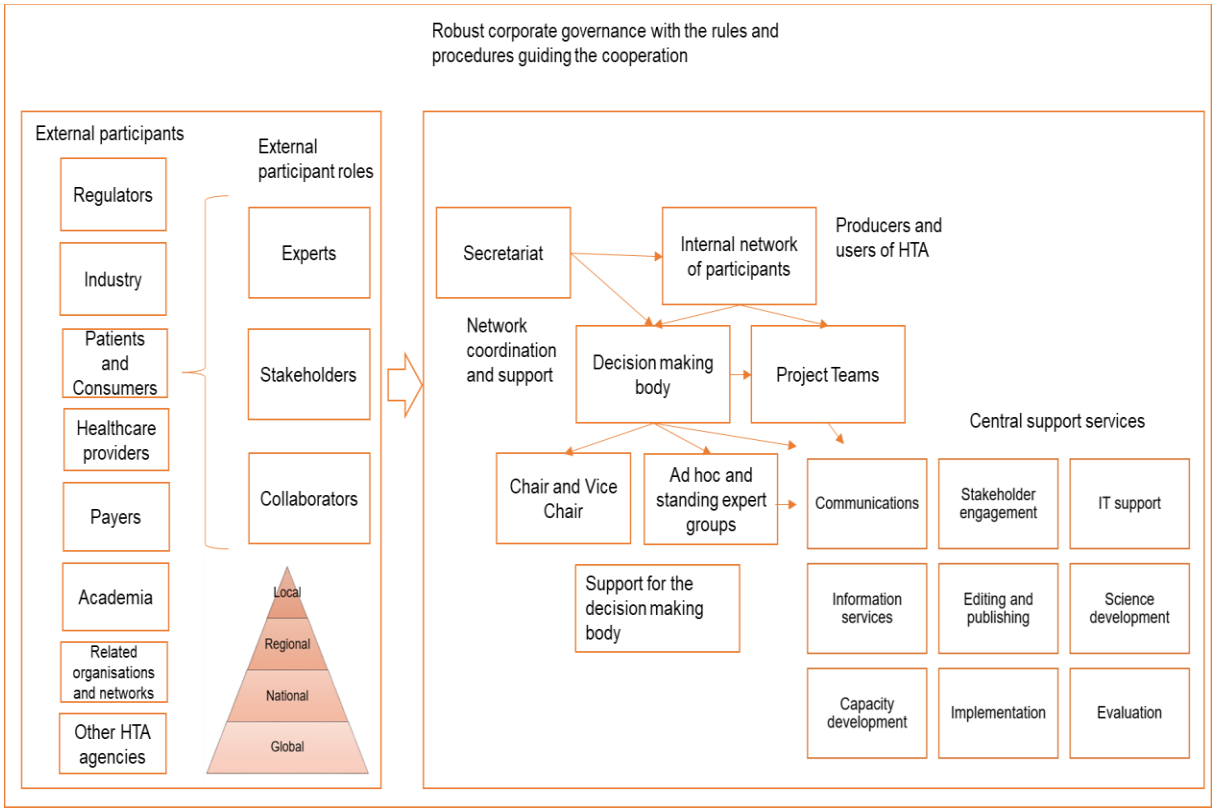


Figure 20-2: Organisational structure of HTA cooperation

20.5 Project teams

Each joint HTA activity is carried out by a project team recruited from the network of internal participants. The structure of a project team is shown in Figure 20-3. Each project team is characterised by having:

- HTA agency selection using a transparent set of criteria based on the required skills and expertise for a joint HTA activity;
- An HTA agency that leads the activities and a second HTA agency that supports them;
- Additional project team members from the internal participants who provide input and review;
- Dedicated project management to manage the activity and the project team;
- Access to scientific and methodological expert advisory groups, for example information retrieval experts and statistical specialists;
- Access to a common set of scientific tools to complete the activity;
- Access to a range of centralised support services, for example publishing and editing, IT, stakeholder engagement and communications;
- Scientific oversight provided by a standing group of experts to ensure consistency in approach within a joint HTA activity;
- Access to independent conflict resolution;
- Approval of their output from the joint HTA activity by the decision-making body;

- Corporate governance support, for example to manage conflicts of interest.

Although joint HTA activities are undertaken by project-specific teams, a comprehensive set of transversal objectives, procedures, policies and structures should be implemented to give consistency in approach across activities.

Table 20-5: Priority areas for further development

Priority areas for further development
Work to gather insight into existing agency capacity and scientific and technical skills. • Analysis of the human resources available to support HTA cooperation and major gaps in human resources and scientific knowledge. A RoadMap identifying how the identified gaps will be addressed. • Analysis of the software, tools and databases agencies currently use and have expertise in using. This analysis should identify where there are common scientific tools already in use and where there are significant variations in the tools used, to inform consideration of whether any further investment in scientific tools to support joint HTA activities is needed.
Agreement on the skills and expertise needed in a project team.
A programme of capacity development based on the findings in the RoadMap described above and the agreement on the skills and expertise needed in a project team to ensure that the pool of participants is sufficiently large to be able to constitute project teams for joint HTA activities.
Definition of the centralised procedures for activity management.
Definition of the roles, responsibility and procedures for the provision of corporate governance, conflict management, scientific oversight and approval.

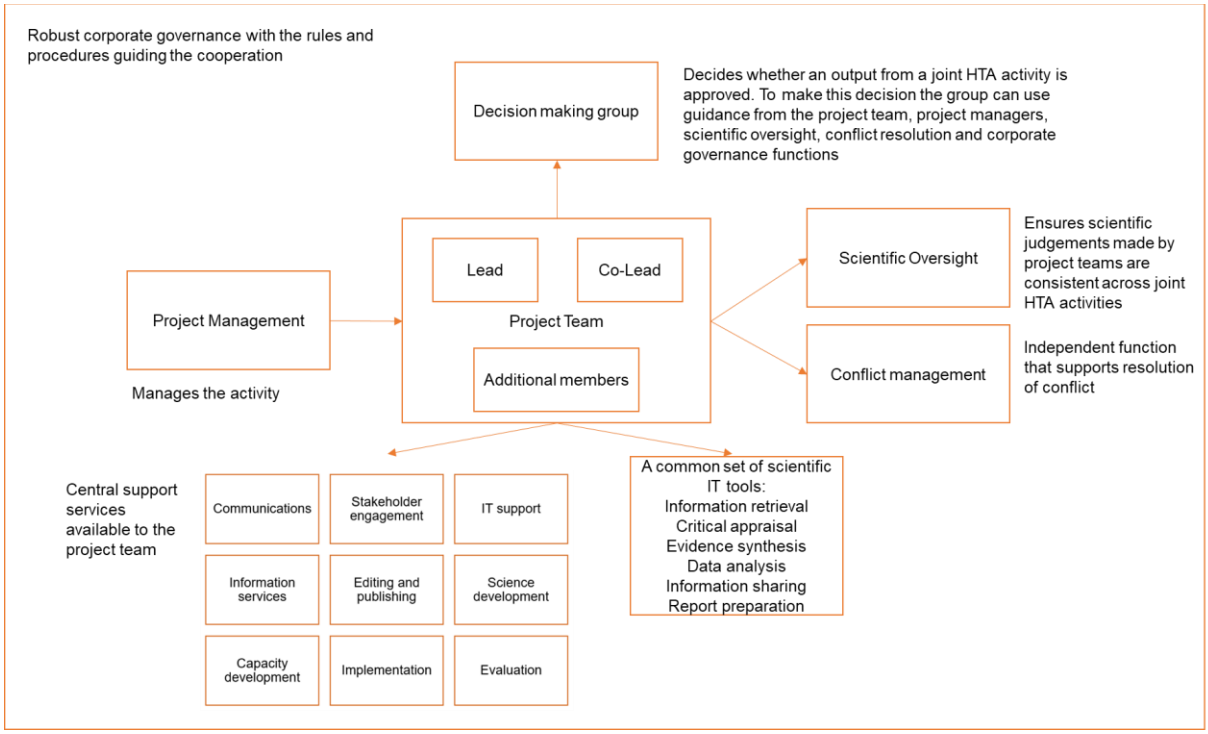


Figure 20-3: Structure of project teams

20.6 External participation

There has been progress in JA3 to develop procedures for engaging stakeholder groups in each joint HTA activity. This experience has shown how different HTA agencies vary in their approach to stakeholder engagement. External participation remains an area where there are divergent options between HTA agencies, but in some areas there is more agreement than others.

- There are more divergent opinions about the involvement of industry and payers than there are about involving patients and healthcare professionals. There is consensus that involvement of patients and healthcare professionals should be routinely expected in an HTA activity;
- There are more divergent opinions about the involvement of stakeholders once reports have been drafted than there are in earlier stages to identify topics and to understand and clarify issues to be addressed in the joint HTA activity. There is consensus that stakeholder engagement in topic identification and project planning is important and appropriate;
- There is consensus that the contribution that external participants provide in a joint HTA activity must be transparent and documented in the output from the activity. Guidance must be given to stakeholders about the input expected and also to project teams about using and documenting the input provided.

Once the framework for cooperation is specified, a stakeholder participation framework is required to outline the principles of engagement in the areas where there remain divergent opinions.

Table 20-6: Priority areas for further development

Priority areas for further development
A participation framework and shared set of principles for stakeholder engagement to be applied transversally across all joint HTA activities. As part of the participation framework: • Definition of principles for involving stakeholders, in particular industry and payers. • Definition of principles for patient involvement and inclusion of patient input in joint HTA outputs. • Principles for involving stakeholders in later stages of the HTA process, including fact checking.
Further development of processes for involving experts and, in particular, healthcare professionals.
Further development of processes for involving payers in joint HTA activities
Preparation of documents describing roles, responsibilities and participation in joint HTA activities of external participants. Consistent availability, specification and structure of these documents: SOPs, manuals, guides or overviews.

20.7 Science, Procedures and Technical Infrastructure

JA3 has made significant progress towards defining the resources needed for a joint HTA activity. Recommendations are made in five areas (Figure 20-4):

Methodological Guidance: HTA cooperation requires a comprehensive suite of methodological guidance. This guidance should be applicable transversally across all joint HTA activities, creating a consistent methodological approach to HTA cooperation. Transversal methodological guidance needs to be accompanied with activity-specific guidance for project teams to advise them on the methodological approach to be taken in a specific joint HTA activity.

JA3 has relied mainly on guidelines developed in JA2, which means that many of those guidelines have not been significantly reviewed for over five years and, in some cases, are no longer considered fit for purpose. Feedback from assessment teams in JA3 suggests that some guidelines are incomplete and not instructive enough to be applied in joint HTA activities. A review of these guidelines remains an outstanding activity.

Procedural Guidance: Procedural guidance is activity-specific and is sensitive to the framework of the cooperation and the timing and resources available.

- JA3 procedures provide a foundation for the procedures used in HTA cooperation going forward, but also need to be adapted to the cooperation framework going forward;
- Procedures should be aligned in their content, presentation and availability across joint HTA activities and be accessed in a similar manner. This promotes ease of engagement and familiarity with the cooperation structures;
- Procedures need to have acceptance from participants to ensure that they are implemented and that there is compliance;
- Procedures need to be sensitive to the timing and resources available for a joint HTA activity. Robust procedures do not necessarily lead to high-quality outputs unless authors are given sufficient time, support, training and resources to apply them.

Infrastructure: The nature of the EUnetHTA joint actions has meant that the IT tools and databases have been developed separately and without proper integration. This has affected their stability, ability to be maintained, and the ease of user engagement. Some progress has been made in JA3 to integrate the tools into a SharePoint system. Further work to assess the feasibility of creating a single integrated IT platform with all the needed functions should be undertaken.

Quality Management System: In JA3, a quality management system was developed to contain all process flows, procedures, templates, IT tools and methodological guidance used in JA/CA. This system allowed internal participants to have a single access point to all the resources required for JA/CA. Due to resource limitations, the system was not applied to other joint HTA activities. However, such a system could have a broad application across all joint HTA activities and also for certain transversal elements such as policy development and evaluation processes.

Table 20-7: Priority areas for further development

Priority areas for further development
Methodological Guidance: • Review of guidelines identified in JA3 as being out of date and/or insufficient to support joint HTA activities (table 18-2). • Development of science documents in identified areas (table 18-3). • Development of guidance for authors about the methodological approach to be applied in different joint HTA activities.
Procedural Guidance: • Continue to work on and adapt the procedures developed in JA3 to fit the requirements of the future framework for HTA cooperation. • Develop any new procedures needed, for example for reassessment procedures. • Review the procedures, participation, timing and resources required for a JA/CA, adjustment as needed to develop a JA/CA that meets the needs of HTA agencies within the resources and timeframe available. • Preparation of documents describing roles, responsibilities and participation in activities of internal participants. Consistent availability, specification and structure of these documents: SOPs, manuals, guides or overviews.
Infrastructure Development: • Feasibility of developing a single integrated IT platform that houses all the required IT functions. This can build on work started in JA3 using the SharePoint platform, with further integration of other applications e.g. Microsoft Teams. • Feasibility of developing an authoring, and publication tool/platform to support the production of outputs from joint HTA activities. • Implementation of a transversal activity management tool.
Quality Management System: • Rollout of the quality management system to other areas and further development of the system.
A system to maintain and update methodological guidance, science documents, tools, procedures and SOPs.

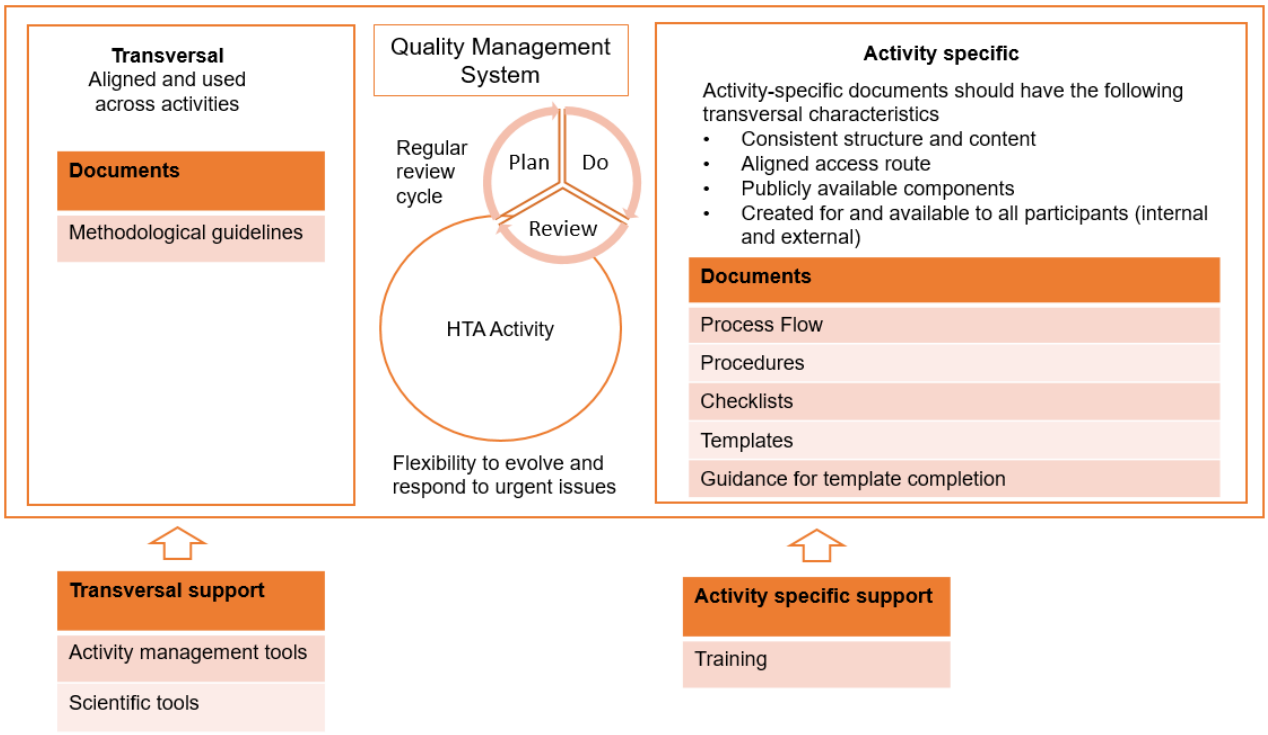


Figure 20-4: Resources for a joint HTA activity