EUnetHTA 21

Project Plan

D5.4 – PRODUCTION OF JCA/CA ON MEDICINAL PRODUCTS AND MEDICAL DEVICES

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Participants

Hands-on Group	Austrian Institute for Health Technology Assessment [AIHTA], Austria Haute Autorité de Santé, [HAS], France National Authority of Medicines and Health Products, I.P., [INFARMED], Portugal
Project Management	Zorginstituut Nederland, [ZIN], the Netherlands
CSCQ	Agencia Española de Medicamentos y Productos Sanitarios [AEMPS], Spain Austrian Institute for Health Technology Assessment [AIHTA], Austria Belgian Health Care Knowledge Centre, [KCE], Belgium Gemeinsamer Bundesausschuss, [G-BA], Germany Haute Autorité de Santé, [HAS], France Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, [IGWIG], Germany Italian Medicines Agency, [AIFA], Italy National Authority of Medicines and Health Products, I.P., [INFARMED], Portugal National Centre for Pharmacoeconomics, St. James Hospital, [NCPE], Ireland National Institute of Pharmacy and Nutrition, [NIPN], Hungary Norwegian Medicines Agency, [NOMA], Norway The Dental and Pharmaceutical Benefits Agency, [TLV], Sweden Zorginstituut Nederland, [ZIN], The Netherlands
CEB	

The work in EUnetHTA 21 is a collaborative effort. While the agencies in the Hands-on Group will be actively writing the deliverable, the entire EUnetHTA 21 consortium is involved in its production throughout various stages. This means that the Committee for Scientific Consistency and Quality (CSCQ) will review and discuss several drafts of the deliverable prior to validation. Afterwards the Consortium Executive Board (CEB) will endorse the final deliverable prior to publication. For further information on stakeholder involvement in this deliverable, please see section 3.2.

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LIST OF ABBREVIATIONS

CEB	Consortium Executive Board
CSCQ	Committee for Scientific Consistency and Quality
EUnetHTA	European Network of Health Technology Assessment
HCP	Health care professional
HTA	Health Technology Assessment
HTD	Health Technology Developer
JA3	EUnetHTA Joint Action 3
JCA	Joint Clinical Assessment
JSC	Joint Scientific Consultation
WP4	Work Package 4 of EUnetHTA Joint Action 3

1 INTRODUCTION

In the technical offer, submitted on 04/05/2021, deliverables for the production of Joint Clinical Assessment (JCA)/Collaborative Assessment (CA) for medicinal products and medical devices have been defined.

This Project Plan describes the general objectives, approach and timelines for the deliverable 5.4.1 on production of JCA/CA.

Please note: only when topics have been identified and submitted for a JCA/CA, a dedicated project plan will be developed for these products. This project plan will follow the template used in Joint Action 3 (JA3) and will focus on the technology under assessment, PICO, methodology for the assessment and the production timelines.

2 BACKGROUND

Two types of clinical assessments can be conducted, namely the JCA and CA. For medicinal products, JCA is the only option since the centralised regulatory process results in various national HTA agencies having the same needs at the same time. For medical devices, the situation is currently different and the timing and place of reimbursement decision-making is more decentralized compared to pharmaceutical products. It is expected that the implementation of the Regulation (EU) 2017/745 for medical devices and further collaborations between HTA bodies (HTAb) should support future alignment of HTA needs. In the meantime, CA is an option to consider in the context of the short time horizon of the tender project.

In accordance with the tender specifications, the following clinical assessments are planned during EUnetHTA 21:

- For medicinal products: 2 JCA or at least, not less than 1 JCA;
- For medical devices; 4 JCA/ CA, or at least, not less than 2 JCA/CA.

During EUnetHTA JA3, 20 JCA for medicinal products were conducted, including Rapid Collaborative Review on COVID-19 treatments (see Annex A-5.4.1-1 for an example JCA of a medicinal product). For “Other Technologies” including medical devices, diagnostics and procedures 2 JCA and 25 CA were performed see Annex A-5.4.1-2 for an example JCA/CA of a medical device). Furthermore, 2 Rapid Collaborative Reviews on COVID-19 diagnostics were prepared.

During this experience, challenges were identified which led to recommendations for a future production process. In summary, challenges that were identified were on 1) timing and topic selection (especially for other technologies); 2) variability in methods and REA content; 3) complexity of the EUnetHTA assessment procedure compared to national procedures; 4) Lack of structured interaction between EUnetHTA and regulator of medical devices; 5) involvement of patients and health care professionals (HCP); 6) Health Technology Developers (HTD) reluctant to submit dossiers; and 7) Quality Control and process validation of REA. A full description of these challenges can be found in the EUnetHTA 21 Technical offer, the FMC White Paper and the WP4 Recommendations for Production Process.

Based on lessons learned from these valuable experiences with joint HTA work, the following EUnetHTA recommendations were produced that can be taken into account for JCA/CA production within the duration of EUnetHTA 21.

1. Timing and topic selection: A topic identification system is required to establish in advance which technologies may be of benefit for a JCA. There needs to be clear eligibility and prioritisation criteria for JCA/CA so that industry can predict which topics will be eligible. Early identification of a technology to be assessed should also increase the possibility of recruiting clinical experts and patients/patient representatives;
2. Variability in methods and REA content: The appropriate content of JCA/CA reports still needs to be negotiated between agencies as it depends on factors including where the agency draws the boundary between assessment and appraisal depending on the agency’s remit, whether the

agency wants to use the joint HTA output in place of a national report or to use the content of the joint HTA output to develop their own report, whether the agency is asked to provide a written detailed technical analysis or a summary document based on their analysis, and the legal status of the agency report. It was recommended that HTA bodies continue the process of reaching a consensus agreement on the appropriate level of depth and content of JCA/CA. Furthermore, to increase consistency between the JCA content, there is a greater need for further methodological guidance for authors to support the production of JCA report;

3. Complexity of EUnetHTA procedure in contrast to national procedures:
    - Ensure that project management of assessments is predictable and guarantees fairness of procedure. Project management should be conducted according to standardised processes. Necessary procedures, manuals, templates and tools should be maintained. Such tools would include those to keep track of timelines, teams and their individual members, changes, and a timeline calculator. The use of a single integrated IT platform that houses all the needed IT functions including secured exchanges between different stakeholders is imperative and can build on work already started in EUnetHTA JA3;
    - Maintain the PICO survey[1] developed during JA3 to structure the scoping phase (phase during which the framework for the evaluation is defined) for pharma JCA and test it for Medical Devices (MD) JCA. By means of this survey, all partners could comment on the relevance of the PICO i.e. the population, intervention, comparators and outcomes chosen to assess relative clinical effectiveness. The process has provided partners the opportunity to have a say in the scope of the assessment in order to ensure national uptake. For more information, see section 4.1;
4. Structured interaction with regulatory bodies:
    - Maintain the structural framework for information sharing between EMA and the assessment team for pharmaceutical JCA;
        - Continue the confidentiality framework as developed in EUnetHTA JA3 for the production of JCA to ensure the data sharing and information exchange can take place between EMA and the HTA assessors and co-assessors of the JCA. Explore with EMA possibilities for earlier interaction on the indication and shaping of the patient population, as this will allow the HTA assessors and co-assessors to have a better understanding of the products and will facilitate a more timely publication of the JCA.
    - Continue to develop an exchange with MD regulatory bodies to facilitate the timely assessment of high-risk medical devices;
5. Patient, Health Care Professional and other expert involvement:
    - Systematic, transparent, and early involvement of experts in joint production;
    - Identification and management of experts should be supported centrally;
    - Manuals and guidance for external and internal participants should be provided;
6. Stakeholder involvement:
    - For all joint HTA requiring stakeholder input, there should be manuals and guidelines to describe the role and responsibilities as well as guidance on the participant's contribution;
    - Stakeholders engagement in HTA processes needs to be given adequate time for stakeholder groups to engage and for project teams to consider and respond to comments received;
7. Quality control and process of validation of REA:

[1] https://eunethta.eu/pico/

- Oversight from a standing group of experts composed of experienced members in HTA from HTAb to ensure that scientific judgments made by assessor/co-assessor are consistent;
- Endorsement of the final product by a decision-making body;
- Group providing oversight & approval to be involved early in the process from the planning stage so that issues that could affect approval are identified in a timely manner and can be resolved without creating process delays;

8. Consistent and formal feedback procedure: Following the experience of EUnetHTA JA3, feedback from external and internal participants can be collected through a mixture of informal feedback at meetings and formal feedback from surveys with the process supported centrally.

Table 2.1. Existing EUnetHTA documents

Title	Scope
Project Plan Template (incl. PICO table)	Template (separate template for medicinal products and medical devices) which standardize the information needs for a project plan, e.g. PICO table, methodology and production timelines
Assessment Report Template	This template will be updated during EUnetHTA 21
Industry Procedure Manual	This manual will be used to inform participating HTD about the process, templates and guidance/methodology that is valid for their respective JCA/CA. This manual will need to be updated to reflect updates made during EUnetHTA 21
Topic proposal form for stakeholders (only for medical devices)	This is a standard form by which stakeholders can suggest topics for JCA/CA
Letter of Intent Template (only for medicinal products)	Standardized template that serves to get a broad understanding of the technology, the claimed indication to EMA and the regulatory timelines
Scoping Document Template (only for medicinal products)	Standardized template that serves to get a broad, but deeper understanding of the technology and the HTD perspective on PICO. This document is used by authors to prepare for a scoping meeting with a HTD. This template will have to be updated based on updates made during EUnetHTA 21
Submission Dossier Template and Requirements	These will be updated during EUnetHTA 21
Feedback survey	An online feedback survey after the finalisation of a JCA was created in JA3. This survey will be updated to reflect the process of JCA/CA production in EUnetHTA 21

3 OBJECTIVE AND METHODS

For all of the objectives below the future EU HTA regulation will serve as the basis and the past JA3 experiences will be taken into account.

The objectives of this deliverable are to:

- Produce JCA/CA for medicinal products (at least 1, maximum 2) and medical devices (at least 2, maximum 4), to continue to improve quality, consistency and national uptake of the JCA/CA and further standardize the production process.
- During the JCA/CA production, test the methodological convergence paths defined at the end of EUnetHTA JA3 (i.e. PICO concept paper and the GRADE framework paper).
- During the JCA/CA production, test the new methodological guidelines that will be developed by EUnetHTA 21 as well as the revised templates and guidelines, responding to identified challenges in EUnetHTA JA3.

3.1 Methods to achieve the objectives

To allow the production of JCA/CA to continue to improve quality, consistency and national uptake of the JCA/CA and further standardize the production process, the challenges as listed above need to be addressed. Please see the sections below for further details on how the work will be conducted.

In addition, it is crucial that feedback from external and internal participants will be collected through informal feedback at meetings and formal feedback from surveys.

Therefore, the production work will consider the following:

3.1.1 Selection of health technologies to assess

Early identification and selection of medicinal products and medical devices to be assessed will be conducted based on the experience from EUnetHTA identification processes[2]; definition of selection criteria will be explored as well as collaboration with regulatory bodies and other external stakeholders. Further details on MD identification and selection will be developed under deliverable D.4.7.4.

Conducting JCA on innovative health technologies which benefited from former EUnetHTA ED or JSC would be a good opportunity to test HTA life cycle approach using the ED/JSC's Final Recommendations as the basis to define the scope of the assessment.

To face the challenge of selecting innovative technology for which HTD will agree to submit a dossier, the very pro-active acquisition process as designed in JA3 will be fine-tuned and be put in place as early as in the first year of the tender.

- For medicinal JCA: An open-call for HTD to identify potential dossiers that could be evaluated in the timeframe of the tender will be launched. Early identification of health technologies to be assessed will also be conducted based on the experience from EUnetHTA identification processes (TISP); refining of selection criteria (including the possibility to have additional selection criteria) will be explored based on the experience in JA3 (TISP) and ongoing horizon scanning initiatives. Collaboration with regulatory bodies and other external stakeholders especially patients organisations will be also explored. Exchange with regulatory bodies will be set up as well as with the JSC core group of the Project. In addition, early selection can be based on the compounds that have benefitted from former EUneHTA ED or JSCs. For medical devices JCA/CA: Further details on MD identification and selection will be developed under deliverable D.4.7.4.
- For High-risk MD, a list of interesting MDs could be drawn from countries with more centralised access. MedTech Europe or other national unions could potentially help to identify or contact HTD. In the future (if HTA bodies can have access to EUDAMED) a list of upcoming high-risk devices could be extracted and used for prioritization and selection.
    - The number of JCA and CAs will depend on the needs of the contracting authority that could vary a lot for MD and the interest expressed by HTDs to submit products for assessments. In the absence of sufficient candidates to submit a new dossier, technology's dossiers previously submitted during JA3 will be used to see if the new methodology would have led to different results.

3.1.2 JCA/CA production – convergence with methodological development

JCA for medicinal products will start after the methodological discussions have been well advanced and the prioritised guidelines and templates have been updated.

JCA/CA of medical devices will also begin after preliminary discussions on methodologies for high-risk medical devices and procedures and templates have been reviewed. While EUnetHTA JA3 provided the opportunity to conduct many joint evaluations of diagnostic tests and procedures (among the 28 evaluations of OT in JA3, 19 were dedicated to assessment of procedure and screening test and nine JCA/CA on medical device), it is important that the tender tests the evaluation of individual high-risk

[2] https://eunethta.eu/services/horizon-scanning/

medical devices. These JCA/CA will cover either one technology for one or more indications, or several technologies within one medical device class for one indication.

Early identification of technology and exchanges with regulatory bodies on predictability of assessment's timelines will help to invite other HTA agencies from the EUnetHTA network to participate as reviewers or observers. The HTA bodies that will be impacted by the future HTA regulation, may be invited to join specific CSCQ meetings to early on review and engage in the JCA/CA production. Once the technologies have been identified, the search for experts and patient representatives can also be conducted. Such interaction (both for regulators, patients and HCP) need to follow the involvement procedures as developed under deliverable 7.4 and 7.2.

Authors, co-authors will be recruited among agencies from the consortium with experience of assessors/co-assessor role during EUnetHTA JA3. As already agreed the following agencies will produce the JCA/CA: AIHTA, HAS for MD JCA/CA; HAS, AEMPS (TBC), INFARMED for pharma JCA.

The JCA Committee for Scientific Consistency and Quality (CSCQ) will review the JCA/CA production at each key steps of the HTA process (PICO survey; review of 1st draft and final REA). This contribution of all members will ensure that each agency's views are taken into account in the final REA for optimal national uptake.

3.1.3 JCA validation and feedback process

A dedicated organisational structure should ensure quality and consistency of all productions following the Quality Management System initiated in JA3 with:

- A JCA/CA secretariat (at ZIN, Netherlands) to coordinate JCA/CA and monitor compliance to procedure/template;
- Assessor/Co-Assessor supported by JCA CSCQ to control scientific quality of the report and compliance to methodological guidelines for the common positions;
- Final endorsement of all production by Consortium Executive Board before final publication.

As these productions are linked to the implementation of procedures and methods that will serve as a basis for future collaboration, it is desirable that as many agencies as possible are involved. For this reason, all consortium members will participate to JCA production via both JCA CSCQ and Consortium Executive Board . Furthermore, additional HTA agencies from EUnetHTA network can be invited to participate to join specific JCA CSCQ meetings to contribute to review process.

The final deliverables are 1) JCA/CA reports of the concerned products and 2) a description and analysis report describing experience of JCA/CA productions during the tender based on formal feedback survey and dedicated meetings with internal and external participants.

3.1.4 Sequencing of the work

The production of JCA/CA is linked to the development or revision of methodological guidelines used for JCA/CA regarding scoping procedure (development of PICO questions in particular the scoping phase), comparators & comparisons, endpoints, applicability of evidence for JCA, validity of clinical studies and on the update of procedural guidelines for the appointment of assessors and co-assessors for JCA and templates of JCA/CA. Therefore, production of JCA/CA will start when the methodological discussions have been well advanced (M12: First draft of methodology) and procedures and templates have been updated.

The first year of EUnetHTA 21 should be dedicated to the preparatory work for JCA/CA productions of high quality with:

- Definition of a system to keep track on consistency of the JCA/CA reports and compliance to methodological guidelines and processes;
- Pro-active acquisition process:
    - Early identification and selection of medicinal products and medical devices to be assessed will be conducted the first year of the tender possibly based on defined

selection criteria and with collaboration with regulatory bodies, other external stakeholders and the JSC core group of the tender.

- For High risk MD, the topic identification will be part of the deliverable 4.7.3 and 4.7.4 on EUDAMED.

- Open Call for HTD submission;
- Recruitment of assessors and co-assessors based on pre-defined active participation of HTA agencies as well as external experts (HCP and patients) once industry confirmed dossier submission;
- Ensure exchange of information with other teams working on methodology and procedure during JCA committee meeting. Combined meeting between JSC and JCA CSCQ will also ensure consistent approach with external experts and other stakeholders. This communication will mimick JA3 transversal groups discussions between work packages.

The second year will be dedicated to production of JCA/CA reports and feedback collection and evaluation. using surveys to document experience of the JCA/CA teams after production during JA3. Some production could start by the end of the first year if methodological discussions sufficiently advanced and revised procedure/templates are finalized.

3.1.5 Project Management of JCA/CA production

The Project Management will be done by the JCA/CA secretariat (at ZIN, Netherlands), meaning this secretariat coordinates the JCA/CA production and monitor compliance to procedure/template.

To ensure an efficient and effective production process of JCA/CA and JSC, while at the same time improving (scientific) consistency and creating a central conflict resolution procedure, the following work will be done:

- Continuation of the JCA/CA project management team at the EUnetHTA 21 secretariat,
  - Ensure that project management of assessments is predictable and guarantees fairness of procedure.
  - Therefore, project management should be conducted according to standardised processes and tools.
  - Necessary procedures, manuals, templates and tools (including the Quality Management System in form of the Companion Guide) as created in JA3 should be maintained and revised according to developments of EUnetHTA 21. Such tools would be those to keep track of timelines, teams and their individual members, changes, and a timeline calculator by using and revising if needed standardised tools
- Follow and implement the CSCQ procedure for continuous review of the JCA/CA production.
- Define a mechanism for conflict resolution for the production of the JCA/CA respective deliverables
- Ensure the IT platform (i.e. Sharepoint) follows the needs as identified in the respective JCA/CA and JSC management tool as developed in EUnetHTA JA3. Required features that have been developed and would need to be incorporate in the IT platform where possible are:
  - 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 tool to calculate timelines for the individual JCA/CA;
  - 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 life cycle approach to joint HTA activities).

- As much as possible, ensure partners in EUnetHTA 21 are using the same IT tools required for the production of joint HTA work. For the purpose of this tender, it will not be made mandatory, but it is anticipated that the following IT tools are standard use within HTA agencies, such as:
    - 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).

Responsibilities of the JCA/CA Secretariat will be:

- Dedicated and Alternate Project Manager to be installed, to calculate and keep track of timelines, progress of the work and arrange internal and external communication on the specific JCA/CA;
- Gather all Declaration of Interest (DOI) forms and EUnetHTA Confidentiality Agreement (ECA) forms of all individuals participating in the JCA/CA and coordinate assessment of this by the Conflict of Interest (COI) Committee;
- Responsible for sharing (confidential) data, such as the HTD submission dossier, with the JCA/CA team;
- Coordinate the review process, both internally and externally (if applicable);
- Ensure SOPs, guidelines and templates are followed and monitor discussions between the JCA/CA team so that issues can be escalated to the CSCQ in a timely manner;
- Responsible for the graphical editing of the final JCA/CA prior to publication.

3.2 Stakeholder inclusion

To ensure the deliverable will be according to the needs of HTA organisations, it is important that HTA bodies outside EUnetHTA 21 consortium (i.e. EUnetHTA), Regulatory bodies (i.e. European Medicines Agency (EMA), and medical device regulators), HTD, and external experts (i.e. patients and healthcare professionals)) are involved in different modalities during the production of JCA/CA.

It is important that feedback from external and internal participants (e.g. assessment team and project manager) will be collected through informal feedback at meetings and formal feedback from surveys.

3.2.1 HTA bodies outside EUnetHTA 21 consortium

As these productions are linked to the implementation of procedures and methods that will serve as a basis for future collaboration, it is desirable that as many agencies as possible are involved. For this reason, additional HTA agencies from EUnetHTA network can be invited to participate to join JCA CSCQ to contribute to review process.

3.2.2 Regulatory bodies

Collaboration with regulatory bodies is planned both in the identification of health technologies and during the JCA/CA with a data exchange respecting the defined framework (see deliverable 7.4 for more information). At the end of the tender, a meeting should also be organised to discuss experience of collaboration and opportunity to prolong discussion on Post-Launch Evidence Generation if relevant (especially for medicinal products).

3.2.3 HTD

Communicate with HTD via calls and meetings to ensure understanding of requirements, processes, content of dossier submission and final REA. HTD could also participate in identifying technology to be assessed. HTD interaction during the JCA process will follow dedicated procedures and will be based

on the outputs of the transversal task "interaction between HTA experts and HTD" (see deliverable 7.1 for more information).

3.2.4 External experts

It is mandatory for each JCA to seek patient and HCP involvement (see deliverable 7.2 for more information).

COI management will follow the dedicated guideline.

4 ORGANISATION OF THE WORK

4.1 Mode of collaboration and frequency of meetings

The work will be distributed evenly between the agencies of the hands-on group (HOG). All HOG members will review each other's work prior to review by the CSCQ. The HOG will appoint one agency to interact with the three CSCQ configurations and the CEB.

More details will follow in the specific project plans of the JCA/CAs.

For topic identification for medicinal JCA, a collaboration with the JSC teams will be established.

4.2 Timelines

Please note that the actual production of JCA/CA on medicinal products and medical devices will start in Year 2 of EUnetHTA 21. In due time separate Project Plans will be developed for the specific JCA/CAs with their respective timelines.