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Guidance on Parallel EMA/EUnetHTA 21 Joint Scientific Consultation

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Abbreviations

AEMPS	Agencia Española de Medicamentos y Productos Sanitarios
AIFA	Agenzia Italiana del Farmaco, Italy
ATMPs	Advanced Therapy Medicinal Products
CAT	Committee for Advanced Therapies
CHMP	Committee for Medicinal Products for Human Use
COMP	Committee for Orphan Medicinal Products
CSCQ	Committee for Scientific Consistency and Quality
CSCQ JSC	Joint Scientific Consultation Committee for Scientific Consistency and Quality
EC	European Commission
EU	European Union
EMA	European Medicines Agency
EUnetHTA 21	European Network for Health Technology Assessment 2021
FAQ	Frequently Asked Questions
G-BA	Gemeinsamer Bundesausschuss, Germany
HAS	Haute Autorité de Santé, France
HCP	Health Care Professional
HOG	Hands-On Group
HTA	Health Technology Assessment
HTAbs	Health Technology Assessment bodies
HTAR	HTA regulation
HTD	Health technologies developer
INFARMED	National Authority of Medicines and Health Products, I.P., Portugal
JA	Joint Actions
JSC	Joint Scientific Consultation
JSC HOG	Joint Scientific Consultation Hands-On Group
KCE/KCE-NIHDI	Centre fédéral d'expertise des soins de santé – Belgian Health Care Knowledge Centre (KCE)
LoI	List of Issues
MAA	Marketing Authorisation Application
NCA	National Competent authority
NCPE	National Centre for Pharmacoeconomics (Ireland)
NIPN	National Institute of Pharmacy and Nutrition, Hungary

NOMA	Norwegian Medicines Agency
PICO	Approach used in evidence-based medicine to define e.g. Population – Intervention – Comparator(s) – Outcome(s)
PSA	Parallel Scientific Advice
PLEG	Post Licensing Evidence Generation
PRAC	Pharmacovigilance Risk Assessment Committee
SAWP	Scientific Advice Working Party
SEED	Shaping European Early Dialogues
SME	Small or Medium Enterprises
TC	Teleconference
TLV	Tandvårds- och läkemedelsförmånsverket (Sweden)
ZIN	Zorginstituut Nederland (The Netherlands)

1 History of changes

This guidance replaces the "Guidance for Parallel Consultation" (EMA/410962/2017 Rev.5) as of the date of publication.

Key modifications in this version compared to EMA/410962/2017 Rev.3 include:

- The Written-only meeting format has been suspended for the current Open Call within EUnetHTA 21 (all partners will continue to collaborate and discuss future options for different meeting formats besides discussion meeting format;
- Transformation of the early dialogue working party (EDWP) into Committee for Scientific Consistency and Quality for Joint Scientific Consultation (CSCQ JSC), update of the definition and composition of the CSCQ JSC and of the information regarding the EUnetHTA 21 JSC Secretariat;
- Renaming "parallel consultation" to "parallel EMA/EUnetHTA 21 Joint Scientific Consultation".

Modifications in the version EMA/410962/2017 Rev.6 compared to EMA/410962/2017 Rev.5 include only minor changes such as a clarification on the discussion meetings that are held virtually at the moment. Discussions on Post Licensing Evidence Generation (PLEG) can be facilitated only in conjunction with request for discussion of pivotal trial design and when contextualized with clinical data expected from the pivotal (phase II/III) studies. Also, there is no option for a follow-up consultation with EUnetHTA 21 during the EUnetHTA 21 project phase.

This latest version EMA/410962/2017 Rev.7 results from the final update of JSC documents during EUnetHTA 21 according to the project plan. In this framework a public consultation with stakeholders was performed from 1-31 July 2023. Comments received have been taken into account wherever feasible to finalise this EUnetHTA 21 output document. Changes include a clarification that the JSC Secretariat provided the underlying rationale of the reasons for declining requests to the Applicants. All products, regardless of whether or not they have undertaken a JSC procedure at one point of their development, may be eligible for national advice from some HTAb (provided that the consultation does not lead to a duplication of the advice given under the past JSC procedure). Reference to the EUnetHTA 21 JSC Frequently Asked Questions (FAQ) section was added as well as a clarification that Day 0 is the formal start of a JSC procedure.

2 Introduction

As the first step to market access, a new medicine requires a marketing authorisation from a medicines regulatory agency. Following regulatory approval, Health Technology Assessment (HTA), providing evidence-based information and analysis, takes place at the national level in accordance with national practices and legislative frameworks[1]. HTA is then used to inform subsequent decisions on coverage (reimbursement) and price of an authorised drug at the national level.

Interactions between medicines' developers, Regulators and Health Technology Assessment bodies (HTAbs) or other possible stakeholders to discuss the development plan at an early stage of a medicinal product's clinical development means that robust evidence can be generated during pre-approval studies to meet the needs of respective decision-makers as efficiently as possible. Thus, a strong interaction between Regulators and HTAbs/other relevant stakeholders is critical to facilitate patients' access to new medicines with added value and hence for the overall benefit of public health.

The European Medicines Agency (EMA) is the EU body responsible for coordinating the existing regulatory and scientific resources put at its disposal by EU Member States for the evaluation, supervision and

1 Development of archetypes for non-ranking classification and comparison of European National Health Technology Assessment systems. Allen et al. Health Policy 2013, Volume 113, Issue 3, December 2013, Pages 305–312

pharmacovigilance of medicinal products, including the provision of Scientific Advice for regulatory purposes.

The European Network for Health Technology Assessment (EUnetHTA) was established to create an effective and sustainable network for HTA across Europe – working together to develop reliable, timely, transparent and transferable information to contribute to HTA in European countries, creating a sustainable system of HTA knowledge sharing, and promoting good practice in HTA methods and processes. In February 2021, a call for tender was launched to foster joint HTA work supporting EU cooperation on HTA beyond May 2021 (when the EU co-funded EUnetHTA Joint Action 3 ended), thus providing relevant input to the new legal framework on HTA. The contract was awarded to the EUnetHTA 21 Consortium in September, 2021. It provides for a maximum of 8 (and not less than 6) Joint Scientific Consultations (JSCs; formerly called Early Dialogues) for medicinal products. The EUnetHTA 21 partners continue to collaborate with EMA on a more efficient procedure while ensuring the best scientific quality and coordination. The medium-term goal is to establish a regular, legally acceptable solution (respecting confidentiality and conflict of interest rules) to share JSC recommendations with the team producing Joint Clinical Assessment (JCA).

EUnetHTA 21 and EMA platform on evidence generation interactions

This platform comprises enhanced collaboration for Parallel regulatory/HTA Scientific Advice between EMA and EUnetHTA 21 (henceforward referred to as Parallel EMA/EUnetHTA 21 Joint Scientific Consultation (JSC)). Parallel EMA/EUnetHTA 21 JSC provides a single gateway for requests for parallel discussions before the start of pivotal clinical trials on initial evidence generation for Marketing Authorisation Application/Reimbursement, and PLEG (only in conjunction with a request for discussion of pivotal trial design) involving EMA and EUnetHTA 21 HTAbs. Partnership between EMA and EUnetHTA 21 also allows for: streamlined logistics, improved HTA coordination through EUnetHTA 21 JSC Secretariat, greater participation via the involvement of EUnetHTA 21 CSCQ JSC[2], and maximum gain from the parallel procedure by optimising opportunities for mutual understanding between Regulators and HTAs. This promotes optimal and robust evidence generation fit-for-purpose for both Regulators and HTAbs, ultimately bringing benefits for public health by enabling access to medicines which are effective to European patients as the ultimate goal.

For all submitted requests, the EUnetHTA 21 JSC Secretariat facilitates centralised HTA recruitment.

All Parallel Scientific Advices will be conducted through this Parallel Consultation Platform.

3 Principles

3.1 Roles and remits

This guidance highlights ideal timelines and actions for each party undertaking a Parallel EMA/EUnetHTA 21 JSC.

This is a multi-stakeholder procedure with EMA and HTAbs being equal partners. As a multi-stakeholder procedure, collaboration and communication between all stakeholders are important to ensure agreement and clarity on the ownership of different actions, and to deliver on the objectives of the exercise.

Each participating body should adhere to the roles and responsibilities under their respective remit, established by the respective Regulations, 726/2004 and 2282/2021.

2 Composition of the CSCQ JSC: AEMPS (Spain), AIFA (Italy), G-BA (Germany), HAS (France), INFARMED (Portugal), KCE/KCE-NIHDI (Belgium), NCPE (Ireland), NIPN (Hungary), NOMA (Norway), TLV (Sweden) and ZIN (Netherlands).

3.2 Confidentiality

By submitting a request for a Parallel EMA/EUnetHTA 21 JSC, the Applicant agrees to the exchange of information between EMA and participating EUnetHTA 21 HTAbs.

The Parallel EMA/EUnetHTA 21 JSC process is confidential.

EMA and associated regulatory experts are bound by the EMA code of conduct, and confidentiality agreements, and operate under the EMA policy on access to documents (Policy/0043).

EUnetHTA 21 prioritises confidentiality and each HTAb participant and associated expert, e.g. patients and healthcare professionals (HCP), is required to submit a signed EUnetHTA 21 Confidentiality Agreement.

Therefore, commercially confidential information provided to the EMA and EUnetHTA 21 within the context of a Parallel EMA/EUnetHTA 21 JSC is not shared with any party outside of the respective EMA and HTA networks in the absence of a signed confidentiality undertaking or the consent of the HTD.

3.3 Conflict of interest

EMA: Conflict of interest of regulatory experts, HCP and patients is handled in line with Policy 44.

EUnetHTA 21: Conflict of interest of EUnetHTA 21 partner HTAbs, HCP and patients is handled through the EUnetHTA 21 Declaration of Interest (DOI) form. Further information can be found in the EUnetHTA 21 Procedure Guidance for handling Declaration of Interest (DOI) form and EUnetHTA 21 Confidentiality Agreement (ECA) forms.

3.4 Status of Parallel EMA/EUnetHTA 21 Joint Scientific Consultation outputs

As an outcome of the Parallel EMA/EUnetHTA 21 JSC procedure, health technologies developers (HTDs, also referred to as Applicants in this document) will receive the EMA Scientific Advice Letter and the EUnetHTA 21 Final Written Recommendations.

The advice provided is not legally binding, for any of the involved parties.

European Medicines' Regulators take the Committee for Medicinal Products for Human Use (CHMP) Scientific Advice/Protocol Assistance provided into consideration during the Marketing Authorisation Application (MAA). The Applicant needs to justify ~~a~~ny deviation from the advice given. Please, see the EMA Scientific Advice Guidance document for further details.

Advice provided by EUnetHTA 21 partners is based on the documentation provided by the Applicant. The recommendation reflects the state-of-the-art of medical science and national requirements at the time of advice.

4 Actors and scope

The process described herein is only for Parallel EMA/EUnetHTA 21 JSC jointly involving EMA and EUnetHTA 21. For regulatory-only, please see EMA website and for Parallel EMA/EUnetHTA 21 JSC please refer to the EUnetHTA 21 Open Call (EUnetHTA 21 JSC website).

The Applicant must ensure that if different consultation formats are used consecutively (e.g. regulatory advice before parallel JSC), the content of the consultation does not lead to a duplication of the advice for participating agencies.

The uncertainties associated with an early developmental stage of a new medicinal product are acknowledged. However, to enable for a proper planning for all parties, it is requested by the Applicant to make any effort possible to ensure the continuation of a JSC process once initiated. In the exceptional cases where the continuation cannot be achieved, a heads-up as early as possible to both EMA and EUnetHTA 21 is mandatory. Given the tight timelines in preparation of a JSC, it is not guaranteed that a re-planning will be successful by that time.

4.1 Regulators: actors and scope

The Scientific Advice Working Party (SAWP) is an EMA standing working party with the remit of providing Scientific Advice and Protocol Assistance to Applicants, advising on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of medicinal products (See "Mandate, objectives and rules of procedure of the Scientific Advice Working Party (SAWP)" (EMEA/CHMP/SAWP/69686/04 Rev 14).

The SAWP Rapporteur is a medicines regulator and a member, or alternate member, of SAWP who is responsible for providing reports further to the Scientific Advice or Protocol Assistance requests, addressing comments from the SAWP, Working Parties, and EMA Committees, drafting the SAWP List of Issues (LoI), acting as one of the 2 co-chairs for the discussion meeting, and drafting the final report for further input and consideration by SAWP and EMA Committees.

The EMA Scientific Officer supports the SAWP Rapporteurs with scientific and administrative coordination. This is the principal EMA contact person to be reached, along with the EMA Procedure Assistant, by the Applicant and EUnetHTA 21 for matters related to an individual procedure.

The EMA Scientific advice secretariat informs the EUnetHTA 21 JSC Secretariat who has been appointed as EMA Scientific Officer after receiving the submission via IRIS[3], while the applicant will be informed automatically by the IRIS system. EMA informs the EUnetHTA 21 JSC Secretariat about participants from the regulatory side (e.g. SAWP Rapporteurs).

For the EMA, through the Parallel Consultation, the Scientific Advice or Protocol Assistance provided to the Applicant is substantive, is prepared pursuant to Article 57 (1.n) of Regulation (EC) No 726/2004) and is adopted by CHMP having been elaborated through the SAWP.

Applicants may request advice on any medicinal products for use in humans, (as defined in Directive 2001/83 (as amended)), irrespective of the medicinal product's eligibility for the centralised procedure, and at any stage of the product lifecycle. This may include very early strategic advice, advice on novel development plans, broad advice, plans for pivotal phase III studies, post-authorisation safety and efficacy studies, advice on the development of registries, or risk management planning incorporating risk minimisation measures.

4.2 EUnetHTA 21 and HTAbs: actors and scope

The CSCQ JSC is a standing committee composed of 11 national HTAbs as permanent members i.e. AEMPS for Spain, AIFA for Italy, G-BA for Germany, HAS for France, INFARMED for Portugal, KCE/KCE-NIHDI for Belgium, NCPE for Ireland, NIPN for Hungary, NOMA for Norway, TLV for Sweden and ZIN for the Netherlands. The CSCQ JSC is the standing working party of the HTAbs for the performance of the scientific advice and is responsible for the following tasks:

- Assess the eligibility of advice requests in view of the selection criteria, as specified in section 4.3.2 as well as in the Open Call for Participation, and report to the JSC Secretariat on the eligibility and acceptance of the scientific advice requests;
- Participate in the performance of the JSC;

[3] IRIS is the secure online platform for handling product-related scientific and regulatory procedures with EMA.

- Validate all deliverables and provide feedback;
- Function as a mediation body in cases where a hands-on group (HOG) cannot reach agreement. The JSC Hands-on Group represents all partners involved in a specific JSC.

The JSC HOG represents all partners involved in a specific JSC. The participation of a minimum of six CSCQ JSC member HTAbs is required. Participation in a JSC as part of the HOG is voluntary for CSCQ members. A EUnetHTA 21 Assessor and Co-Assessor will be assigned for each JSC from among the JSC HOG.

The EUnetHTA 21 Assessor undertakes scientific coordination on behalf of HTAbs. For all procedures, the Assessor facilitates discussion between HTAbs in advance of meetings, interacts with the EMA during joint meetings and acts as a co-chair for the HTAbs during the discussion meeting. The Assessor is responsible for drafting the EUnetHTA 21 List of Issues (LoI), acting as one of the two co-chairs for the discussion meeting with the Applicant, drafting the recommendations for further input and consideration by JSC HOG as well as CSCQ JSC and providing EUnetHTA 21 Final Written Recommendations to the Applicant addressing comments from the JSC HOG as well as the CSCQ JSC.

The EUnetHTA 21 Co-Assessor collects and consolidates responses from the JSC HOG and presents consolidated HTAb answers during the discussion meeting together with the Assessor. The Co-Assessor interacts with the Assessor and EMA on scientific matters. The EUnetHTA 21 Co-Assessor supports the Assessor in the different tasks listed before.

The EUnetHTA 21 JSC Secretariat is responsible for all practical coordination of HTAb participation in a Parallel EMA/EUnetHTA 21 JSC. Together with the EMA Scientific Officer, on the regulatory side, the EUnetHTA 21 JSC Secretariat acts as the sole HTAb contact point for all Parallel EMA/EUnetHTA 21 JSCs. Additionally, the EUnetHTA 21 JSC Secretariat is responsible for insuring the receivability of a request and all project management on the HTAb side. Finally, the EUnetHTA 21 JSC Secretariat is responsible for engaging patients and HCPs at the European level to provide expert input regarding HTA relevant aspects related to i.a. the condition, treatment and expectations of patients and the proposed development plan including endpoints etc. Parallel EMA/EUnetHTA 21 JSC focuses on advice before the start of pivotal clinical trials on initial evidence generation for MAA/HTA assessment and PLEG. However, discussions on PLEG can be facilitated only in conjunction with request for discussion of pivotal trial design and when contextualized with clinical data expected from the pivotal (phase II/III) studies.

4.3 HTAb involvement in Parallel EMA/EUnetHTA 21 Joint Scientific Consultation

4.3.1 Open Call

The EUnetHTA 21 JSC Secretariat published Open Calls for applications for Parallel EMA/EUnetHTA 21 JSC. In order to apply for a JSC, HTDs should complete the EUnetHTA 21 JSC application form available on the EUnetHTA website or upon request (EUnetHTA21-JSC@g-ba.de) and submit their application and annexes (if applicable) via Eudralink to the EUnetHTA 21 JSC Secretariat (EUnetHTA21-JSC@g-ba.de). The Applicant's request for an EMA/EUnetHTA 21 JSC should provide sufficient information to substantiate the claimed basis for selection and follow the guidance notes provided with the form. In all cases, selection criteria of the HTA regulation (HTAR) will apply (see 4.3.2). Once the call is closed, the CSCQ JSC members will review the applications.

EUnetHTA 21 reserves the right to contact the Applicant in order to discuss their request.

There is no option for a follow-up consultation with EUnetHTA 21 during the project phase. All relevant questions must be submitted for a single JSC application.

All Applicants will be informed of the CSCQ JSC decision within three weeks of the end of the call. The EUnetHTA 21 JSC Secretariat communicates the outcome of the selection to all Applicants and EMA once the decision is final. For those request that have been rejected EUnetHTA 21 JSC Secretariat provides

the underlying rationale for the reasons of declining the request to the HTD. For those requests that are selected, information will be provided regarding the participating HTAbs to the Applicant and EMA according to the Parallel EMA/EUnetHTA 21 JSC process outlined in **Table 2**.

Other products which are not selected for a parallel EMA/EUnetHTA 21 JSC could pursue a regular Scientific Advice procedure with EMA and may be eligible for national advice from some HTAbs. All products, regardless of whether or not they have undertaken a JSC procedure at one point of their development, may be eligible for national advice from some HTAb (provided that the consultation does not lead to a duplication of the advice given under the past JSC procedure).

4.3.2 CSCQ JSC selection criteria

Due to the tender specifications in EUnetHTA 21, the number of products to be selected for the JSC is limited. As the number of Applicants is expected to exceed the number of slots, a selection of products will be necessary. EUnetHTA 21 will apply the same selection criteria as defined in the HTAR. A prerequisite for a JSC is that the pivotal clinical trial (pivotal phase II/ or III) has not yet started.

The criteria for selecting from eligible JSC requests for medicinal products are:

a) Unmet medical needs (no treatment or only unsatisfactory treatment available);
b) First in class;
c) Potential impact on patients, public health, or healthcare systems;
d) Significant cross-border dimension;
e) Major Union-wide added value; or
f) Union clinical research priorities.

Oncology products and/or ATMPs and indications for which there is no established guidance for clinical development (i.e. in absence of recent HTA evaluation in a similar indication) are given preferred consideration but not exclusively.

In the application form the HTD should elaborate on the selection criteria respectively and provide an explanation why the criteria are met and the product is eligible for an advice procedure, at the time of the application. An elaboration of the EUnetHTA 21 CSCQ on the selection criteria can be found in the Frequently Asked Questions (FAQ) section on the EUnetHTA 21 website: https://www.eunethta.eu/jscfaq/.

4.3.3 Parallel EMA/EUnetHTA 21 Joint Scientific Consultation format and outcome

There is one single procedure for Parallel EMA/EUnetHTA 21 JSCs within the two Open Calls in EUnetHTA 21; the consultations take place in a discussion meeting format. All Parallel EMA/EUnetHTA 21 JSCs are supported by the EUnetHTA 21 JSC Secretariat, thereby benefiting from HTA scientific and administrative coordination, consolidated HTA comments and List of Issues (LoI), a concerted effort to find agreement among the JSC HOG regarding specific issues as well as a consolidated document containing EUnetHTA 21's Final Written Recommendations.

The generation of consolidated HTA outputs through the JSC HOG involves identifying aspects of development programs for which there is a shared position amongst HTAbs and attempting to reach consensus whenever possible. Where necessary individual positions will be presented in the document's appendix. The final output is the EUnetHTA 21 Final Written Recommendations, a single written report including: consolidated EUnetHTA 21 recommendations for shared positions, individual HTAb answers to state diverging positions or to clarify additional national specifications and anonymised transcripts of European level patient and/or HCP input obtained through the procedure. The entire procedure will be approximately four and a half months in duration starting from reception of the draft briefing document, three and a half months from the start of procedure D 0. The Applicant needs to provide written answers to a EUnetHTA 21 LoI. The Parallel EMA/EUnetHTA 21 JSC with a discussion meeting allows for a direct

exchange between the participating HTAbs, EMA and the Applicant. The discussion meeting is hosted by EMA and is held virtually. The Applicant will be provided with the Final Written Recommendations from HTAbs only at the end of the procedure as indicated in the published timeline scheme. Exchanges between HTAbs and EMA and the high-quality output expected of EUnetHTA 21 are guaranteed for this procedure as well. The full procedure is detailed in **Table 2**.

4.4 Other stakeholders

The inclusion of patients and clinical experts in Parallel EMA/EUnetHTA 21 JSCs is expected on a routine basis.

EMA

Regulators' clinical experts are identified through National Competent Authorities (NCA) and SAWP members. An HCP representative may also be invited by the EMA through the EMA HCP Working Party framework, as well as other stakeholders as appropriate.

Individual patient experts are identified through patient organisations under the framework for interaction between the EMA and patients and consumers, and their organisations (EMA/637573/2014).

Where possible, patients are invited to attend the discussion meeting; briefing of chairpersons (on the inclusion of a patient) and patients (on the aims and nature of the meeting) by EMA Scientific Officer is essential. Any additional time or facilities required by patients should be considered.

EMA exchanges information with EUnetHTA 21 JSC Secretariat on the participation of clinical experts and/or patient experts.

EUnetHTA 21

EUnetHTA 21 is committed to involving experts (patients (representatives) and HCP) in its work. Hearing directly from patients about the outcomes that matter to them and how their condition impacts their quality of life and hearing directly from HCP about natural disease history and current disease management are areas that are important from an HTA perspective.

EUnetHTA 21 systematically endeavors to involve experts in all Parallel EMA/EUnetHTA 21 JSCs. The EUnetHTA 21 JSC Secretariat coordinates European level expert recruitment and involvement. European level patients and/or clinical experts are involved via interview/written statement and participate in the discussion meeting (if applicable). The involved experts express their personal opinions and do not act as representatives for any stakeholder organization.

National patients and clinical experts are involved at Member State level, provided that a national procedure exists. The inclusion of these experts remains the responsibility of the participating HTA bodies (HTAbs).

Other experts with specific expertise may also be involved if there is an explicit need. The selection and involvement procedures for all experts are outlined in the EUnetHTA 21 D7.2/3 Guidance for the interaction with patient representatives, healthcare professionals and other experts.

The EUnetHTA 21 JSC Secretariat exchanges information with EMA on the participation of patients and/or clinical experts.

5 Process

5.1 Simultaneous notification

For all Parallel EMA/EUnetHTA 21 JSCs, the Applicants who received a notification of selection by EUnetHTA 21 after the Open Call (see section 4.3) should notify the EMA Scientific Advice Secretariat by means of an application submitted via the IRIS platform. The EMA and EUnetHTA 21 Secretariat should simultaneously receive the draft briefing package by the published deadline for the intended procedure start date (for submission details, please refer to 5.2 "default without presubmission teleconference (TC)").

This IRIS submission deadline is approximately 1 month (30 days) before the formal procedure start date (day 0 or SAWP 1) and 3 months before the intended discussion meeting (day 60 or SAWP 3 meeting). For accurate submission deadlines, please refer to the relevant submission deadlines on the EMA website.

EMA and EUnetHTA 21 JSC Secretariat will then mutually agree the allocation of discussion meeting slots considering the batch of requests for the intended start date. EMA will confirm the date and time of the discussion meeting in writing to the EUnetHTA 21 JSC Secretariat and the Applicant by approximately day -40.

5.2 Presubmission phase

For all Parallel EMA/EUnetHTA 21 JSCs, the presubmission phase starts when the Applicant submits the request to the EMA through IRIS and sends the draft briefing package to the EUnetHTA 21 JSC Secretariat via Eudralink (https://eudralink.ema.europa.eu/).

Default without presubmission teleconference (TC)

By default, the presubmission phase is based on written comments on the draft briefing document.

The draft briefing package should be submitted at least 30 days before the due start date (day 0 or SAWP1) of the procedure. (See published parallel EMA/EUnetHTA 21 JSC published timetables for a 70 day procedure; SAWP 3 provides the intended discussion meeting date).

In addition to the standard EMA timetables, EMA sets up a timetable in consultation with the EUnetHTA 21 JSC Secretariat for each procedure including closed EMA/EUnetHTA 21 interactions. Calendar meeting requests are sent by EMA to the EUnetHTA 21 JSC Secretariat and other regulatory participants shortly after a meeting is confirmed.

The Applicant simultaneously submits the request through IRIS and sends the draft briefing document to the EUnetHTA 21 JSC Secretariat[4] in accordance with the agreed timeline. It is important that the timelines are adhered to allow for the participants to have sufficient time with the draft briefing document in order to provide feedback to the Applicant, and also that there is sufficient time for the Applicant's revision before the agreed formal start of the procedure. Initial written comments from the EMA and EUnetHTA 21 JSC Secretariat (collated comments from HTAbs) are provided directly to the Applicant by 15 working days, where necessary for the optimisation of the draft submission prior to the start of the procedure. However, EUnetHTA 21 reserves the right to contact the Applicant in order to request further clarification at any time within the procedure, if needed.

Comments are shared with the Applicant by the EMA Scientific Officer and EUnetHTA 21 JSC Secretariat (if applicable) in terms of a check for completeness: the scope, wording and clarity of the questions, whether the material provided in the briefing package is sufficient to answer the questions posed, whether all the right questions have been asked or if additional questions should be added, and to

[4] The submission to EUnetHTA 21 must be done via Eudralink (https://eudralink.ema.europa.eu/) which will allow for the confidential exchange of information between EUnetHTA 21 and the Applicant.

consider whether the questions are appropriately addressed to HTAbs, Regulators or both. Both EMA and HTAB reserve the right to answer selected questions that have been directed to the other entity if deemed appropriate.

Finalising the briefing document

The Applicant submits a revised final briefing document with all annexes and references having addressed the EMA comments and EUnetHTA 21 points of clarification (if any) through IRIS at least 5 full working days before the start of the procedure. One version should be in "track changes" mode and the other should be "clean". EMA conducts an administrative check to ensure the briefing package is fit for purpose (i.e. that all annexes and references are present and readable, and that any essential changes have been made to the briefing document).

Following confirmation of validation from EMA, the Applicant submits the final briefing document through IRIS and sends the document also to the EUnetHTA 21 JSC Secretariat via Eudralink (https://eudralink.ema.europa.eu/), according to the shared timeline. One version should be in "track changes" mode and the other one should be "clean". There is no formal confirmation of the validation by the EUnetHTA 21 JSC Secretariat but a proactive reach out if files are identified to be missing. The Applicant should ensure that the final briefing document has been received by both parties.

The presubmission phase ends with the circulation of the final briefing document prior to SAWP 1 (Wednesday before start of SAWP; SAWP1 defined according to the published timelines) as in the published Parallel Scientific Advice timelines. The submission of the final briefing package marks the start of JSC procedure D 0.

There is no option for a follow-up consultation with EUnetHTA 21 during the project phase. All relevant questions must be submitted in the briefing package for the JSC.

5.3 Evaluation phase

Lists of Issues (LoI)

For all Parallel EMA/EUnetHTA 21 JSCs, Lists of Issues (LoI) facilitate the discussion during the discussion meeting by indicating the focus of Regulators' and HTAbs' discussion.

In the regulatory process, the SAWP discusses the first reports (preliminary views) at the SAWP 2 meeting and drafts a Regulators' LoI by approximately day 40 of the procedure.

In the EUnetHTA 21 process, CSCQ JSC members participating in the advice (JSC HOG) discuss draft positions and major issues (following PICO (Population, Intervention, Comparator, Outcome)) pre-listed by the Assessor and Co-Assessor during an e-meeting around day 30. The EUnetHTA LoI is shared with the HTD around day +35 of the procedure.

Exchange between EMA and HTAbs

EMA and HTAb LoI are also exchanged between EMA and HTA Coordination Contact Point.

The EMA arranges a closed preparatory virtual meeting between EMA and EUnetHTA 21 (JSC Secretariat, Assessor and Co-Assessor), to take place around one week prior to the discussion meeting, focusing on the issues identified by Regulators and HTAbs.

The purpose of the pre-discussion meeting is to exchange and understand respective (preliminary) positions of the different Regulator and HTAb participants on the major aspects of the proposed development plan. Potential solutions that could facilitate one trial, or at least one development plan, could be discussed in advance of the discussion meeting. The Regulator's and the HTAb's chairperson for the discussion meeting should be agreed in the meeting.

Preparation for discussion meeting

The Applicant can contact the EMA Scientific Officer and/or EUnetHTA 21 JSC Secretariat regarding the format of the discussion meeting. This is to ensure that the meeting fulfils the needs of involved stakeholders. The Applicant should send any written responses to the EUnetHTA 21 LoI 12 working days before the discussion meeting directly to EUnetHTA 21 JSC Secretariat. For EMAs LoI, the Applicants' written response is expected 5 working days before the start of the discussion meeting week (SAWP3 meeting week, according to the published timelines).

The Applicant should submit the final presentation and list of participants to the EMA via IRIS and to the EUnetHTA 21 JSC Secretariat, 2 working days before the end of the week preceding the discussion meeting week (SAWP3 meeting week, according to the published timelines). Any changes to the presentation after this date will not be accepted. The presentation can include a very brief introduction, rationale and status of the program. An upper limit of 5 slides for this introduction is recommended to maximise the time available for the questions and discussion. Once shared with the meeting participants, according to the agreed timelines, the presentation should not be amended by the Applicant. There should be no major changes to the development plan compared to the final briefing document, unless the process in topic "Amended development plans" has been followed.

The EUnetHTA 21 JSC Secretariat is asked to send their final list of attendees to the EMA also in advance of the meeting (1 week before the discussion meeting). Applicants may have up to 12 representatives which can be increased to 14 in case of applicants between collaborating companies. The EMA circulates a preliminary list of all participants 2 days in advance of the discussion meeting. The discussion meeting is hosted by EMA and is held virtually.

Amended development plans triggered by the Lists of Issues/written response to List of Issues or external factors

Amended development plans triggered by the Lists of Issues or external factors can be accommodated to some extent during the evaluation phase. However, to facilitate sufficient time for review of the amended development plan, it is stressed that the Applicant should advise all parties of their intention to submit an amended development plan as early as possible, before the discussion meeting. The amended plan must be received by all parties together with a clear comparative table of changes in the plans and justification for the changes.

For EUnetHTA 21, the written response to LoI and, if applicable, necessary information regarding the amended development plan must be received at the latest by 12 working days before the discussion meeting. Any substantial changes to the development plan submitted past this date cannot be addressed within the discussion meeting or reflected in the minutes.

For EMA's LoI, the Applicants' Written Response and, if applicable, necessary information regarding the amended development plan is expected 5 working days before the start of the discussion meeting week (SAWP3 meeting week, according to the published timelines).

Discussion meeting

The meeting is hosted by EMA (at the moment virtually).

The aims of the discussion meeting are:

- To discuss issues of concern or disagreement from EMA and/or HTAbs with the Applicant's proposal regarding major aspects of trial designs.
- To get a mutual understanding of each body's constraints as it has to be acknowledged that Regulators and HTAbs are operating within distinct remits (benefit/risk evaluation vs. added value or cost-effectiveness' evaluation). Possible resulting divergences between HTAbs and Regulators positions on major aspects of the trial design will be discussed.

- To share and discuss preliminary positions on major aspects of trial designs from EUnetHTA 21 with all participants.
- To discuss potential solutions that could facilitate one trial design or at least one development plan.

The discussion meeting has 2 co-chairs: one from EMA and one from the HTAbs. The meeting duration will depend on the range of issues to be discussed, the maximum length of the meeting is 3 hours. If it is agreed between the EMA and the HTAbs prior to the discussion meeting that the content of the discussion is limited, the meeting can be set at 1.5 hours. The Applicant will be informed about the length of the discussion meeting in due time.

Before the Applicant enters the room, the Regulators and the HTAbs have the opportunity to have a closed session in order to exchange on organisational items and to interact on any possible changes of position after the Applicant's responses and presentation. This pre-meeting could be extended if necessary (e.g. late changes to the development plan).

The meeting with the Applicant is interactive, focusing on the issues raised by the Regulator and the HTAbs in the LoI. The chairperson of the HTAb side (the Assessor) presents the common position of the participating HTAb. If at any point the Assessor presents the individual position of his or her own agency, this is made particularly clear. Wherever possible the issues of both Regulators and HTAbs should be grouped together and structured following PICO (Population, Intervention, Comparator, Outcome) to enable for a joint discussion of the stakeholders. During the discussion meeting, the views of each stakeholder should be clearly represented on each issue. It is usual to pause after each question/issue for discussion. Time should be allowed for summing up at the end of the meeting.

Following the discussion meeting, a closed debriefing between HTAbs and Regulators should be held. This is dedicated to the recap, identification and discussion of any outstanding divergences, where such divergences mean that a single development plan/trial could not be carried out. There might be situations in which the divergences cannot be resolved due to differences in the Regulators' and HTAbs' assessment questions and remit.

The Applicant is expected to provide detailed minutes of the discussion meeting, within 5 working days directly to EMA. The minutes should reflect the views for each participating stakeholder in the discussion meeting discussion. Areas of agreement and divergence of opinion between Regulators and HTAbs can be summarised by the Applicant. Minutes are regarded as an Applicant's record of the meeting and will not, in general, be endorsed by the participating bodies. The minutes should be sent also to the HTA Coordination Contact Point for information. The minutes will not be commented by HTAbs.

Table 1. Outline of actions for Applicant, EMA and EUnetHTA 21 in Parallel EMA/EUnetHTA 21 JSCs

Day	Applicant (HTD)	EMA	EUnetHTA 21
Submission of draft briefing package: Start of presubmission phase			
D - 30	➢ **Applicant** submits the draft briefing document with annexes and references simultaneously to the **EUnetHTA 21 JSC Secretariat** via Eudralink[5] and to the **EMA** via IRIS.	**IRIS** automatically confirms receipt. Communication of EMA contact point (EMA Scientific Officer) to Applicant and EUnetHTA 21 JSC Secretariat. IRIS submission triggers **appointment of 2 SAWP Rapporteurs** and, where appropriate, a SAWP Rapporteur for questions relating to significant benefit (only applicable for protocol assistance) by the SAWP.	**Main contact for all HTA matters: EUnetHTA 21 JSC Secretariat** ➢ **EUnetHTA 21 JSC Secretariat** confirms receipt to the Applicant. ➢ Appointment of **Assessor and Co-Assessor**, information shared with EMA. ➢ **EUnetHTA 21 JSC Secretariat** communicates the draft briefing document, annexes and references to **JSC HOG + CSCQ JSC.** ➢ Assessor and Co-Assessor can request any necessary **clarifications** to the Applicant copied to EMA Scientific Advice secretariat at any time.
D - 15		**Feedback on draft** ➢ Where applicable, comments on the draft briefing document are sent to Applicant through IRIS by ~D -15 and also sent to the **EUnetHTA 21 JSC Secretariat**☐ ➢ Additional Experts/patients representatives are identified and shared with **EUnetHTA 21 JSC Secretariat.**	➢ European level patient (representative)/clinical expert are identified by the **EUnetHTA 21 JSC Secretariat** and information is shared with EMA (also possible at a later stage of the procedure).
D - 10		Administrative meeting between EMA and EUnetHTA 21 JSC Secretariat.	

[5] https://eudralink.ema.europa.eu/

Day	Applicant (HTD)	EMA	EUnetHTA 21
Validation/reception of briefing package			
D - 5	**Submission** The **Applicant** submits the briefing package together with annexes and references in response to the request(s) for clarification to the EMA via IRIS and to EUnetHTA 21 via Eudralink. One version of briefing document should be in "track changes" mode and the other should be "clean".	**Validation of final briefing document** Notification of positive validation of the final briefing document by EMA Scientific Advice secretariat to the Applicant via IRIS and information of the EUnetHTA 21 JSC Secretariat thereof at D -2 together with final instructions.	**Reception of final briefing document:** ➢ There is no formal confirmation of the validation by the HTA Coordination Contact Point but a proactive reach out if files are identified to be missing.
Submission of final briefing package: Start of procedure D 0			
D -2 - 0	The **Applicant** submits final briefing package including annexes and references to the **EMA** via IRIS **and to the EUnetHTA 21 JSC Secretariat** via Eudralink.		➢ **EUnetHTA 21 JSC Secretariat** shares the final briefing document with **JSC HOG + CSCQ JSC.**
Evaluation Phase			
		➢ Discussion of the first reports during SAWP meeting focusing on controversial issues followed by production of a draft List of Issues (LoI), which outlines the topics of Regulators' interest to be addressed by the Applicant in the discussionmeeting.	➢ Preliminary discussion (e-meeting) on JSC HOGs` position on main topics (PICO) of the development proposed and exchanges on related issues. Production of a **EUnetHTA 21 List of Issues (LoI)**, which outlines the topics of HTAbs interest

Day	Applicant (HTD)	EMA	EUnetHTA 21
			to be addressed by the Applicant in the discussion meeting. ➢ **JSC HOG** starts to discuss the draft written positions.
~D + 35-40		**EUnetHTA 21 JSC Secretariat and EMA exchange their respective LoI and send the lists to the Applicant.**	
Applicant's Written Response to List of Issues (LoI)			
D + 45-50	➢ **Applicant** sends their Written Responses (if applicable) to the LoI raised by EUnetHTA 21 via Eudralink to the **EUnetHTA 21 JSC Secretariat** (if applicable: notification of amended development plan with changes and justifications). ➢ **Applicant** sends their Written Responses (if applicable) to the LoI raised by the **EMA** via IRIS.		➢ **EUnetHTA 21 JSC Secretariat** distributes the Applicant's Written Response and any notification of amended development plan with changes and justification (if applicable) to **JSC HOG.**

Day	Applicant (HTD)	EMA	EUnetHTA 21
Preparation for discussion meeting			
~D + 55	➢ **Applicant** submits PowerPoint presentation to **EMA via IRIS and EUnetHTA 21 JSC Secretariat via Eudralink**, at least 2 full working days before the week preceding the discussion meeting week (SAWP3 meeting week), addressing the Lists of Issues for both HTAbs and Regulators. The Applicant should group related issues together. Further changes after this date will not be accepted. ➢ Applicant submits list of participants.	➢ The EMA arranges a closed preparatory e-meeting between EMA and EUnetHTA 21 (JSC Secretariat, Assessor and Co-Assessor), to take place around one week prior to the discussion meeting, focusing on the issues identified by Regulators and HTAbs.	
~D + 55	➢	EMA and SAWP Rapporteurs take part in a Bilateral e-meeting with the EUnetHTA 21 JSC Secretariat, EUnetHTA 21 Assessor and Co-Assessor.	

Day	Applicant (HTD)	EMA	EUnetHTA 21
Discussion meeting (virtually)			
D + 60	➢ The meeting is hosted by EMA (at the moment virtually). ➢ The meeting will normally have 2 co-chairs: one from the Regulators and one from the HTAbs (the **Assessor**). **Tripartite session: Discussion meeting EMA and EUnetHTA 21 HTAbs with the Applicant.** The meeting duration will depend on the range of issues to be discussed (maximum 3 h), with 15 minutes closed pre-, and 15 minutes closed post-discussion meeting (EMA and EUnetHTA 21). The pre-meeting of EMA and EUnetHTA 21 includes organisational items, sharing draft positions, related expert's feedback received by the two parties (if applicable) and discussing last minute changes. This pre-meeting could be extended if necessary (e.g. late changes to the development plan). The **Applicant** addresses key issues that were identified by **EUnetHTA 21 JSC and EMA**. An interactive discussion follows on the key issue.		
D + 70		➢ The Regulators' **Final Advice Letter** is adopted by the CHMP (and by the COMP in case of questions on significant benefit for Protocol Assistance), made available to Applicant via IRIS and sent to the **EUnetHTA 21 JSC Secretariat.**	➢ Finalisation of EUnetHTA 21 Final Written Recommendations.
D + 82			➢ **EUnetHTA 21 Final Written Recommendations sent to Applicant and EMA.** ➢ Feedback questionnaire sent to Applicant, HTAbs and involved patient (representative)/HCP.
D + 95	**Applicant** completes and returns feedback questionnaire to the **EUnetHTA 21 JSC Secretariat.**		

6 Practical issues

6.1 Fees

The EMA charges fees for this procedure, which are the same as for standard Scientific Advice/Protocol Assistance including the application of any fee incentives. For more information see Fees payable to the European Medicines Agency.

The participation of HTA bodies in the JSCs offering consolidated HTA outputs in the framework of the EUnetHTA 21 service contract is covered by EUnetHTA 21 budget.

6.2 Contact points

The EUnetHTA 21 JSC Secretariat (EUnetHTA21-JSC@g-ba.de) is the single point of EUnetHTA 21 contact in relation to all HTA aspects, unless otherwise indicated.

The EMA point of contact (with back-up) is identified via IRIS. The Applicant should keep the EUnetHTA 21 JSC Secretariat up to date with changes in contact details. Changes in contacts should also be implemented by Applicants directly in IRIS.

6.3 Processing of documents

The Parallel EMA/EUnetHTA 21 JSC uses Eudralink for exchanging documents between the Applicant and the EUnetHTA 21 JSC Secretariat. Document exchange between the Applicant and EMA takes place through the IRIS platform.

The Applicant is responsible for sending all relevant documents directly to the HTA Coordination Contact Point and EMA in a simultaneous manner. The Applicant must ensure that receipt of documents has been confirmed by all the participants.

Document version control, numbering, and adherence to timelines are essential to ensure all parties have the appropriate document at the correct time. It is strongly advised to avoid making significant changes to the documentation/clinical development close to the discussion meeting except where this has been discussed and agreed with participants. This is in order to guarantee an appropriate time for the revision and the evaluation by Regulators and HTAbs.

The Applicant provides consent to document exchange between EMA and EUnetHTA 21 in the Application Form.

6.4 Briefing document for Parallel EMA/EUnetHTA 21 Joint Scientific Consultation

A common briefing document is used; each question can be addressed to the Regulators or the HTAbs alone, or to both. Quality and nonclinical questions are possible during a Parallel EMA/EUnetHTA 21 JSC procedure and should be posed to Regulators only. In the same manner questions related to health economics are possible and should be directed to HTAbs. The labelling of questions is a guide but does not prevent interested bodies answering questions deemed also relevant and of interest although originally raised to the other entity.

Applicants are encouraged to submit detailed information concerning the choice of patient reported outcomes and any substantiated PLEG plans (if applicable) already with the draft briefing document. However, Applicants are to acknowledge that PLEG can only be discussed in conjunction with a request for discussion of pivotal trial design and when contextualized with clinical data expected from the pivotal (phase II/III) studies. Use of the associated briefing document template is required (See published template for Parallel Consultation).

7 Other

7.1 Advice format

The EMA will provide via IRIS the CHMP final Scientific Advice/Protocol Assistance letter to the Applicant in accordance with the published timelines.

The EUnetHTA 21 JSC Secretariat sends out validated Final Written Recommendations at day +82.

Final outcome letters are exchanged between EMA and the EUnetHTA 21 JSC Secretariat.

7.2 Follow-up procedures

A follow-up procedure for a EUnetHTA 21 Parallel EMA/EUnetHTA 21 Joint Scientific Consultation procedure during EUnetHTA 21 is not foreseen.

8 Summary of documents

Table 2. Description of documents

All current documents can be found on the EUnetHTA 21 JSC website.

Documents	Description
Open Call Application Form	Application form for the formal expression of interest by an Applicant (available for submission by the Application during Open Call periods on the EUnetHTA 21 website or upon request via EUnetHTA21-JSC@g-ba.de)
Draft briefing document	Draft briefing document comprising the questions and Applicant's positions, as well all the relevant information, annexes and references, important to assess such questions.
Final briefing document	Finalised version of the draft briefing document addressing regulators' comments and HTAb's points of clarification, including all annexes and references - with adaptations in text and reference list highlighted.
SAWP List of Issues (LoI), EUnetHTA 21 List of Issues (LoI)	Documents outlining the concerns or disagreements with the Applicant's proposal. Further justifications, clarification or changes to the Applicant's proposals are requested.
Final CHMP Scientific Advice/	Documents with written answers to the Applicant's questions.

Documents	Description
Protocol Assistance letter, EUnetHTA 21 Final Written Recommendations	