EUnetHTA 21 Public Consultation
Comments and Responses
D6.2.1 Briefing Document Template & D6.4.1 External Guidance with EMA

Comments received
AMS Advanced Medical Services GmbH, Germany
Bayer AG & Bayer Vital GmbH, Germany
BioPharma First Consultancy, Netherlands
Cancer Patients Europe – CPE, Belgium
Ecker + Ecker GmbH, Germany
European Confederation of Pharmaceutical Entrepreneurs (EUCOPE), Belgium
European Federation of Pharmaceutical Industries and Associations (EFPIA), Belgium
European Federation of Statisticians in the Pharmaceutical Industry (EFSPI) HTA SIG, Europe (various)
European Society for Medical Oncology (ESMO), Switzerland
European Union of General Practitioners/Family Doctors – UEMO, Belgium
Lumanity, Irland/Netherlands
Lymphoma Coalition - Lymphoma Coalition Europe (LCE), France
Osteogenesis Imperfecta Federation Europe (OIFE), Belgium
Patient Focused Medicines Development (PFMD), Belgium
Roche, Switzerland
SKC Beratungsgesellschaft mbH (SKC), Germany

Sub-deliverable	Comment from	Page number	Line/ section number	Comment and suggestion for rewording	Response Hands-on-Group
D6.4.1 External Guidance with EMA	Dr. Thomas Ecker Ecker + Ecker GmbH	General		The noticeable difference in the format of this deliverable from others already submitted under EUnetHTA 21 raises questions. Here, a uniform format would be desirable.	Thank you for your comment.
	Dr. Thomas Ecker Ecker + Ecker GmbH	General		While going through the document, the reader gains the impression that significant portions of it appear to be extracted from the pre-existing documents related to the open calls for the EUnetHTA 21 Procedure (March 2021–September 2023). Unfortunately, this deliverable therefore fails to serve its intended purpose, which is to prepare for JSC under EU HTA. Moreover, the final deliverable will be published once the period of open calls is completed and the interim period has started. This has three consequences: (a) Information provided seems outdated (e.g., reference to “open calls”, EUnetHTA 21 website) (b) The information presented in this delivable contradicts the information provided in the guidance for JSC for the interim period (EMA/250551/2023). (c) Key aspects of JSC under EU HTA are not addressed. The final deliverable should incorporate all the aspects mentioned.	Thank you for your comment. The document is intended to describe the procedure of a Joint Scientific consultation (JSC) under EUnetHTA 21 as specified in the service contract. It is the responsibility of the HTA Coordination Group (HTACG) and the respective JSC subgroup to adapt the guidance document to the structure and procedural workflow under the HTA Regulation. Regarding a) As mentioned the guidance describes the work under EUnetHTA 21. b) The Guidance on Parallel EMA/HTA body (HTAb) Scientific Advice for the Interim Period describes the process of a parallel HTA/EMA consultation to facilitate aligned work. A parallel consultation during the interim period should not be mistaken for an EUnetHTA 21 JSC and especially not for a JSC under the HTA Regulation. c) The HTACG and the respective JSC subgroup are responsible for

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					this transfer work. Discussion on key aspect have started within the JSC subgroup and relevant documents for JSC under the HTA Regulation will be adopted by the HTACG by the end of the implementation phase, end of 2024, at the latest.
	Dr. Thomas Ecker Ecker + Ecker GmbH	6		It would be helpful to provide a typology of different formats of (pure) HTA and parallel HTA and regulatory advices, as both formats can be done in a joint fashion. The subsequent text refers to parallel joint scientific consultations only, whereas the title of the deliverable ("D6.4 Procedural Guidance JSC") indicates a broader approach.	Thank you for your comment. The HTA Regulation does indeed allow for JSC with or without with the involvement of EMA via a parallel process. However, for EUnetHTA 21, the aim was to conduct all JSC in parallel with EMA, as this format is the most complex approach and valuable for all parties. Minor adjustments are needed for a guidance document on HTA-only JSC, as not involving the EMA would streamline the process but would not change its fundamental structure. It was a request of the Technical offer to explicitly mention the HTA—only option in D6.2.1 Briefing Document Template.

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	Dr. Thomas Ecker Ecker + Ecker GmbH	7		Parallel JSC is limited to interaction on pivotal trial design. However, this fails to align with the HTD's actual information requirements, which is information to support and prepare for the JCA. Key aspects that would be central for HTD on HTA are not covered in this guideline, e.g. - No obligation to participate for HTAbs - No information on consolidation of PICOs No binding advice	Thank you for your comment. The guidance describes the processes and steps for an EUnetHTA 21 JSC, taking into account the EUnetHTA 21 structure of a hands-on group per consultation and the CSCQ as the overarching committee. The processes will be assessed for their applicability and transferability to the committees of the HTA Regulation, i.e. the HTACG and the JSC subgroup. Recommendations on the proposed development provided by the participating HTAbs in the EUnetHTA 21 Final Written Recommendations as the final output document are non-binding. For participating HTAbs it reflects the state-of-the-art of medical knowledge and national/regional requirements at the time of the advice which could be subject to changes over time. However, the status of a JSC recommendation under the HTA Regulation will be discussed again and deviations from these will have to be explained by the Health Technology Developer (HTD) in the Joint Clinical Assessment (JCA) dossier.
	Dr. Thomas Ecker Ecker + Ecker GmbH	8	168–171	Statement in guideline: *Therefore, commercially confidential information*	Thanks for your comment. This statement aims to ensure that no

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				provided to the EMA and EUnetHTA 21 within the context of a Parallel EMA/EUnetHTA 21 JSC is not shared with any party before authorisation outside of the respective EMA and HTA networks in the absence of a signed confidentiality undertaking or the consent of the sponsor. Comment: Would you be so kind to elaborate why confidentiality should end with authorization? This seems rather surprising as the HTA process would be still ongoing at this point of time. The EU HTA regulation clearly states, that "anynomised, aggregated, non-confidential summary information on joint scientific consultations" will be made available via the IT platform to the general public (HTAR Article 30 (3(k))).	confidential data is disclosed before a confidentiality agreement has been signed, as data and intellectual property protection is of course considered mandatory. However, involvement of external experts also needs to be facilitated. EUnetHTA 21 worked with a Confidentiality Agreement (ECA) form to ensure confidentiality and informed the HTD accordingly. Nevertheless, the confidentiality rules do not end with the marketing authorisation. To clear up any misunderstandings, the term "before authorisation" is removed.
	Dr. Thomas Ecker Ecker + Ecker GmbH	7	133 ff	According to this paragraph only parallel EMA/HTA JSC are possible; D6.2.1 Briefing Document Template (p. 1, line 26) explicitly also mentions the format of HTA-only JSC.	Thank you for your comment. During EUnetHTA 21 is aimed for and achieved to perform all JSCs in parallel with EMA. It was a request of the Technical Offer to explicitly mention the HTA—only option in D6.2.1 Briefing Document Template. Also, the HTA Regulation leaves room also for HTA-only advices. It will be up to the HTA Coordination Group (CG) and JSC subgroup to elaborate on the definitive procedure and timelines for an HTA-only advice.
	Dr. Thomas Ecker	10	265 ff	Statement in guideline:	Thank you very much for your

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	Ecker + Ecker GmbH			*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.* Comment: Input from patient representatives and Healthcare Professionals (HCPs) on endpoints are strongly encouraged. According to the EU HTA Regulation Article 18 (6 and 7) it shall be ensured by the designated subgroup that patients, clinical experts and other relevant experts are given an opportunity to provide input during the preparation of the draft joint scientific consultation outcome document as well as organize a face-to-face or virtual meeting for an exchange of views with the HTD and patients, clinical experts and other relevant experts. A confirmatory statement in the guideline would be helpful.	comment. Of course, there are no limitations to the aspects on which clinical experts and patients would like to comment. As stated, the aspects listed are only "inter alter" ("among others"). Referring to the "proposed development" included key elements of trials such as endpoints, treatment duration etc. However, endpoints was added.
D6.2 Template Briefing Book	Roche	General		Roche appreciates all the EUnetHTA21 work done so far. As these guideline documents for JSC seem only to describe respective procedures under EUnetHTA21 we want to call out that clarity is required for the future of JSCs under the HTAR. Roche would appreciate having an appropriate public consultation for JSC guidance and Briefing Book template during the respective implementing act procedure.	Thank you for your comment. The document is intended to describe the procedure of a JSC under EUnetHTA 21 as specified in the service contract. It is the responsibility of the HTACG and the respective JSC subgroup to adapt the guidance document to the structure and procedural workflow under the HTA Regulation.
	Roche	6	108-109	*"If scientific consultation has been previously requested from national HTA bodies or EUnetHTA. If yes, please*	Thank you for your comment. There are mechanisms in place in

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				include the full advice documents as an annex to your briefing document." In general Roche supports transparency within the (p)JSC procedure with respect to previous advices. However, sharing those documents requires an appropriate and aligned upon confidentiality framework between all involved parties (e.g. (p)JSC attendees, JCA-Subgroup members, national HTA authorities, HTD). In particular supporting information which might be shared during national advice may contain highly confidential, country-specific information which is not in scope of the JSC. Therefore, also with an appropriate confidentiality framework in place, it should be optional for the HTD to share the full advice documents. <u>Suggestion to replace with:</u> *"If scientific consultation has been previously requested from national HTA bodies or EUnetHTA, the HTD can provide the results from the advice as an annex to the briefing document (optional) once an appropriate confidentiality framework is in place."*	EUnetHTA 21 to maintain confidentiality and an appropriate framework will also be ensured under the HTA Regulation.
	Roche	8	158-160	*"Furthermore, as the existence of a medical need is included in the Committee for Scientific Consistency and Quality (CSCQ) eligibility assessment for parallel EMA/EUnetHTA 21 JSC, related questions are out of the scope of parallel EMA/EUnetHTA 21 JSC"* This applies to the current and to be closed out EUnetHTA21 framework (see general comment above). Roche wants to call out that understanding the medical need is fundamental to inform clinical	Thank you for this comment. It had been assumed that a potential medical need had been sufficiently described by the HTD in the Application form for a JSC to fulfil the selection criteria applied during EUnetHTA 21. Therefore, discussing unmet medical need is not a priority. However, if the HTD wishes to do so due to a complex treatment

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				development programs. As such related questions should be included in the Briefing Book and be addressed in the advice setting.	setting or multiple competitors in the development stage, this can still be addressed during a JSC. Adjusted to "related questions do not seem a priority topic for the Parallel EMA/EUnetHTA 21 JSC, but can be addressed if needed.".
	Roche	10	211	Roche suggests adding *"dosing frequency" as proposed area to the questions on clinical development.*	Has been added: "including dosing (frequency)"
	Roche	10	227	In some disease areas, the treatment landscape might change significantly in a short period of time. In such cases, a follow-up procedure might be necessary e.g. to discuss additional evidence generation activities beyond the pivotal clinical trial(s). Roche suggests adding *the option of a follow-up consultation to allow better informed later JCAs for all involved stakeholders.*	Thank you for your comment. The regulation clearly states that a JSC should provide advice on the planning of a pivotal study. As this demand is considered relevant, further discussions on this topic will take place in the JSC subgroup, but also other relevant subgroups and the HTACG.
	Roche	12	302-313	Roche appreciates the opportunity to discuss questions on PLEG and suggests adding questions on the additional evidence package in this section.	Thank you for your comment. As mentioned above, the examples given are not exhaustive. In this context, we would like to point out once again that consultations on PLEG are only conducted only in conjunction with request for discussion of pivotal trial design and when contextualized with clinical data from the pivotal (phase II/III) studies.
	Roche	16-17	413-464	Suggestion to remove the description and questions related to health economic assessment as all economic considerations are out of scope for EU HTA and remain	Thank you for your comment. However, as stated in the disclaimer of the document, health

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				in the country's responsibility. As such, they should be asked and answered at the national level.	economic assessments are considered relevant for many HTAbs and the provision of advice in this regard is based on a voluntary basis according to Article 23 of the EU HTA Regulation. This will also be considered for the JSC future work under the HTA Regulation.
				Please take also into consideration the following comments regarding the Interim Procedure published on EMA/G-BA website	Thank you very much for your comment. However, this is out of the scope of this public consultation.
	Roche	General to interim procedure published on EMA/G-BA website		Roche regrets that no public consultation took place for the interim procedure before coming into effect. Please take the following comments regarding the Interim Procedure published on EMA/G-BA website into account.	Thank you very much for your comment. However, this is out of the scope of this public consultation.
	Roche	General to interim procedure published on EMA/G-BA website		Roche would appreciate an update of the interim procedure as soon as the final EUnetHTA21 guidance is available so that the interim procedure at least reflects the current up to date thinking for EU Level (p)JSCs.	Thank you very much for your comment. However, this is out of the scope of this public consultation.
	Roche	General to Interim procedure published on EMA/G-BA website		A final consolidated EU-HTA recommendation document should be transferred to the HTD on top of the HTAb-specific recommendations. A consolidated document would be useful for the forthcoming preparation of the JCA submission dossier whereas the HTAb-specific (non-consolidated) recommendations would be useful for the forthcoming national submissions for appraisal	Thank you very much for your comment. However, this is out of the scope of this public consultation.

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	Roche	General to Interim procedure published on EMA/G-BA website		Suggestion to remove the description and questions related to health economic assessment as all economic considerations are out of scope for EU HTA and remains in the country's HTA responsibility. As such, they, and so, should be asked and answered at the national level.	Thank you very much for your comment. However, this is out of the scope of this public consultation.
D6.4 Procedural Guidance JSC	Roche	General		Roche appreciates all the EUnetHTA21 work done so far. As these guideline documents for JSC seem only to describe respective procedures under EUnetHTA21 we want to call out that clarity is required for the future of JSCs under the HTAR. Roche would appreciate having an appropriate public consultation for JSC guidance and Briefing Book template during the respective implementing act procedure.	Thank you for your comment. The document is intended to describe the procedure of a JSC under EUnetHTA 21 as specified in the service contract. It is the responsibility of the HTACG and the respective JSC subgroup to adapt the guidance document to the structure and procedural workflow under the HTA Regulation.
	Roche	General		Roche asks for enough capacity to ensure that each HTD can request and have the possibility to undergo a JSC, as needed. This would prevent discrimination of HTDs. Roche would recommend establishing a rolling system which is synchronised with application timelines for EMA advice and allows for JSC submissions whenever appropriate. The current open call system does not fit the needs and shifting timelines of drug development.	Thank you again. It is the responsibility of the HTA CG and the respective JSC subgroup to adapt the guidance document to the structure and procedural workflow under the HTA Regulation. This will also take into account capacities and request periods, timelines etc. in accordance with the HTA Regulation.
	Roche	General		Roche suggests implementing a fee-based system for JSCs similar to the EMA process aiming at avoiding capacity restrictions.	Thank you for your comment, we have taken note of it. The evaluation of such an option is foreseen under the HTA Regulation: Art. 31(c).

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	Roche	General		Roche would appreciate to get more information on how the involvement of different Member States is coordinated, to ensure a truly pan european perspective informing best a later JCA, independent from the assessing HTAb. Roche welcomes implementing an EMA-like system with EU HTA JSC assessor and co-assessor which would help to ensure comprehensive responses.	Thank you for your comment. The HTA Regulation foresees an assessor and a co-assessor for each JSC. The specific responsibilities and tasks as well as the interaction with the JSC subgroup and HTACG are currently being discussed and will be continued in the coming months.
	Roche	General		A final consolidated EU-HTA recommendation document should be transferred to the HTD on top of the HTAb-specific recommendations. A consolidated document would be useful for the forthcoming preparation of JCA dossier whereas the HTAb-specific (non-consolidated) recommendations would be useful for the forthcoming national submissions for appraisal.	Thank you very much for your comment. For all EUnetHTA 21 JSCs, the inal outcome document is the Final Written Recommendations, which includes a common position and additional comments from the individual HTAbs if there is a divergent position or additional information is required. This Final Written Recommendation document is forwarded to the HTD at the end of the procedure.
	Roche	General		Timelines mentioned within the text are not comprehensive and not entirely in alignment with the summary Table 1. Roche suggests clarifying and aligning accordingly.	Thank you for this comment. This will be double-checked.
	Roche	General		Roche suggests building a database of EU patients and HCPs and to train patients and HCPs on EU HTA procedures and implications in order to ensure capacity and capability to systematically get relevant experts involved for JSCs. Roche suggests further to allow for national experts to	Thank you for your comment. This will be taken into consideration and discussed for future JSC.

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				be a part of the JSC process in cases where no relevant EU expert with HTA experience is available.	
	Roche	7	160-171	Roche appreciates confidential treatment of the JSC. Thus, the details on the confidentiality procedure and framework need to be implemented before starting the first JSC under the HTAR. It needs to be further clarified that confidentiality is ensured e.g. in case of withdrawal.	Thank you for your comment. Ensuring confidentiality is of great importance. EUnetHTA 21 has trustworthy mechanisms in place to ensure that no unauthorised persons have access before signing the appropriate confidentiality agreement (ECA). Similar mechanisms are also put in place for the HTACG and JSC subgroup.
	Roche	8	187-189	*"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."* Roche generally agrees, however, for recommendations of the (p)JSC which still holds through at the time of the JCA scoping process they should be reflected in the development of the consolodidated EU level PICO.	Thank you for your comment. This will be taken into consideration.
	Roche	12	355-356	On page 11 of D7.2 Guidance on interaction with patients and clinical experts, it's stated that ''EUnetHTA21 recommends that in JCAs patient representatives and HCPs can also provide input as stakeholders representing the interests of their patient association and sharing the views of their organisation (e.g., clinical society)." Roche suggests applying the same approach for JSC.	Thank you for your comment. Due to confidentiality, it is not possible to collect input from patients and clinical experts as stakeholders during a JSC.
	Roche	13	417-418	''Following confirmation of validation from EMA, the	Thank you very much for your

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				Applicant submits the final briefing document through IRIS and sends the document also to the EUnetHTA21 JSC Secretariat via Eudralink'' Related to table 1 page 18, if the submission at day -5 was acceptable, an additional submission at day -2 should not be mandatory.	comment. The submission of the final briefing package by the applicant to the EMA and EUnetHTA 21 is a mandatory step of the procedure. EUnetHTA 21 did not do a validation step and did not request several versions of the same document if there was no adjustment needed.
	Roche	15	501	*"The Applicant will be informed about the length of the discussion meeting in due time."* Roche suggests to keep meeting length as a default of 3 hours to allow sufficient time for for meaningful discussion.	Thank you for your comment. The regular meeting time is set at a maximum of 3 hours. However, in a few cases, consideration has been given to shortening the discussion time due to limited discussion content. However, this would only apply in exceptional and reasonable cases.
	Roche	16	522-523	Roche recommends EMA and HTAb to acknowledge the meeting minutes sent by the HTD in order to ensure that they are accurate and reflect the viewpoints of all participants.	Thank you for your comment. It is common EMA practice to receive minutes from the HTD. EUnetHTA 21 only receives them for transparency reasons. The official output document on the HTA side is the Final Written Recommendation document.
	Roche	21	Table 1	''D+82 EUnetHTA Final Written Recommendations sent to Applicant and EMA.'' Roche appreciates the detailed time schedules and emphasizes that the process should be optimized to be as quick as possible, that's why we suggest to send EUnetHTA21 final written recommendations at D+70,	Thank you for your comment. However, procedural steps such as final confirmation by the CSCQ JSC and medical editing do not allow for a shorter period of time. However, we will look into possibilities for further alignment

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				to align with EMA final advice letter timeline.	here.
	Roche	22	559-560	Suggestion to remove the sentence ‘’In the same manner questions related to health economics are possible and should be directed to HTAb’’ as all economic considerations are out of scope for EU HTA and remains the country’s HTA responsibility. As such, they should be asked and answered at the national level.	Thank you for your comment. However, as stated in the disclaimer of the document, health economic assessments are considered relevant for many HTAbs and the provision of advice in this regard is based on a voluntary basis according to Article 23 of the EU HTA Regulation.
	Roche	23	577-579	In some disease areas, the treatment landscape might change significantly in a short period of time. In such cases, a follow-up procedure might be necessary e.g. to discuss additional evidence generation activities beyond the pivotal clinical trial(s). Roche suggests adding *the option of a follow-up consultation to allow better informed later JCAs for all involved stakeholders.*	Thank you for your comment. The regulation clearly states that a JSC should provide advice on the planning of a pivotal study. However, as this demand is considered relevant, further discussions on this topic will take place in the subgroups and the HTACG.
	Roche	General to interim procedure published on EMA/G-BA website		Roche is grateful for having a bridging process which will be handled by G-BA from September 2023 to January 2025. Nevertheless, it is important that leading HTAbs give comprehensive advice, that there are enough slots to ensure that each HTD can request and have the possibility to undergo a JSC and that the advice provides meaningful information about the future EU-PICOs to prepare for future JCAs.	Thank you very much for your comment. However, this is out of the scope of this public consultation.
	Roche	General to interim procedure published on EMA/G-		Confidentiality and an appropriate handling of conflict of interest needs to be guaranteed independent from the involved HTAb and their national laws.	Thank you very much for your comment. However, this is out of the scope of this public consultation.

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		BA website			
	Roche	General to interim procedure published on EMA/G-BA website		A final consolidated EU-HTA recommendation document should be transferred to the HTD on top of the HTAb-specific recommendations. A consolidated document would be useful for the forthcoming preparation of the JCA submission dossier whereas the HTAb-specific (non-consolidated) recommendations would be useful for the forthcoming national submissions for appraisal	Thank you very much for your comment. However, this is out of the scope of this public consultation.
	Roche	General to interim procedure published on EMA/G-BA website		Roche welcomes the involvement of Patient's and HCP's experts in the procedure and proposes to allow for national experts to be a part of the JSC process in cases where no relevant EU expert with HTA experience is available.	Thank you very much for your comment. However, this is out of the scope of this public consultation.
	Roche	General to interim procedure published on EMA/G-BA website		Roche appreciates the possibility of submissions on a rolling basis and emphasises that for this it is crucial to ensure enough capacities in the future JSC process. Roche suggests to reduce the application period for an advice from three to one month in advance as the more extended the procedure is, the less stability of the development plan of the molecule can be anticipated.	Thank you very much for your comment. However, this is out of the scope of this public consultation.
	Roche	General to interim procedure published on EMA/G-BA website		Roche appreciates the general option of a follow-up procedure. Indeed, in some disease areas, the treatment landscape might change significantly in a short period of time. In such cases, a follow-up procedure might be necessary e.g. to discuss additional evidence generation activities beyond the pivotal clinical trial(s). Roche emphasises the necessity of *this option of a*	Thank you very much for your comment. However, this is out of the scope of this public consultation. Further discussions on this topic will take place in the JSC subgroup, but also other relevant subgroups and the HTACG.

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				follow-up consultation in the future EU HTA JSC guidance to allow better informed later JCAs for all involved stakeholders.	
D6.4.1 External Guidance with EMA	PFMD	GENERAL		PFMD welcomes the opportunity to respond to the EUnetHTA 21 public consultation on "Guidance on Parallel EMA/EUnetHTA 21 Joint Scientific 4 Consultation". PFMD, as a global not-for-profit collaborative initiative, is dedicated to ensuring patient-centered product development and healthcare systems in collaboration with patients and all stakeholders. With 47 member organizations representing industry, patient communities, academia, and healthcare institutions, we actively engage in initiatives prioritizing the patient perspective in healthcare decision-making. With this in mind, we commend the efforts to consider Joint Scientific Consultation by the EMA and EUnetHTA 21 in order to streamline and increase efficiencies and decrease patient burden, within the healthcare system. *There are several key principles that are essential for this Joint Scientific Consultation process to be efficient and effective: inclusion of all relevant stakeholders, early and ongoing patient engagement throughout the review process, inclusion of patient experience data (PED) for the totality of evidence, interconnected patient engagement and patient experience data plans, and processes to ensure transparency and accountability. These are described in further detail below.*	Thank you for your introductory comment.

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D6.4.1 External Guidance with EMA	PFMD	GENERAL		It is important to involve all relevant stakeholders in discussions about the evidence needed to meet the needs and expectations of decision-makers. This will ensure faster access to innovative medicines for patients. The optimization of data generation is instrumental in avoiding redundancies during the clinical development program and potential delays in accessing new medicines. The remits of EMA and HTA bodies (HTAb) are different but not exclusive from each other, as the same set of data could serve different purposes. It illustrates the shifting paradigm in generating the totality of evidence to support the regulatory evaluation of the Benefit/Risk balance of medicines and the HTA evaluation of the added value and cost-effectiveness. Ultimately, it benefits patients by expediting the drug development process and bringing medicines to patients faster while lowering their exposure to the potential risks associated with clinical investigations. In the article Building from Patient Experiences to Deliver Patient-Focused Healthcare Systems in Collaboration with Patients: A Call to Action | SpringerLink, we propose a more aligned approach to collecting PED where all segments of healthcare and stakeholder groups understand and learn from patient perspectives and experiences to avoid duplication of effort and decrease the burden on the patient community.	Thank you for your comment, we have taken note of it.

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D6.4.1 External Guidance with EMA	PFMD	GENERAL		As part of this process, we underscore the joint procedure foresees the inclusion of patients. This means the early and ongoing opportunities for patient engagement in order to identify true patient need and ensure decision-making that supports what is most important to patients. This has to be done systematically. Patients' voices have to be heard through such procedures.	Thank you for your comment. Indeed, strong efforts have been made during EUnetHTA for a systematic involvement of patients, see D7.2 In fact, 6 out of 7 EUnetHTA 21 JSC have been conducted with European level patient involvement and input.
D6.4.1 External Guidance with EMA	PFMD	GENERAL		Patient Experience Data (PED) should also be part of the totality of the evidence. PED does involve not only quantitative sources of evidence (e.g., patient-reported outcomes or patient-reported experience measures) but also qualitative sources (i.e., any information obtained as part of patient engagement activities that reflect the wider perspective of patients' experience, for example, the outcome of focus groups, surveys or interviews). The weight of PED in the totality of evidence when assessing the Benefit/Risk balance depends on the type of disease, indication, or patient population. There is no one size fits all approach. Every PED development plan should have a patient engagement plan, which ensures the PED plan is anchored to an unmet need informed by the patient community, co-determines what PED will be measured, and informs how PED will be collected to ensure viability, quality and minimizes patient burden. Patient engagement occurs across the evidence pathway, from prioritization, early dialogue, and design to generation,	Thank you for your comment, we have taken note of it.

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				analysis, and communication.	
D6.4.1 External Guidance with EMA	PFMD	GENERAL		The utilization of PED in decision-making processes ensures that there is a patient engagement plan and that this plan is credible, implemented, and adapted to ensure the best patient representation throughout any process where PED is utilized for decisions, e.g. drug development, medical devices innovation, regulatory approvals, HTA decisions, health system/ services design and strengthening, digital transformation etc.	Thank you for your comment, we have taken note of it.
D6.4.1 External Guidance with EMA	PFMD	GENERAL		Equally important is for the patient community to receive feedback on how PED is generated, analyzed, and utilized in decision-making. Patients should have access to the data following decisions, and PED should be made publicly available to improve the understanding of diseases and their impact, inform treatment decisions, and/or reduce duplication of effort.	Thank you for your comment, we have taken note of it.
D6.4.1 External Guidance with EMA	PFMD	GENERAL		In the JSC, the above PE and PED guidances should be adhered to by all stakeholders, and accurately reflect what is described in guidance and policy documents. Consistent and regular monitoring and evaluation of patient engagement in PED ensures continuous feedback and improvement of the PE process, outcomes, and impact.	Thank you for your comment, we have taken note of it.
D6.4.1 External Guidance with EMA	PFMD	GENERAL		PFMD's Patient Engagement & Patient Experience Data project aims to better understand what experiences are most significant and valuable to patients and their families/caregivers, when and how these experiences can be measured, and their impact on decision-making. We are working to transform the first-ever co-created Global Patient Experience Data Navigator into a Global	Thank you for your comment, we have taken note of it. Your efforts are well noted and appreciated.

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				PE & PED Roadmap by incorporating patient engagement in the design, generation, analysis, and use of PED. These efforts are essential to maximize the impact of PE initiatives and drive meaningful improvements in patient experiences and outcomes.	
D6.4.1 External Guidance with EMA	PFMD	6	115	Added value: this is a common terminology that is called in in many instances in the HTA Regulation. It is foundational to the HTA assessment like the Benefit/Risk balance is for the Regulatory Agencies. Is there a definition of Added Value?	Thank you for your comment. As a Joint Clinical Assessment (JCA) report is only descriptive, the assessment of added value or added benefit is the responsibility of the respective Member State (MS).
D6.4.1 External Guidance with EMA	PFMD	8	180	Health Technologies developers (HTDs): the document mentions either HTD or the Applicant. If designating the same entity, the same term should be used throughout the document. If designating different entities, it should be clarified.	Thank you. Clarification added in 3.4: “health technologies developers (HTDs, also referred to as Applicants in this document)”.
D6.4.1 External Guidance with EMA	PFMD	8	181	We understand that 2 documents will be issued at the end of the procedure, one from EMA and one from EUnetHTA. Could a common letter be issued with first the common recommendations for both EMA and EUnetHTA, then a list of EMA recommendations, then a list of EUnetHTA recommendations?	Thank you very much for your comment. The different remits of HTA bodies and regulators should be kept in mind at all times. The consultation process with HTA and EMA takes place in parallel and it is not appropriate to merge the list of issues nor the consultation letters. However, exchange between the 2 entities to increase mutual understanding is facilitated during the process and common positions are made clear during the discussion meeting.

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D6.4.1 External Guidance with EMA	PFMD	8	196 - 198	Although we understand the purpose of this statement, it may be practically challenging to delineate the questions raised in different consultations. I.e. Given that the briefing document is common, some questions asked during a EMA Scientific advice may be asked during the joint consultation.	Thank you for your comment. The statement points out that questions that have already been asked recently in a separate EMA scientific advice should not be asked again in a JSC, as EMA has already commented on them and no divergent answer is to be expected. Duplication of work needs to be avoided to use available resources most efficiently.
D6.4.1 External Guidance with EMA	PFMD	9	220 - 224	To foster efficiencies during the procedure, we recommend a common platform between EMA and EUnetHTA to be developed in which all communications and informations exchange could take place	Thank you for your comment. Technical and legal ways are being worked out to make this possible for the work under the HTA Regulation.
D6.4.1 External Guidance with EMA	PFMD	9	247 - 248	The JSC HOG is composed of 6 HTAbs at minimum. It is not clear which mechanism is adopted to make sure that the HOG members represent the views of the CSCQ. E.g. is there an automatic binding by members not being in the HOG?	Thank you for your comment. At the end of the process, the CSCQ JSC receives the Final Written Recommendations for a final quality check and CSCQ JSC members always have the opportunity to attend all relevant meetings.
D6.4.1 External Guidance with EMA	PFMD	10	255 - 256	Same as above	See above.
D6.4.1 External	PFMD	10	266 - 271	This section needs to be expanded and made more directive. Patient and HCP stakeholders should always	Thank you for your comment. We agree, that expert input should

Sub-deliverable	Comment from	Page number	Line/ section number	Comment and suggestion for rewording	Response Hands-on-Group
Guidance with EMA				be sought to take part within this process to provide input relating to, the condition, current treatments, views on inclusion/exclusion criteria, views on QoL measures, practical feasibility of proposed trial protocols… etc Consider adding a link to the PARADIGM toolkit on patient involvement into Early Dialogues along with: "Tools and resources need to be used and/or developed to ensure that patient input into early dialogues is supported by education, guidance and following good practices. A range of tools has already been developed with the input from 11 EU HTA bodies" https://imi-paradigm.eu/petoolbox/pe-in-ed-hta/	always be sought for all JSC. The concepts of expert involvement are set out in D7.2/3 and were intensively discussed during the development of the document. The details are not laid out in this document but in deliverable D7.2/3. Expert involvement will further be discussed when developing the new guidance under the HTA Regulation.
D6.4.1 External Guidance with EMA	PFMD	10	270 - 271	The timing for discussing PLEG is not clear. The text refers to the need to discuss PLEG in conjunction with discussion on pivotal trials while also mentioning the need to contextualize with data from pivotal trials. There is conflicting timing and one may also consider that PLEG may need to be discussed separately from pivotal trials.	Thank you for your comment. As stated, no JSCs will be conducted for PLEG questions only. Questions on PLEG are only allowed in conjunction with questions on a pivotal study as context is needed for a meaningful discussion. PLEG discussion is most useful at an early time point as gaps in the development plan should be identified and discussed early on.
D6.4.1 External Guidance with EMA	PFMD	10	275 - 278	As per the text, applicants can only apply when calls for applications are published. If the program development timelines do not match with the calls timelines while fulfilling the HTAR criteria, there is no flexibility?	Thank you for your comment. Indeed, only a certain selection of time slots was available in EUnetHTA 21. However, the application process for JSCs under the HTAR will be revised by the HTACG and the JSC subgroup and more frequent

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					request periods will be available to facilitate a proper timing.
D6.4.1 External Guidance with EMA	PFMD	11	299	Unmet Medical Need: how is it defined in the context of this guidance? It is important to align with the ongoing discussions in the context of the revision of the EU Pharmaceutical legislation.	Thank you for this comment and reference. Currently EUnetHTA 21 defines unmet medical need as: According to Article 4 paragraph 2 of Commission Regulation (EC) No. 507/2006 unmet medical needs mean a condition for which there exists no satisfactory method of diagnosis, prevention or treatment in the Union or, even if such a method exists, in relation to which the medicinal product concerned will be of major therapeutic advantage to those affected. Especially concerning rare, life-threatening or chronically debilitating diseases. A description of the available diagnostic, prevention or treatment options/standard of care (SOC), including all relevant treatment modalities should be included. The effect of available methods should also be described together with a description of how the medical need is not fulfilled by the available treatment options. Justification will be more convincing if based as much as possible on epidemiological data about the disease (e.g., life expectancy, symptoms and

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					duration, health-related quality of life). The claims could be substantiated e.g., from published literature or registries or healthcare databases.
D6.4.1 External Guidance with EMA	PFMD	11	323	This paragraph should spell out how the EMA recommendations are produced.	Thank you for your comment. The basic procedure of the EMA is described in section "4.1 Regulatory authorities: Actors and scope".
D6.4.1 External Guidance with EMA	PFMD	11	334 - 335	As indicated above (row 266 - 271), the patients should be included in **all** JSC. Is this what is meant when speaking about “a routine basis”?	Thank you for your comment. We agree, and that is what is meant by “on a routine basis”.
D6.4.1 External Guidance with EMA	PFMD	12	340 - 361	From the section, it seems that the involved patient representatives are not the same for EMA and EUnetHTA. Although we understand that the functioning of EMA and EUnetHTA are different for engaging patient representatives and that there is the EU versus the national dimensions, we believe that the procedure would benefit common patient representatives in the procedure. This would allow a holistic position of patient representatives on EMA and EUnetHTA considerations.	Thank you for your comment. The aim was to include e.g. patients from both sides to increase the available input. At the moment, there are different structures and procedures in place to involve experts as this is a clear aim of both HTA bodies and regulators and had been set up individually. Possibilities for further alignment will be discussed under the HTA Regulation.
D6.4.1 External Guidance with EMA	PFMD	12	355	“The involved experts express their personal opinions and do not act as representatives for any stakeholder organization”: How can this be enforced?	Thank you for your comment. On the one hand, the patient or clinical expert must confirm this with his or her statement; on the other hand, it is often apparent

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					from the character of the contribution whether it is an individual opinion or a general organisational view.
D6.4.1 External Guidance with EMA	PFMD	14	428	Evaluation phase: A list of considerations by EMA and EUnetHTA would be beneficial for all stakeholders Examples are provided at rows 558 - 559 but should be further elaborated with additional details.	Thank you for your comment. The extent of the section is considered to be sufficient.
D6.4.1 External Guidance with EMA	PFMD	16	516	"where such divergences mean that a single development plan/trial could not be carried out". A single plan could still be carried out with adequate amendments.	Thank you for your comment. This is, after all, the purpose of the debriefing, to discuss such fundamental issues. Efforts are made to provide common recommendations.
D6.4.1 External Guidance with EMA	PFMD	22	563 - 564	Choice of Patient Reported Outcomes (PRO): the importance of this is a very important point. This should be extended to Patient Experience Data (PED) as well as Real World Data of which use in development and beyond is being increasingly adopted by other regulatory and HTA bodies. At PFMD we believe that Patient Engagement Data (PED) of which a PRO is one method to collect PED, should include patient engagement for the co-design and contextualization of PED. The two together are essential for enabling effective decision-making for better patient outcomes.	Thank you for your comment. We agree, that expert input should always be sought for all JSC. The basic concepts of expert involvement are set out in D7.2/3 and were intensively discussed during the development of the document.
D6.2.1 Briefing Document Template	AMS	general	N/A	It is unclear how many HTAbs are involved in the advice and how these HTAbs are chosen. Can the HTD make suggestions? **Suggestion:**	D6.4.1 External Guidance with EMA: "4.2 EUnetHTA 21 and HTAbs: actors and scope – The participation of a minimum of six CSCQ JSC member HTAbs is

Sub-deliverable	Comment from	Page number	Line/ section number	Comment and suggestion for rewording	Response Hands-on-Group
				The HTD shoud make a suggestion about the number of HTAbs involved and how these HTAbs are chosen.	required." Added: "Participation in a JSC as part of the HOG is voluntary." The HTD cannot chose and participation was dependant on available ressources of the CSCQ JSC HTA bodies.
D6.2.1 Briefing Document Template	AMS	1	Line 7	In the case of multiple intended indications, should a separate document be submitted for each indication, or can the respective indications be addressed together in one document and separated by subheadings? **Suggestion:** It should be stated clearly in the beginning of the template whether multiple indications can be addressed in one template.	Thank you for your comment. Sentence adjusted: "The consultation is carried out on the basis of one intended indication."
D6.2.1 Briefing Document Template	AMS	5-7	Summary and Section 1.	The summary and background section seem very exhaustive and in general too long. We suggest a mandatory up to 3 page summary and additionally an optional full background section if deemed necessary e.g., first contact with EMA/HTAbs and the HTD regarding a specific product. **Suggestion for rewording:** "*1. Background information (optional)"*	Thank you for your comment. However, the background information is considered mandatory and it is up to the HTD to provide background information in an exhaustive manner or less detailed. The option of a summary has been added.
D6.2.1 Briefing Document Template	AMS	5	Line 59-61/section 1.1	Is it necessary to carry out a systematic search in all available therapeutic guidelines to identify alternative treatments as potential comparators in this indication and list them all? Should the discussion of the current standard treatment focus only on the European standard of care/guidelines or also on North American guidelines?	Thank you for your comment. All relevant systematic information should be provided in sufficient detail. Yes, the current standard treatment should focus on the European guidelines.

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				Please specify which guidelines are suitable: ALL (European/EU national/North American) or a selection of them? The template asks for the labelling status of alternative treatments not only in Europe, but also in North America and refers to the importance of the availability of treatment alternatives for reimbursement decisions. However, since reimbursement decisions in European countries only take the respectively available treatment alternatives into account, we propose that the discussion of the current standard treatment should focus on European guidelines or national guidelines. **Suggestion for rewording:** *"Evolution of treatment should be discussed, including current standard therapy **in Europe** (referencing relevant guidelines and variations between the countries) […]."*	Added "in Europe".
D6.2.1 Briefing Document Template	AMS	5	Line 62-65/section 1.1	The sentence is incomplete. **Suggestion for rewording:** *"Thus, a solid discussion of all technologies (drugs, devices, procedures) that present relevant alternatives for the treatment of the pathology (stage, line of treatment) together with their labelling status in Europe and North America **is recommended**."*	Thank you for your comment. Sentence amended: "Thus, a solid discussion of all technologies (drugs, devices, procedures) that present relevant alternatives for the treatment of the disease (stage, line of treatment) together with their labelling status in Europe, North America and other non-EU countries should be provided."
D6.2.1 Briefing Document Template	AMS	5	Line 65/section 1.1	Could this be specified? E.g., is an ongoing Phase-II Study already considered an advanced phase of development?	Thank you for your comment. This is deliberately kept vague, as an ongoing phase II trial may be considered a sufficiently

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				Suggestion: This could be clarified in brackets: e.g. (Phase-III clinical trial upward)	advanced stage of development in some cases and indications.
D6.2.1 Briefing Document Template	AMS	5	Line 78/section 1.3	Does "*pharmacological classification*" refer to the Anatomical Therapeutic Chemical Classification (ATC) System? If the ATC code is required here, this should be specified in the template.	Thank you for your comment. An ATC code is usually not available at the current stage of development. Therefore, "pharmacological classification" is considered sufficient.
D6.2.1 Briefing Document Template	AMS	8	Line 167-175/section 2.	A general "*Request for Guidance on best practice*" by EMA/HTAbs without choosing a specific approach should be considered. Suggestion for rewording: In line 168 the sentence should be extended by "*[…] or a general request for guidance on best practice*."	Thank you for your comment. However, this is not considered directly relevant here.
D6.2.1 Briefing Document Template	AMS	11	section 2.5.3	A subheading "Q*uestions regarding comparator*" is missing. (A separate subheading is available for all other PICO-Questions.)	Thank you for your comment. It has been corrected.
D6.2.1 Briefing Document Template	AMS	15	Line 393-408/section 3.4.1	We expect that all these basic methods don't have to be discussed in each advice meeting. A general EU HTA methods paper should inform all HTAbs on most if not all the points mentioned. While it is acknowledged that for certain indications/studies a more specific discussion might be useful, a reliable set of methods is crucial for a successful JCA. Suggestion for rewording: On page 14 line 392 after the words *"is optional."* a half sentenced should be added: "*If not already specified in detail in the EU HTA (JCA) methods paper, […] it is…"*	Thank you for your comment. This will be considered by the JSC subgroup when adjusting the document.
D6.4.1	AMS	general	general	The document is not up to date and almost identical to	Thank you for your comment.

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External Guidance with EMA				the EMA guidance document EMA/410962/2017 Rev.6 available on the EMA web site including links that refer to documents that are obsolete. Suggestion: It would have been helpful to openly refer to the former document as the relevant document for JSC under EUnetHTA21 and that any changes to the document resulted from experience during those procedures.	Indeed, the document is based on the previous guidelines. However, a new and final EUnetHTA 21 version will be published after the implementation of the changes received through the public consultation. This final revision is planned according to the EUnetHTA 21 project plan and will serve as a basis for the future document under the HTA Regulation.
D6.4.1 External Guidance with EMA	AMS	9	Line 235-238/section 4.2	As the CSCQ JSC is only the standing working party of EUnetHTA21 and will be obsolete after September 2023, are the mentioned HTAbs also the members of the JSC Subgroup? **Suggestion:** Wherever possible references to responsible parties beyond EUnetHTA21 should be included.	Thank you for your comment. This is out of scope as this guidance only applies to EUnetHTA 21. The HTACG and the JSC subgroup are responsible for adapting it to the procedure under the HTA Regulation.
D6.4.1 External Guidance with EMA	AMS	7 and 9	Line 195, section 4. and Line 274, Section 4.3.1	The time for open calls already expired. We suggest to remove section 4.3.1. However, the process for application for a JSC after the regulation came into force is not described so far (responsible HTAb, time frame, selection of criteria).	Thank you for your comment. This is out of scope as this guidance only applies to EUnetHTA 21. The HTACG and the JSC subgroup are responsible for adapting it to the procedure under the HTA Regulation.
D6.4.1 External Guidance with EMA	AMS	11	Line 300/section 4.3.2	It is unclear whether the criterion "*first in class*" also includes first-in-class drugs within a specific indication when the same drug class is already used in another therapeutic indication.	Thank you for your comment. There is currently an EUnetHTA 21 interpretation on the selection criteria available on the EUnetHTA 21 website: https://www.eunethta.eu/jscfaq/

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					Link added to guidance.
D6.4.1 External Guidance with EMA	AMS	11	Line 304/section 4.3.2	It is unclear what the criterion "*Union clinical research priorities*" refers to. Suggestion: Include a link to relevant EMA documents in which these priorities are specified.	Thank you very much for your comment. There is currently an EUnetHTA 21 interpretation on the selection criteria available on the EUnetHTA 21 website.: https://www.eunethta.eu/jscfaq/ Link added to guidance.
D6.4.1 External Guidance with EMA	AMS	11	Line 308-310/section 4.3.2	It is unclear if any or all or a proportion of the criteria have to be fulfilled in order be eligible for a JSC procedure. Additionally in the future it is unclear how long a "*first advice*" is valid. Suggestion for rewording: "*At least ONE of the eligibility criteria above has to be fulfilled in order to qualify for a JSC procedure.*"	Thank you for your comment. This is out of scope as this guidance only applies to EUnetHTA 21. The HTACG and the JSC subgroup are responsible for adapting it to the procedure under the HTA Regulation.
D6.4.1 External Guidance with EMA	AMS	13	Line 421-422 /section 5.2	It would be preferrable if EMA/HTAbs could use the same electronic data exchange platform (e.g., IRIS) that also provides an automated response upon data upload. Currently it's unclear how the applicant can make sure that the final briefing document has been received. **Suggestion for rewording:** Delete the sentence an replace by appropriate new wording.	Thank you for your comment. Technical and legal ways are being worked out to make more joint structures possible for the work in the JSC subgroup and HTACG.
D6.4.1 External Guidance with EMA	AMS	13, 18	Line 411-419/section 5.2	There is a discrepancy between information on page 13 and table 1 on page 18: - According to table 1, the Applicant submits the revised briefing package to the EMA via IRIS and to EUnetHTA 21 via Eudralink on day – 5. - According to the information on page 13, the Applicant submits the revised briefing	Thank you for your comment. There is no discrepancy. The EMA procedure includes a validation step, whereas EUnetHTA 21 does not. If changes are made at this step, EUnetHTA 21 has to receive the updated briefing document as

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				document to the EMA through IRIS on day – 5 and only after administrative check by the EMA also to the EUnetHTA 21 JSC Secretariat via Eudralink.	well, of course.
D6.4.1 External Guidance with EMA	AMS	17	Line 526, Table 1	Although we understand that detailed procedural rules of the EU HTA will be specified elsewhere, the "*D6.4.1 External Guidance with EMA*" should provide – at least as a proposal – information on the JSC procedure concerning timelines and thus, support the predictability of the process. According to Article 17(4) of the HTAR the Coordination Group informs the HTD having requested a JSC in a published request period within 15 working days after the end of this period whether the HTD's request for a JSC is accepted. However, it remains unclear when the Coordination Group will initiate this JSC according to Article 18(1) and when the HTD will be informed, in particular, on the timepoint to submit the draft briefing package. For the HTD, the knowledge of the time remaining until the submission is important for planning the preparatory work within its organisation. In addition, timelines have to be coordinated and agreed upon with the EMA's schedule for scientific advice.	Thank you for your comment. As stated in the guidance document "All Applicants will be informed of the CSCQ JSC decision within three weeks after termination of the call." With regard to future consultations, it is up to the JSC subgroup and the HTACG to develop an appropriate system according to the HTA Regulation.
D6.4.1 External Guidance with EMA	AMS	16	Line 526, Table 1	In table 1 on page 16 day – 40 is missing: on page 11, section 5.1, line 377-380 it is stated "*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*."	Thank you for your comment. The table describes the procedure from D-30 (submission of draft briefing package), therefore the administrative task of scheduling the discussion meeting does not need to be included.

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D6.2.1 Briefing Document Template	Daniel Widmer UEMO	6	88-90	We propose to be more explicit: if a trained nurse is needed, or a specific surgeon, or a training for the GP or a therapeutic education for the patient, or clinical monitoring or laboratory tests.	Thank you for your comment. However, this is not considered directly relevant here.
D6.4.1 External Guidance with EMA	Daniel Widmer UEMO	12	348-363	On the commitment of experts, including the HCPs. The proposed paper is not talking about stakeholders organizations that can also intervene, especially if they have a European vision. UEMO, for example, can provide information on the workforce in each country that would allow the introduction of a new technology. Not all countries have this option nor the same infrastructure. In addition, UEMO can propose experts in the field for general medicine.	Thank you for your comment. Due to confidentiality, it is not possible to collect input from patients and clinical experts as stakeholders during the JSC process.
D6.4.1 External Guidance with EMA	Daniel Widmer UEMO	general		You will also have to think about discussing the energy cost of a new technology at the Early Dialogue stage.	Thank you for your comment. However, this is currently considered out of scope.
D6.2.1 Briefing Document Template	Renu Patel Lumanity HEOR	General	Not applicable	It is stated that the template can be used for both joint regulatory/ HTA consultation as well as HTA-only scientific consultation. Please consider highlighting those questions considered for joint or regulatory only and not required for HTA-only scientific consultation.	Thank you for your comment. It is considered clear that e.g. "2.5.1. Regulatory questions" would not apply for an HTA-only advice. The differences between the 2 procedures might be laid out in further detail in the future document under the HTA Regulation.
	Sallie Latimer Lumanity HEOR	5	Section 1.1	Please provide clarity on expectations for European vs national level data / information, particularly in relation to epidemiological data and treatment pathways which we would expect to differ at national level.	Thank you for your comment. We have added “in Europe”.

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				Are European level data acceptable for these topics with only major deviations at a national level to be flagged?	
	Renu Patel Lumanity HEOR	11	Section 2.5.3, line 253	How do EunetHTA anticipate that questions in section 2.5.3 will differ those in section 2.5?	Thank you for your comment. Section 2.5.3 aims at questions that are specifically directed at HTA and ask about special features in this remit.
	Renu Patel Lumanity HEOR	12	Section 2.6, line 312	Can EunetHTA clarify that discussion of RWE/ registry data sources are not precluded from discussion when companies are at the pre-pivotal clinical trial design stage? For example, if companies would like to get advice on potential RWE data sources to inform background information on disease and / or comparator effectiveness etc.	Thank you. Proper context is needed for a meaningful discussion on PLEG. PLEG discussion is most useful at an early time point as gaps in the development plan should be identified and discussed early on.
	Renu Patel Lumanity HEOR	16	Section 4, Line 413 and 4.2, line 444	We understand that health economic assessment is voluntary and not within scope of either JCA or JSC but how would this work in practice across jurisdictions? Is it anticipated that there will be multiple answers from different countries/ jurisdictions based on their specific considerations?	Thank you for your comment. For JSCs under EUnetHTA 21, divergent positions of individual HTAb, not only related to health economics, have indeed been presented in the Final Written Recommendation along with the common position.
D6.4.1 External Guidance with EMA	Renu Patel Lumanity HEOR	8	Section 2, Lines 131-132	It is stated that the medium-term goal is to share JSC recommendations with the team producing JCA. Is it envisaged that manufacturers following guidance given at JSC can use this as the justification for their trial design at JCA?	Recommendations on the proposed development provided by the participating HTAbs in the EUnetHTA 21 Final Written Recommendations as the final output document are non-binding. For participating HTAbs it reflects the state-of-the-art of medical

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					knowledge and national/regional requirements at the time of the advice which could be subject to changes over time. However, the status of a JSC recommendation under the HTA Regulation will be discussed again and deviations from these will have to be explained by the Health Technology Developer (HTD) in the Joint Clinical Assessment (JCA) dossier.
	Sallie Latimer Lumanity HEOR			Is the expectation that the JSC subgroup of the HTA-R Coordination Group will take the EUnetHTA 21 roles described in this guidance after the EUnetHTA 21 service contract ends?	Thank you for your comment. It is expected that the HTACG and the JSC subgroup will take the guidance document into account when developing the JSC procedure under the HTA Regulation.
D6.2.1 Briefing Document Template	Prof. Matthias P. Schönermark, M.D., Ph.D, Ingo Hantke, Dr. rer. nat., Laura Könenkamp, Dr. rer. nat., Elisa Zavatta, M.A. SKC Beratungsgesellschaft mbH	General		The Briefing Document Template is comprehensive and covers all potentially relevant aspects. Therefore, it bears the risk of overwhelming the assessors and diluting the actual open question. Having that in mind it appears reasonable to include a phrase contextualizing the entire document: Only context and aspects that are considered relevant for the consultation should be provided. All other information is considered optional.	Thank you for your comment. It is the responsibility of the HTD to provide the necessary information to answer the questions asked. Experience so far has shown that this is usually done adequately.
D6.4.1 External Guidance	Prof. Matthias P. Schönermark, M.D., Ph.D, Ingo Hantke, Dr.	8	Section: 3.4 line: 185	Original wording: „The Applicant needs to fully justify any deviations from the advice given.”	Thank you for your comment. The wording seems appropriate. It is the responsibility of the HTD to

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with EMA	rer. nat., Laura Könenkamp, Dr. rer. nat., Elisa Zavatta, M.A. SKC Beratungsgesellschaft mbH			Comment: It should be at the discretion of the pharmaceutical manufacturer whether a declaration is to be made. A mandatory statement and the word 'fully' are misleading and not adequate. It is not clear from the request, on the one hand, how extensive and profound the declaration should be and, on the other hand, whether consequences are to be expected if the explanation is insufficient. The details and the consequences are unclear and should be specified if these are intended. Suggestion for rewording: *"The Applicant should justify to an appropriate extent any deviations from the advice given."*	provide sufficient justification for the deviation. Beyond that, no general statements can be made about consequences of a deviation from the recommendations. However, "fully" has been deleted to ensure some flexibility for different scenarios.
	Prof. Matthias P. Schönermark, M.D., Ph.D, Ingo Hantke, Dr. rer. nat., Laura Könenkamp, Dr. rer. nat., Elisa Zavatta, M.A. SKC Beratungsgesellschaft mbH	10	Section: 4.3.1 line: 284	Original wording: "There is no option for a follow-up consultation with EUnetHTA 21 during the project phase." Comment: Although it is clear that no follow-up consultation with EUnetHTA 21 will be possible beyond September 16, 2023, there needs to be the possibility to take advantage of a second consultation in case of unforeseen major changes significantly affecting the answers / (anticipated) assessment of the JSC / JCA after the start of the period of validity of the EU HTA regulation for oncologics and ATMPs on January 12, 2025. If considered reasonable to avoid redundancies, a time limit could be defined for this, i.e., a time frame in which no further appointment for consultation is possible.	Thank you for your comment. The regulation clearly states that a JSC should provide advice on the planning of a pivotal study. However, as this demand is considered relevant, further discussions on this topic will take place in the JSC subgroup, but also other relevant subgroups and the HTACG.. This may also include follow-up consultations if there are significant new developments or paradigm shifts.

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	Prof. Matthias P. Schönermark, M.D., Ph.D, Ingo Hantke, Dr. rer. nat., Laura Könenkamp, Dr. rer. nat., Elisa Zavatta, M.A. SKC Beratungsgesellschaft mbH	10	Section: 4.3.2 line: 295	Original wording: "As the number of Applicants is expected to exceed the number of slots, a selection of products will be necessary." Comment: The limitation of consultations is considered critical. There should be enough appointments for every pharmaceutical manufacturer to **at least** have the opportunity to obtain advice. In general, these resources should be created.	Thank you for your comment. This will be part of the discussions in the HTACG and the JSC subgroup.
	Prof. Matthias P. Schönermark, M.D., Ph.D, Ingo Hantke, Dr. rer. nat., Laura Könenkamp, Dr. rer. nat., Elisa Zavatta, M.A. SKC Beratungsgesellschaft mbH	16	Section 5.3 line 519	Original wording: "The Applicant is expected to provide detailed minutes of the discussion meeting, within 5 working days directly to EMA." Comment: Is unclear why a documentation should be done by the pharmaceutical manufacturer albeit it is not commented by EMA or EUnetHTA 21. The purpose and use are not comprehensible and should be specified. Furthermore, this aspect should be included in the overview table as this is a clear step in the process (table 1).	The minutes are for documentation purposes only. They have no direct influence on the drafting of the recommendations. The Final Written Recommendation document is the final output document that an HTD can refer to in the future.
D6.2.1 Briefing Document Template	ESMO	8	146-151	It would be desirable to count with an appendix with examples of questions of every section. Examples of 'proper' questions and 'wrong' questions may be helpful.	Thank you for your comment. We will take this into account for future considerations.
D6.4.1 External Guidance with EMA	ESMO	10	294-297	Considering a pre-defined number of slots for rare disease therapies could be a way to foment development in this field.	Thank you for your comment. With regard to future consultations, it is up to the JSC subgroup and the HTACG to develop an appropriate system.

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D6.4.1 External Guidance with EMA	ESMO	10-11	293-310	It would be desirable to provide a checklist with the evaluable points for the selection. This would work for transparency and allows the applicants to measure the probability of being selected. Also it would be desirable to have a document with the punctuation of all evaluable points.	Thank you for your comment. There is currently an EUnetHTA 21 interpretation on the selection criteria available on the EUnetHTA 21 website. Link was added to the guidance.
D6.4.1 External Guidance with EMA	ESMO	11	301	Regarding the potential impact on patients, quality of life should be a mandatory endpoint, especially for metastatic disease.	Thank you for your comment. We can confirm that this is usually part of the recommendations given.
D6.4.1 External Guidance with EMA	ESMO	16	519-524	There might be discrepancies amongst the applicant and the HTAbs/Regulator concerning the content of the minutes. This situation should be addressed. The process (timing, means of communication) for rectification or agreements by the two parts should be explained.	The minutes are for documentation purposes only. They have no direct influence on the drafting of the recommendations. The Final Written Recommendation document is the final output document that an HTD can refer to in the future.
D6.4.1 External Guidance with EMA	ESMO	General	n/a	Special attention should be given to facilitating consultations and interaction concerning new methods for rare molecular entities, which hold great potential to support the development of more effective therapies for patients with cancer.	Thank you for your comment. We will take this into account for future considerations.
	Matteo Scarabelli - EFPIA	General		The present Briefing Book and Guidance Document have been originally issued in 2022 to support the Joint Scientific Consultations in parallel with EMA Scientific Advice, in the framework of EUnetHTA 21 service contract, which is now about to end as these documents are submitted to public consultation. At the same time, a new “interim model” for Parallel	Thank you for your opening remarks. This final review was planned due to the EUnetHTA 21 project plan and the revised document will serve as a basis for the discussion within the JSC subgroup under the HTA Regulation.

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				EMA/HTAb Scientific Advice have been announced to last until end of 2024. For this new phase, stakeholders (including potential applicants) have been instructed to rather refer to a different version of these documents than the one they are now consulted on. EFPIA regretfully acknowledges the contradiction of being consulted on documents that are already out of date, without having been asked to provide input in a more appropriate time and on documents that could have made such input more meaningful. For this public consultation, EFPIA submission will therefore give a special focus on the implementation of JSCs in the new HTAR setting as of 2025. EFPIA calls on the newly established EU Coordination Group, to the EMA and to the European Commission, to give due consideration to the input received via the present consultation, as well as to ensure the establishment and continuation of a meaningful form of dialogue and/or consultation with relevant stakeholders over the implementation of JSCs. The dialogue with stakeholders – and especially with the health technology Developers (HTDs) – is essential to ensure that the advice/consultation procedure is fit for the purpose of providing the sponsors with high-quality recommendations and improving patient access to the best of innovation.	All comments received will be given due consideration also for the future JSC framework. Thank you for providing your comments.

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D6.2.1 Briefing Document Template	Matteo Scarabelli - EFPIA	General		EFPIA would recommend a dedicated Briefing Book template for Joint HTA scientific consultations (or non-parallel procedures, with HTA only advices) and/or clearer guidance on which sections are relevant for parallel consultations only.	Thank you for your comment. It is considered clear that questions such as "2.5.1.< Regulatory questions" would not apply to a HTA-only consultation. The differences between the 2 procedures might be laid out in further detail in the future document under the HTA Regulation.
D6.2.1 Briefing Document Template	Matteo Scarabelli - EFPIA	5	61-62	*1.1. Background information on the disease to be treated.* *"For reimbursement decisions the availability of treatment alternatives is a critical issue".* EFPIA would recommend this sentence to be adjusted in order to be in line with the scope of the HTA Regulation. Reimbursement decisions are in the remit of national policy makers (as mentioned in the External Guidance document in *Section 3 <Principles>*) *"For **future joint clinical assessment,** the availability of treatment alternatives is a critical issue".*	Thank you for your comment. The sentence is considered accurate but JCA has been added.
D6.2.1 Briefing Document Template	Matteo Scarabelli - EFPIA	5	81	*1.3.1. Characteristics of the product* *"Orphan product"* EFPIA would suggest editing as follows: "Orphan ***medicinal*** product" or "orphan ***designated*** product"	Thank you for your comment. The change has been made to "orphan medicinal product".

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D6.2.1 Briefing Document Template	Matteo Scarabelli - EFPIA	6	108-109	*1.6 Clinical Development* *"If scientific consultation has been previously requested from national HTA bodies or EUnetHTA (21). If yes, please include the full advice documents as an annex to your briefing document."* EFPIA would like to remind that seeking advice at national level is meant to inform the generation of country-specific information (clinical and/or health economic evidence) in view of the future discussions on pricing and reimbursement, which fall therefore out of the remit of EMA/HTA parallel JSC and are highly commercially confidential (as mentioned in *Section 2, page 8, line 155-158* of the Briefing Book and *on Section 3 <Principles>* of the External Guidance Document). Sharing such information during a parallel EMA/HTA JSC should therefore be optional for the applicant HTD, rather than an obligation, limited to the clinical aspects covered by the national advice letter and protected by a strong confidentiality framework. The HTD will then be able either to share the national advice letter, or to fill the corresponding sections of the Briefing Book with the corresponding clinical information/recommendation. EFPIA recommends therefore editing the quoted sentence as follow:	Thanks. Changed to: "If scientific consultation has been previously requested from national HTA bodies or EUnetHTA (21). If yes, please include the full advice documents for the <u>European procedures</u> as an annex to the briefing document."

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				"If a scientific consultation has been previously requested from national HTD bodies or EUnetHTA, ***the applicant HTD may share, on a voluntary basis, the output document of the aforementioned consultation (advice letter) or fill the JSC briefing book with relevant clinical information from the national recommendation letter****".*	
D6.2.1 Briefing Document Template	Matteo Scarabelli - EFPIA	8	152-154	*2. Questions and Applicant's position* *"The wording of the question should be clear and concise …//… 'Does the CHMP agree that/with …'? OR 'Do HTA bodies agree that/with…?'",* EFPIA suggest to also add the example of common question: ***"or 'Do the CHMP and HTA bodies agree that/with…?' when the applicant seeks the perspective of both remits on a given question."***	Thanks. Added ""Do the CHMP and HTA bodies agree that/with…?" as another example.
D6.2.1 Briefing Document Template	Matteo Scarabelli - EFPIA	8	154-155	*2. Questions and applicant's position* *"Both EMA and EUnetHTA 21 reserve the right to answer selected questions that have been directed to the other entity if deemed appropriate".* EFPIA would like to remind that SA/JSC is a service intended to provide advice to the applicant in view of an eventual submission for two different processes (marketing authorization and joint clinical assessment).	Thank you for your comment. EUnetHTA 21 reserves the right to provide valuable advice on any aspect that is considered relevant. The 2 entities are distinct in their remit but also have a significant overlap in the discussed topics. Therefore, it seems appropriate to answer such questions if the other entity has some valuable input to give and provide feedback from

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				The applicant should get the clearest possible advice/recommendation to its questions, especially when divergences may arise. There is therefore a crucial need for a **clear governance in the discussions** and in the formulation of the answers within the meetings. When an applicant's question targets only one of the two remits represented in a Parallel Consultation procedure, "opinions" or "comments" from another entity should be allowed, although not translated into a prescriptive response. As the remit and the target of the question is clear, so should be the answer. EFPIA would recommend editing the quoted paragraph as follows: *"Both EMA and EUnetHTA 21 reserve the right to **comment on** selected questions that have been directed to the other entity if deemed appropriate".* *<See also comment above on examples of wording to submit clear and unambiguous questions>.*	another viewpoint. It would be a missed chance not to share such input. This practice has been appreciated by HTD for the EUnetHTA 21 JSC.
D6.2.1 Briefing Document Template	Matteo Scarabelli - EFPIA	8	155-157	*2. Questions and Applicant's positions* *"Questions concerning the future appraisals and/or reimbursement/coverage decision will not be considered by HTA bodies, in accordance with the general principles of Parallel EMA/EUnetHTA 21 JSC".*	Thank you for your comment. This has been added. Appraisal can only be national but this wording might clarify even better.

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				EFPIA would recommend editing as follows, to improve clarity: "Questions concerning the future ***national*** appraisals and/or reimbursement/coverage decision will not be considered by HTA bodies, in accordance with the general principles".	
D6.2.1 Briefing Document Template	Matteo Scarabelli - EFPIA	8	158-160	*2. Questions and Applicant's position* *"Furthermore, as the existence of a medical need is included in the Committee for Scientific Consistency and Quality (CSCQ) eligibility assessment for parallel EMA/EUnetHTA 21 JSC, related questions are out of the scope of parallel EMA/EUnetHTA 21 JSC".* EFPIA considers that the applicant HTD should have the right and the opportunity to present its own development case and related questions when submitting the Briefing Book. This should include the right to formulate questions on the (unmet) medical needs from the developer perspective. *EFPIA would recommend **removing** the quoted sentence.*	Thank you for this comment. It had been assumed that a potential medical need had been sufficiently described by the HTD in the Application form for a JSC to fulfil the selection criteria applied during EUnetHTA 21. Therefore, discussing unmet medical need is not a priority. However, if the HTD wishes to do so due to a complex treatment setting or multiple competitors in the development stage, this can still be addressed during a JSC. Adjusted to "related questions do not seem a priority topic for the Parallel EMA/EUnetHTA 21 JSC, but can be addressed if needed.".
D6.2.1 Briefing Document Template	Matteo Scarabelli - EFPIA	10	227-228	*2.5.2 <Regulators' and EUnetHTA 21 Questions>* *«There is no option for a follow-up consultation with EUnetHTA 21 during the project phase».*	Thank you for your comment. The regulation clearly states that a JSC should provide advice on the planning of a pivotal study. However, as this demand is considered relevant, further

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				EFPIA recommends that the future JSC model under the HTAR will benefit from the opportunity of follow-up advice, as it is routinely available in the regulatory space, where follow-up is allowed to get further advice on the technology. The options for follow-up advice or "late" consultation should be open for HTDs both at EU HTA level and national level. The objective of these options is to ensure that HTDs can receive the best quality advice and that innovation has the best chance to reach the patients.	discussions on this topic will take place in the JSC subgroup, but also other relevant subgroups and the HTACG.. This may also include follow-up consultations if there are significant new developments or paradigm shifts. For EUnetHTA 21 it was not possible and the statement in the document is therefore correct.
D6.2.1 Briefing Document Template	Matteo Scarabelli - EFPIA	10	230	*2.5.2 <Regulators' and EUnetHTA 21 Questions>* *"Questions should be presented following the topics as described above."* As there are no mandatory areas or questions for discussion and that other topics could arise than the ones described in the BB template, EFPIA would suggest editing as follows: *Questions should be presented following the topics as described above* ***when relevant. Any other questions on clinical development can be placed after those topics****"*.	Thank you. Added: "Questions should be presented following the topics as described above. Any other questions on clinical development can be placed after those topics."
D6.2.1 Briefing Document Template	Matteo Scarabelli - EFPIA	11	253-291	*2.5.3 <Questions regarding HTA>*	Thank you for your comment. It has been corrected.

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				EFPIA would suggests including in this section an additional paragraph on the comparator(s), as the following: *"Questions regarding comparator(s) // Question {x} // Applicant's position"*	
D6.2.1 Briefing Document Template	Matteo Scarabelli - EFPIA	12	312-313	*2.6. Questions on Post-Launch Evidence generation (PLEG)* *"Please note, discussions on PLEG can be facilitated only in conjunction with request for discussion of pivotal trial design and when contextualized with clinical data from the pivotal (phase II/III) studies".* EFPIA recommends the text to be adjusted as follows: *Discussions on PLEG can be facilitated* ***~~only~~*** *in conjunction with request for discussion of pivotal trial design and when contextualized with* ***the planned*** *pivotal (phase II/III) studies».* Justification: EFPIA sees a potential contradiction between the recommendation to discuss PLEG only when related to pivotal study design and the simultaneous request to contextualize PLEG-questions with the help of clinical data from those same pivotal studies that are supposed to be discussed as are not yet started (and therefore with data that the HTD cannot provide as they are not yet be generated).	Thank you for your comment. Added "[…] clinical data <u>expected</u> from pivotal (phase II/III) studies." Proper context is needed for a meaningful discussion. PLEG discussion is most useful at an early time point as gaps in the development plan should be identified and discussed early on. For the possibility of a follow-up advice, please refer to the answer above.

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				Furthermore, EFPIA would welcome the opportunity of a follow-up dialogue/advice in the period between the JSC and the JCA to address potential changes in the environment or to receive advice and guidance on the methods to address evidence gaps, as well as post launch evidence generation. This would improve predictability for both the developer and HTA bodies.	
D6.2.1 Briefing Document Template	Matteo Scarabelli - EFPIA	14	390-392	*3.4.1< Relative Effectiveness>* *"Guidance on consideration of relative effectiveness evidence should be brought together in a separate section before the section on economic evaluation plans and is optional".* It is unclear to EFPIA what data is requested to be presented in this section *versus* what should be presented in the clinical sections above *(i.e., Section <2.5.3: Questions regarding HTA>)*. Further clarity is therefore needed about what is requested under the *Relative Effectiveness* section and about the specific types of information that should be presented *versus* the information disclosed in the previous sections. EFPIA would recommend either to provide such ***clarification*** or to ***remove*** this section if there is no substantial difference in the information/questions to be submitted.	Thank you for your comment. Section 2.5.3 refers to questions specific to HTA that relate to the elements set out in Section 2.5. Explanation added for 3.4.1.
D6.2.1 Briefing	Matteo Scarabelli - EFPIA	16-17	413-464	*4. Health economic assessment (optional)*	Thank you for your comment. However, as stated in the

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Document Template				EFPIA recommends keeping the focus of parallel consultations (involving both Regulators and HTAb) and of JSCs on the clinical aspects only. Moreover, considering the scope of the HTA Regulation, EFPIA believes that the focus of the JSC should be to inform the generation of evidence that would support the JCA. This is also why it is so crucial to ensure that national advice is available in addition to JSC (Cf. General comment on External Guidance document). Health economic assessment questions should naturally be addressed in a dedicated discussion with HTA bodies and payers within more appropriate frame such as national advice procedures, as those are better suited to discuss local specific model requirements. Therefore, sections related to the health economic model questions should not be part of the BB.	disclaimer of the document, health economic assessments are considered relevant for many HTAbs and the provision of advice in this regard is based on a voluntary basis according to Article 23 of the EU HTA Regulation. It was a demand by HTA bodies not to miss this opportunity of an early exchange on economic assessment aspects with the HTD. This had been appreciated by the HTDs during the EUnetHTA 21 JSCs.
D6.4.1 External Guidance with EMA	Matteo Scarabelli - EFPIA	General		The present Guidance – originated from a document issued in September 2022 – reflects the collaboration between the EMA and EUnetHTA 21 during the 2021-2023 service contract. While welcoming the publication of the present guidance, EFPIA and its member companies look ahead through the HTAR implementation, for which further guidance will be appreciated, particularly reflecting the vision of the HTA bodies on Joint Scientific Consultation under the EU HTA Coordination	Thank you for your comment. This is taken note of and will be a future discussion within the JSC subgroup.

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				Group and JSC Sub-group. In the context of the HTA Regulation, in fact, two options for joint scientific consultation co-exist: HTA-only JSC and EMA/HTA parallel JSC. The JSC procedures entirely managed by the Coordination Group / JSC subgroup are considered equally important as the JSC procedures conducted in parallel with the EMA. Therefore, in addition to the present deliverables, EFPIA and its member companies would recommend developing also a dedicated Briefing Book and the relative Guidance documents for HTA-only Joint Scientific Consultations.	
D6.4.1 External Guidance with EMA	Matteo Scarabelli - EFPIA	General		**Providing guidance on the JSC process** Moving forward into the new HTAR framework, EFPIA and its member companies have identified aspects on which further guidance would be needed. ***- Coordination, inclusiveness, and alignment on the outcome*** Under the future HTAR setting, the consultation is carried out by the Coordination Group via the designated JSC subgroup. It is therefore essential to have further guidance on how the assessor/co-assessors from the designated subgroup will coordinate with other Member States throughout the main process steps: definition of the of List of Issues,	Thank you for your comment on these relevant points. With regard to future consultations, it is up to the JSC subgroup and the HTACG to develop an appropriate system according to the HTA Regulation.

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				preparation of the discussion meeting, alignment on the recommendation, and consolidation of the outcome document. In particular, the JSC procedure should aim at enabling HTA bodies to align on the recommendation/advice, and at including all Member States from the Coordination Group in the elaboration/endorsement of the outcome document. ***- JSC and JCA: a continuum enabled by actionable recommendations*** Procedural provisions should be established to facilitate the alignment of HTA bodies on their JSC recommendation. This could help to establish a strong link between JSC and JCA – especially regarding the PICO –. When the PICO is sufficiently context-specific and the recommendation is consolidated by consensus, the JSC would then serve its objective of aligning all stakeholders on evidence expectations from the development plan and supporting the submission of a robust and consistent evidence package for JCA. For this to succeed, the recommendation/advice should be “actionable”, which means that it should be realistically implementable into the development plan, with a clear scope and objective: the submission for a European joint clinical assessment.	

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				This would be in line with the clear provision included the *HTAR, Art 16.1, "Those consultations shall facilitate the generation of evidence that meets the likely evidence requirements of a subsequent joint clinical assessment".*	
D6.4.1 External Guidance with EMA	Matteo Scarabelli - EFPIA	General		**Securing necessary capacity for JSC** EFPIA would like to highlight the importance of securing adequate resources and capacity to meet the demand for Joint Scientific Consultations within the new EU joint HTA framework. Early engagement with sponsors/developers is considered an area of critical importance, as it can ensure that the evidence provided by HTD meet the needs of Regulators and HTAbs. This is decisive to facilitate drug developments that could reach the market and in view of improving patient access. As expressed in its public positions, EFPIA considers that for the successful implementation of the HTAR **sufficient capacity, expertise, and resources** must be ensured for joint scientific consultation, which **would exclude the need for the application of selection criteria.** Consequently, the capacity for Joint Scientific Consultation should be increased to an optimal level to provide equal opportunity amongst HTDs and satisfy	Thank you for your comment. It is the responsibility of the HTACG and the respective JSC subgroup to adapt the guidance document to the structure and procedural workflow under the HTA Regulation. This will also take into account capacities, request periods, timelines etc. in accordance with the HTA Regulation.

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				the overall demand for advice/recommendation. Cf Annex 1. *EFPIA position on the framework for Joint Scientific Consultation under the EU HTA Regulation*	
D6.4.1 External Guidance with EMA	Matteo Scarabelli - EFPIA	General		**Selection criteria** EFPIA considers that the implementation of the HTAR should aim at building a workable, predictable, and sustainable system, with sufficient capacity for all requests for joint scientific consultations, where there would be no need for prioritization and selection criteria. EFPIA members companies reported that application of prioritization and/or selection criteria was one of the main root causes for non-application to JSC during the Pilot phase conducted by EUnetHTA 21: this undermined the predictability of the system and the benefit of the service. It is therefore imperative that all institutions and stakeholders committed in the HTAR implementation work at avoiding limitations on the ability for HTDs to seek JSCs for all technologies and indications. Cf. Annex 2. *Root causes for non-application in EMA/EUnetHTA 21 Parallel JSC.*	It is the responsibility of the HTACG and the respective JSC subgroup to adapt the guidance document to the structure and procedural workflow under the HTA Regulation. This will also take into account capacities, request periods, timelines etc. in accordance with the HTAR. EUnetHTA 21 provided an interpretation and application procedure for the HTA Regulation selection criteria during the actual project phase. This will serve as a basis to define the future process. According to the HTA Regulation selection criteria will be applied if the number of requests exceeds the capacities. The interpretation of these criteria will be discussed with the JSC subgroup and the HTACG and further elaboration on these for the HTD will be most helpful. As the number of JSC requests from January 12 2025 onwards cannot be predicted at this timepoint, the application of the selection criteria needs to be considered for a future scenario.

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D6.4.1 External Guidance with EMA	Matteo Scarabelli - EFPIA	General		**Implementation of a workable model** ***- Experience with EUnetHTA 21 call-base system (vs rolling submissions model)*** The experience of EUnetHTA 21 have highlighted fundamental challenges related to the call-based model for HTA Joint Scientific Consultation. Those are even exacerbated when it comes to EMA/HTA parallel JSC. Advice/consultation opportunities are thoughtfully planned time ahead by companies/sponsors when designing the product development plan. The call-based system is likely to create a misalignment with the regulatory scientific advice – as this could be plan for any time – and with the company development plans, disincentivizing the applications. EFPIA considers the call-based model unworkable for a permanent JSC system and this should not be implemented under the new HTAR framework. EFPIA recommends implementing a rolling submission model, synchronized with the Regulatory Scientific Advice timeline. Cf. Annex 2. *Root causes for non-application in EMA/EUnetHTA 21 Parallel JSC.* ***- Aligning Regulatory advice and HTA consultation timeline, process, and outcome delivery.***	Thank you for your comment. It is the responsibility of the HTACG and the respective JSC subgroup to adapt the guidance document to the structure and procedural workflow under the HTA Regulation. This will also take into account capacities, request periods, timelines etc. in accordance with the HTA Regulation. Under the HTA Regulation request periods are foreseen. It is agreed that this should happen in higher frequencies and short intervals to allow for a maximised flexibility. Further alignment in terms of the timeline will be discussed.

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				EFPIA would strongly recommend that the timing (process and outcomes) of Regulatory advice and Joint HTA consultations are aligned. • From a calendar perspective, this would ensure the predictability that allows health technology developers to plan in advance and include the request for advice/consultation into their development plans. • Looking at the process timeline, any misalignment would be critical for the necessary consistency of the procedure and for a timely delivery of the outcomes. Especially in case of parallel procedures, this may compromise the process and the uptake of the advice by the HTDs. For these reasons, EFPIA recommends considering a rolling submission dates system to ensure the alignment required by the HTAR: *Cf.* ***HTAR Art 16.5****: "Such parallel consultations shall …///… have* ***synchronized timing****".* ***- Length of the procedure*** The Guidance document seems to assume a longer timeline for the overall joint-HTA procedure – compared with Regulatory advice, even in the parallel setting – without clear justification.	

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				Especially when experienced in a parallel setting, such delays will result in structural misalignment, making it even more difficult to integrate the two outcomes in the same development pathway/plan. EFPIA would recommend seeking the best efficiency (and at least the same level) in both procedures as any delay may negatively impact the development pathway toward patient access.	
D6.4.1 External Guidance with EMA	Matteo Scarabelli - EFPIA	General		**National Advice as an essential and complementary component** EFPIA would recommend preserving the option of national level advice as this will remain essential to complete advice received at European level and address context-specific questions that are part of the national policymakers' remit. Such an option would therefore continue to play an essential and complementary role in supporting innovative treatment to reach patients.	Thank you for your comment. We agree that national consultations remain relevant as long as they do not conflict with a JSC or the recommendations given. However, duplication in terms of content clearly needs to be avoided.
D6.4.1 External Guidance with EMA	Matteo Scarabelli - EFPIA	3		*Page numbering:* Page 3 should be page 2, and so onwards.	Thank you. This has been corrected.
D6.4.1 External Guidance with EMA	Matteo Scarabelli - EFPIA	6	86	*1.History of changes* *«The written only meeting format has been suspended».* EFPIA welcomes any format of interaction that can	Thank you for your suggestion. With regard to future consultations, it is up to the JSC subgroup and the HTACG to develop an appropriate system according to the HTA Regulation. Options to use available

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				improve the capacity of Regulators and HTA bodies to engage in advice/consultation with the HTDs. In that sense, EFPIA recommends the option of a written procedure to be maintained for selected circumstances in case HTD would ask for it, such as follow-up advice in situations where, for example, the treatment landscape has changed since the initial JSC.	resources most efficiently will be discussed. A discussion meeting for JSCs is stipulated by the Regulation.
D6.4.1 External Guidance with EMA	Matteo Scarabelli - EFPIA	6 (and 10)	95-97 (269-271)	*1. History of changes* *"Discussions on PLEG can be facilitated only in conjunction with request for discussion of pivotal trial design **and** when contextualized with clinical data from the pivotal (phase II/III) studies".* As per previous comment, EFPIA would recommend avoiding the contradiction of this statement, by editing as follow: *Discussions on PLEG can be facilitated ~~only~~ in conjunction with request for discussion of pivotal trial design and when contextualized with **the planned** pivotal (phase II/III) studies».* Furthermore, EFPIA would also recommend HTA bodies to align on the Regulators' approach as outlined in *Section 4.1 <Regulators: actors and scope>* of this same Guidance at *page 9 lines 228-233*: *"Applicants may request advice on any medicinal products for use in humans, (as defined in Directive 2001/83 (as amended)), irrespective of the medicinal*	Thank you for your comment. Added "[…] clinical data <u>expected</u> from pivotal (phase II/III) studies."

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				*product's eligibility for the centralized 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-authorization safety an efficacy studies, advice on the development of registries, or risk management planning incorporating risk minimization measures."*	
D6.4.1 External Guidance with EMA	Matteo Scarabelli - EFPIA	7	130-132	*2. Introduction* *«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)**»* EFPIA welcomes such wording, as it gives substance to the following: •In the frame of EU HTA, JSC and JCA shall be addressed and considered as a continuum, where the scientific consultation aims at generating the appropriate evidence for the clinical assessment. •For an informed JCA, the assessors must have a good understanding of the clinical development, and especially of the discussion that took place on comparator, population or outcomes at JSC stage (not the outcome only). •A shared understanding of the development means more predictability for the HTD and	Thank you for your comment. While we agree, it is up to the JSC subgroup and the HTACG to develop an appropriate system for further consultation, therefore further statements would be outside the scope of this guideline.

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				higher quality for the submissions. For these reasons, EFPIA also recommends including a mention of the option foreseen by the HTAR, that the assessors from JSC can – in principle – also be appointed for JCA when relevant expertise-wise. Or, at least, to support close involvement of the two level of assessors, particularly at the stage of the scoping).	
D6.4.1 External Guidance with EMA	Matteo Scarabelli - EFPIA	7	158	*3.1 Roles and remits* *«Each participating body should adhere to the roles and responsibilities under their respective remit».* EFPIA would like to suggest expanding this statement, to precise the remits of the organizations involved, and so avoid confusions later in the document. This could read: *"Each participating body should adhere to the roles and responsibilities under their respective remit,* ***established by the respective Regulations, 726/2004 and 2282/2021.*** Justification: The Reg 726/2004 gives to the European Medicines Agency the responsibility for evaluating whether a development is likely to meet the criteria to receive a community marketing authorization, while the HTAR 2282/2021 creates the framework for Member States to jointly assess the relative effectiveness and the level of	Thank you. This has been added to the text.

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				certainty of the clinical evidence of EU authorized products (and medical devices).	
D6.4.1 External Guidance with EMA	Matteo Scarabelli - EFPIA	7-8	159-171	*3.2 Confidentiality* «*The Parallel EMA/EUnetHTA 21 JSC process is confidential*, ***including all the information and documentations submitted or exchanged between all involved parties.*** ***In order to participate, all parties subscribe to the same confidentiality rules and remain bound to those, including in the situation of a withdrawal».*** EFPIA recommends the development of a confidentiality framework for all the activities of the EU HTA Cooperation that involve information submitted by the Health Technology Developer. Such a framework should meet the same expectations for protection of confidential information as provided at Regulatory level, based on accountability of every individual involved in the procedure. Finally, it is crucial for such a framework to be co-developed in collaboration with the health technology developers and consolidated via an appropriate consultation. For instance, in case of JSC request withdrawal by the applicant, which is a plausible possibility that must be envisaged (as mentioned in <*Section 4*>), EFPIA considers important to clarify how confidentiality applies	Thank you for your comment. As described in the confidentiality agreement form (ECA) linked in the guidance, there is no time limit on the validity of confidentiality, so the termination of the consultation does not affect the confidentiality assurance. As it is crucial to ensure confidentiality, a detailed framework will be developed under the HTA Regulation, building on the EUnetHTA 21 experiences.

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				in such a circumstance.	
D6.4.1 External Guidance with EMA	Matteo Scarabelli - EFPIA	8	168-171	*3.2 Confidentiality* As per previous comment, EFPIA would like to ask for clarification about the mention of *"HTA networks"*, their nature, scope, and role – and especially about their remits in handling confidential information.	Thank you for your comment. As mentioned in the guidance on page 6. HTA networks refer to EUnetHTA 21 as an HTA network. Confidentiality was ensured during EUnetHTA 21 for the entire network by using the respective form.
D6.4.1 External Guidance with EMA	Matteo Scarabelli - EFPIA	8	172-177	*3.3. Conflict of Interest.* *[Here the text refers to the last EUnetHTA Joint Action 3 Guidance on the subject, that EFPIA recommended to use as a starting point in its submission on the D.7.2/3 Guidance on "Patients and HCP involvement".]* EFPIA would recommend the EMA and the Coordination Group to aim at aligning as much as possible their rules for assessing and managing potential conflicting interests. The situation where an external expert (e.g., patient or clinician) might be allowed to join a parallel consultation under the rules of the EMA but not for the EU HTA ones (or even for the national advice), should be avoided.	Thank you for your comment. It is the responsibility of the HTACG and the JSC subgroup to develop a system for handling conflict of interest. However, we agree that efforts should be made to align the standard to avoid confusion and increase effectiveness.
D6.4.1 External Guidance with EMA	Matteo Scarabelli - EFPIA	8	182	*3.4 Status of Parallel EMA/EUnetHTA 21 Joint Scientific Consultation outputs* *«The advice provided by each stakeholder is not legally binding».* EFPIA suggests editing as follow:	Thank you for your comment. Half sentence has been added.

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				*«The advice provided by each stakeholder is not legally binding, **for any of the involved parties»**.*	
D6.4.1 External Guidance with EMA	Matteo Scarabelli - EFPIA	8	187-189	*3.4 Status of Parallel EMA/EUnetHTA 21 Joint Scientific Consultation outputs* *"The recommendation reflects the state of the art of medical science…//.. at the time of the advice"* EFPIA agrees with the present statement and would recommend considering it when taking into account the JSC output during the scoping phase of the JCA process.	Thank you for your comment. This will indeed be part of future considerations.
D6.4.1 External Guidance with EMA	Matteo Scarabelli - EFPIA	9	234-271	*4.2 EUnetHTA 21 and HTAbs: actors and scope* *"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".* As expressed in its general comments, EFPIA member companies reported that application of prioritization and/or selection criteria was one of the main root causes for non-application to JSC during the Pilot phase conducted by EUnetHTA 21, as this undermined	Thank you for your comment. The guidance document describes the procedure under EUnetHTA 21 and the paragraph is therefore correct. It is the responsibility of the HTACG and the JSC subgroup to develop a selection procedure in accordance with the HTA Regulation.

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				the predictability of the system and the benefit of the service. EFPIA considers that the implementation of the HTAR should aim at building a workable, predictable, and sustainable system, with sufficient capacity for all requests of joint scientific consultations where there would be no need for prioritization and selection criteria. *EFPIA recommend **removing the quote paragraph** (for the additional reason that it will be out of date once EUnetHTA 21 and the CSCQ will reach their end).* *Cf. Annex 2. Root causes for non-application in EMA/EUnetHTA 21 parallel JSC*	
D6.4.1 External Guidance with EMA	Matteo Scarabelli - EFPIA	9-10	247-249	*4.2 EUnetHTA 21 and HTAbs: actors and scope* *"Assessor and Co-Assessor will be assigned for each JSC from among the JSC HOG [Hands-on Group]"* EFPIA would appreciate to have more visibility on the role of the JSC coordination sub-group and more guidance over the process for selection of assessors and co-assessors (beyond the vague indication of Deliverable 5.3.1) As expressed in its public positions, EFPIA considers the experience, the qualification, and the continuous capacity building and upskills of the assessors (across all Member States HTA bodies) a crucial element for a	Thank you for your comment. This will be part of future discussions within the HTACG and the JSC subgroup. A guidance on the assignment of assessors and co-assessors is foreseen to facilitate this process under the HTA Regulation.

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				successful and effective implementation of JSC.	
D6.4.1 External Guidance with EMA	Matteo Scarabelli - EFPIA	10	274-292	*4.3.1 Open Call (entire paragraph)* As stated in one previous general comment, the call-based model faces some fundamental implementation challenges, such as: • The best timing for the HTD to seek advice depends on multiple factors and may not coincide with the timing of an open call. • Unintended misalignments between Regulatory S.A. and JSC make it more difficult for HTDs to forecast and include a consultation (parallel or HTA-only) within the development plan. • HTDs should be given the possibility to apply for advice/consultation when it is the most appropriate for them will increase the rate of application and the impact of the advice. For these reasons, EFPIA would suggest either to ***remove or to review this entire section*** based on the aforementioned considerations. EFPIA would also recommend including the reference to a rolling submission dates system synchronized with EMA Scientific Advice, as best model for the implementation of JSCs (parallel and HTA-only) under the HTAR framework.	Thank you for your comment. The guidance document describes the procedure under EUnetHTA 21 and therefore this section is correct. The HTACG and the JSC subgroup are responsible for developing an appropriate application system for JSCs under the HTA Regulation. Please see response above for further details.
D6.4.1 External	Matteo Scarabelli - EFPIA	10	280-281	*4.3.1 Open Call (I)*	Thank you for your comment. The guidance document describes the procedure under EUnetHTA 21

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Guidance with EMA				*"In all cases, selection criteria of the HTA regulation (HTAR) will apply (see 4.3.2)."* As highlighted in previous comments, EFPIA considers that sufficient capacity for JSC should be secured for a successful and efficient implementation of the HTAR. Furthermore, the prioritization of JSC as foreseen by HTAR **do not apply** by default and on a regular/systematic basis to **all products or cases** – as it applies only in the exceptional situation of an exceeding number of requests against the overall capacity. EFPIA strongly recommend therefore to ***remove*** the quoted statement, as it goes against HTAR.	and the statement is therefore correct. It is the responsibility of the HTACG and the JSC subgroup to develop a selection procedure in accordance with the HTA Regulation. Please see response above for further details.
D6.4.1 External Guidance with EMA	Matteo Scarabelli - EFPIA	10	284-285	*4.3.1 Open Call (II)* *«There is no option for a follow-up consultation with EUnetHTA 21 during the project phase».* *(Cf Comment on Briefing Book Template, p. 10, L. 227-228)* As per previous comment on the BB template, EFPIA recommends that the future JSC model under the HTAR will benefit from the opportunity of follow-up advice, as it is routinely available in the regulatory space, where follow-up is allowed to get further advice on the technology.	Thank you for your comment. The regulation clearly states that a JSC should provide advice on the planning of a pivotal study. As this demand is considered relevant, further discussions on this topic will take place in the JSC subgroup. Please see response above for further details.

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				The options for follow-up advice or "late" consultation should be open for HTDs both at EU HTA level and national level. The objective of these options is to ensure that HTDs can receive the best quality advice and that innovation has the best chance to reach the patients.	
D6.4.1 External Guidance with EMA	Matteo Scarabelli - EFPIA	10	286	*4.3.1 Open call (III)* *"All Applicants will be informed of the CSCQ JSC decision within **three weeks** after termination of the call".* EFPIA notices that the timing of the communication to the applicant has been delayed from the *two weeks* of the original 2022 version of this Guidance, to *three weeks* in the present version. For the future system under the HTAR, EFPIA recommends moving from the open call model to rolling submission one. This would facilitate keeping the timeline for HTA JSCs aligned with the one of the Regulatory Scientific Advice. That's because time-discrepancies would create difficulties in navigate the process, not to mention the delays that it will generate in the delivery and implementation of the process outcomes. This would help the Coordination Group to avoid delays that might affect the implementation of the	Thank you for your comment. It is the responsibility of the HTA CG and the respective JSC subgroup to adapt the guidance document to the structure and procedural workflow under the HTA Regulation. This will also take into account capacities, request periods, timelines etc. in accordance with the HTA Regulation.

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				recommendation, with potential unintended consequences on the development pathway and on the expected time-to-patients.	
D6.4.1 External Guidance with EMA	Matteo Scarabelli - EFPIA	10	291-292	*4.3.1 Open call (IV)* *"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"* As per previous general comment, EFPIA considers that sufficient capacity should be implemented to meet the demand for JSC as it happens for EMA scientific advice. Furthermore, national scientific consultations – when applicable – should remain available for HTDs, regardless of whether those products have been accepted for JSC at EU level. Those products might need further advice due a changed treatment landscape or to discuss specific questions related to the national policy context. EFPIA would therefore recommend **removing** the quoted sentence or, as an alternative, including the following statement: *"**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*	Thank you for your comment. We agree that national consultations remain relevant as long as they do not conflict with a JSC or the recommendations given. Added: 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).

Sub-deliverable	Comment from	Page number	Line/ section number	Comment and suggestion for rewording	Response Hands-on-Group
				from some HTAb (provided that the consultation does not lead to a duplication of the advice).	
D6.4.1 External Guidance with EMA	Matteo Scarabelli - EFPIA	10-11	293-310	*4.3.2 CSCQ JSC selection criteria (entire paragraph)* As expressed in its public positions, EFPIA considers that sufficient capacity for JSC should be secured for a successful and efficient implementation of the HTAR. *(Cf Annex 1. EFPIA position on the framework for Joint Scientific Consultation under the EU HTA Regulation)* As also highlighted in is general comments, EFPIA members companies reported that application of prioritization and/or selection criteria was one of the main root causes for non-application to JSC during the Pilot phase conducted by EUnetHTA 21: this undermined the predictability of the system and the benefit of the service. *(Cf. Annex 2. Root causes for non-application in EMA/EUnetHTA 21 parallel JSC)* EFPIA considers that limiting HTDs from receiving a JSC reduces the predictability for both the company and HTA agencies with regards to PICOs and evidence expectations for the JCA. *EFPIA recommends **removing the entire paragraph** (for the additional reason that it will be out of date once EUnetHTA 21 and the CSCQ will reach their end)*	Thank you for your comment. The guidance document describes the procedure under EUnetHTA 21 is the section therefore is correct. It is the responsibility of the HTACG and the JSC subgroup to develop a selection procedure in accordance with the HTA Regulation.
D6.4.1 External	Matteo Scarabelli - EFPIA	11	296-297	*4.3.2 CSCQ JSC selection criteria (I)*	Thank you for your comment. The HTA Regulation clearly states that a product is eligible for a JSC if the

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Guidance with EMA				*«**A prerequisite for a JSC** is that the clinical trial (pivotal phase II/ or III) has not yet started".* EFPIA understands the intended objective of the statement: asking the applicants to seek JSC early enough on their development timeline to make the advice meaningful. Nonetheless, EFPIA considers that "pre-requisite" or limitation on JSC applications will be detrimental to the following objectives: • Seeking coordination/alignment between S.A. and JSC (and so creating a consistent advice/consultation environment) • Making the advice/consultation fit for applicants to navigate it • Facilitating request for early advice. EFPIA recommends referring to the approach proposed in this same Guidance for Regulatory Scientific Advice – *Section 4.1, page 9, lines 228-223*: "*Applicant may request advice […] at any stage of the product lifecycle".*	clinical trials are still in the planning phase (Art. 16(2)).
D6.4.1 External Guidance with EMA	Matteo Scarabelli - EFPIA	11	305-307	*4.3.2 CSCQ JSC selection criteria (II)* *"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 also given preferred consideration".*	Thank you for your comment. However, as the guidance refers to the EUnetHTA 21 procedure, the statement remains valid. A health technology shall be eligible for joint scientific consultations pursuant to paragraph 1 of this Article where it

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				EFPIA suggest ***removing*** the quoted sentence. Justification: According to HTAR, the selective scope that applies to JCA between 2025 and 2030 **does not apply to JSC**, which place such a restriction in contradiction with HTAR.	is likely to be the subject of joint clinical assessment (Art. 16(2). This implies that the selective scope for JCA between 2025 and 2030 could be also relevant for JSC. Nevertheless, it is the responsibility of the HT CG and the JSC subgroup to develop a selection process in accordance with the HTA Regulation.
D6.4.1 External Guidance with EMA	Matteo Scarabelli - EFPIA	10	308-310	*4.3.2 CSCQ JSC selection criteria (III)* *"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"* As expressed in its public positions, EFPIA considers that **sufficient capacity for JSC** should be secured for a successful and efficient implementation of the HTAR, which **would exclude the need for the application of selection criteria.** EFPIA would also like to remind that the prioritization of JSC as foreseen by HTAR **do not apply by default.** That is why there is no ground to compel the applicant to build its Briefing Book on criteria that may not apply – and may not fit its development case.	Thank you for your comment. The guidance document describes the procedure under EUnetHTA 21 and therefore the sentence is correct. This is also to provide guidance for HTDs regarding the interpretation of the selection criteria.

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				EFPIA strongly recommend therefore to ***remove*** the quoted statement, as it goes against HTAR.	
D6.4.1 External Guidance with EMA	Matteo Scarabelli - EFPIA	11	334-335	*4.4 Other stakeholders (I)* *«The inclusion of patients and clinical experts in Parallel EMA/EUnetHTA 21 JSCs is expected on a routine basis».* EFPIA welcomes this statement as it considers that input from patient and clinical experts is an irreplaceable and essential element for high quality clinical research and development, as well as their participation in JSC discussions. EFPIA also recommends that the applicant is informed upfront about the approach that will be followed to gather input during the JSC procedure, including the selection process and the level of access to information – which should be the same among experts involved on the EMA and on the HTA side – and whether experts will participate in the actual JSC meeting. As per its submission to the consultation on D7.2, EFPIA strongly recommends: •Providing a transparent and efficient recruitment and selection process of patients and healthcare professionals, both as individual experts and/or as representatives of their organizations. •Including transparency on who and how is	Thank you for your comment. We agree and would like to emphasise that this is already common practice. In line with D7.2/3, we have also included "other experts".

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				responsible for the recruitment of experts. •Relying on a common Secretariat for all JSCs procedure, to ensure consistency across the procedures. •Prioritizing the development of a process to involve methodological experts. Furthermore, the involvement of external experts should not be limited to patients and clinicians, but could include also other relevant experts, for instance medical devices experts, methodologists trained in difference aspects and formats of evidence generation, disease/trial experts (e.g., for drug-device combinations).	
D6.4.1 External Guidance with EMA	Matteo Scarabelli - EFPIA	12	352-363	*4.4 Other stakeholders (II)* As already reported in its submission to the consultation on D7.2/3, EFPIA considers that the involvement of external experts needs to be done in such a way that all participants see their right and position respected within the role and the mandate of their contribution to the procedure. In the context of the advice/consultation, highly commercially sensitive information on current developments is shared. The relevant sections of the briefing book and the draft outcome documents shall circulate only within the experts involved in the procedure, who access those under strict confidentiality provisions and for the	Thank you for your comment. Agreed, appropriate measures have been followed during EUnetHTA 21 to ensure confidentiality, also after finalisation of the procedure.

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				exclusive purposes accuracy check on their input in the recommendation, via Eudralink). Once finalized, no report or outcome document shall be shared or left behind with anyone else than the developer, to which the advice is intended.	
D6.4.1 External Guidance with EMA	Matteo Scarabelli - EFPIA	12-16	366-524	*5. process* It seems that there are some divergences between the way the process is explained in the present guidance and the instructions provided for the EUnetHTA 21 Open Calls, where the process started after the acceptance of the health technology by EUnetHTA 21, while here the "start" of the procedure is fixed at the reception of the draft Briefing Book. In the same sense, and to ensure consistency, two other points might benefit for further clarification: • the reference to the final BB submission "5 days before the start of the procedure"; • the exact determination of "Day 0" with regard to the start of the procedure. As per previous comments, EFPIA would welcome a clarification of the overall timeline, which might be facilitated by building it on interim milestones. Furthermore, EFPIA would recommend seeking as much alignment as possible of the HTA consultation process to the Regulatory scientific advice, especially when the two run in parallel.	Thank you for this comment. The timing will be checked again. Start of the procedure is D 0: reception of the final briefing document. The overall duration starting with the receipt of the draft briefing document is 4,5 months, 3,5 months from start of the procedure D 0.

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D6.4.1 External Guidance with EMA	Matteo Scarabelli - EFPIA	13	407-409	*5. Process* *- 5.2 Presubmission phase* *"Both EMA and HTAB reserve the right to answer selected questions that have been directed to the other entity if deemed appropriate".* As per previous comment on the Briefing Book Template, EFPIA would like to remind that SA/JSC is a service intended to provide advice to the applicant in view of an eventual submission for two different processes (marketing authorization and joint clinical assessment). The applicant should get the clearest possible advice/recommendation to its questions, especially when divergences may arise. There is therefore a crucial need for a **clear governance in the discussions** and in the formulation of the answers within the meetings. When an applicant's question targets only one of the two remits represented in a Parallel Consultation procedure, "opinions" or "comments" from another entity should be allowed, although not translated into a prescriptive response. As the remit and the target of the question is clear, so should be the answer. EFPIA would recommend editing the quoted paragraph	Thank you for your comment. Please refer to our response above.

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				as follows: *"Both EMA and EUnetHTA 21 reserve the right to **comment on** selected questions that have been directed to the other entity if deemed appropriate".*	
D6.4.1 External Guidance with EMA	Matteo Scarabelli - EFPIA	p14 p. 14 p15,	429-437 451-453; 473-483;	*5. Process* *- 5.3 Evaluation phase* *429-437 – List of Issues* *"**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 …// … around **day +35** of the procedure".* *451-453 – Preparation discussion meeting* *"The Applicant should send any **written responses to the EUneHTA 21 LoI 12 working days** before the F2F meeting".* "*For EMAs LoI, the Applicants' written response is expected 5 working days before the start of the F2F meeting week".* *477-483 – Amended development plan triggered by List of Issues […]* *"**For EUnetHTA 21**, the written response to LoI and, if applicable, necessary information regarding the*	Thank you for this. Point well taken, further alignment will be considered.

Sub-deliverable	Comment from	Page number	Line/ section number	Comment and suggestion for rewording	Response Hands-on-Group
		p 17	Table 1.	*amended development plan must be received at the latest by **12 working days** before the discussion meeting".* *"**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".* *Table 1, page 17* *"**Day +70**: **The Regulators' Final Advice Letter** is adopted by the CHMP (…) made available to the applicant via IRIS and sent to the EUnetHTA 21 JSC secretariat".* *"**Day +82**: **EUnetHTA 21 Final Written recommendations** sent the to the applicant and EMA".* EFPIA observed that the timing of the certain important milestones – e.g. feedback on the List of Issues and amended development plan – presents misalignment between the two process and/or between the two legs of the parallel consultation process – e.g. as for the validation of the final briefing books. Therefore, alignment would be welcome on the timing of the following milestones for both separated processes and for the parallel one: •Drafting and sharing of the first List of Issues •Timeframe/deadline for the applicant written response to LoI	

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				• Feedback to the applicant on the List of Issues and on the amended development plan • Delivery of the final output (advice/recommendation). – In this last case, it would be particularly welcome to accelerate the process by bring down the timing of the HTA output to the same timing of the EMA one. In line with previous comments, EFPIA would recommend seeking alignment between the timing of the procedures for regulatory advice and joint HTA consultation to help the applicant navigate the process and, as a result, improve its quality and efficiency – especially when the two processes are meant to run in parallel.	
D6.4.1 External Guidance with EMA	Matteo Scarabelli - EFPIA	15-16	484-524	*5.3 Evaluation phase* - *Discussion meeting (entire paragraph)* EFPIA would recommend the Coordination Group developing and including best practices regarding the format and the conduction of the discussion meeting, to ensure the most efficient and effective advice being deliver. In particular • allowing the applicant to include in its delegation an adequate number of experts based on the questions in scope. • involving experienced moderators to conduct the meeting and ensure all the questions are	Thank you for your comment. The number of participants was limited to ensure that the most relevant colleagues can attend, this limit can be extended upon request. EMA coordinators and HTA assessors and co-assessors are leading the discussion in a most comprehensive way. It is indeed an aim of the JSC to deliver meaningful recommendations to the industry. The minutes are for documentation purposes only. They have no direct influence on the drafting of the recommendations. The Final

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				discussed and the objectives are met, with the adequate level of detail. • aiming at formulating actionable recommendations for the developer. • establishing the endorsement of the minutes as regular good practice, to ensure the advice provided has been well captured and that the discussions are faithfully reflected.	Written Recommendation document is the final document that an HTD can refer to in the future.
D6.4.1 External Guidance with EMA	Matteo Scarabelli - EFPIA	15	498-500	*5.3 Evaluation phase* *- Discussion meeting (I)* *"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".* EFPIA considers that the standard 3-hour meeting – including 30 minutes introduction – represents the minimum time to cover the LoI appropriately. Shortening this time based on unilateral considerations on the agenda items risks compromising the discussion. In all cases, if the option of reducing the time allocation might be considered, that should be agreed with the applicant. For that reason, EFPIA also suggest editing the indication on "due time" accordingly.	Thank you for your comment. The regular meeting time is set at a maximum of 3 hours. However, in a few cases, consideration has been given to shortening the discussion time due to limited discussion content. However, this would only apply in exceptional and reasonable cases.

Sub-deliverable	Comment from	Page number	Line/ section number	Comment and suggestion for rewording	Response Hands-on-Group
				EFPIA recommends editing the quoted sentence as follows: *"If it is agreed between the EMA and the HTAbs* ***and the applicant – in the stage of the LoI preparation –*** *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".*~~ *Cf. Comment on page 21, Table 1 (second)*	
D6.4.1 External Guidance with EMA	Matteo Scarabelli - EFPIA	15	509-511	*5.3 Evaluation phase* - *Discussion meeting (II)* *"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".* EFPIA would suggest editing as follows: ***When relevant regarding the applicant questions from the Briefing Book,*** *the issues of both Regulators and HTAbs* ***may*** *be grouped together and structured following PICO (Population, Intervention, Comparator, Outcome) to enable for an* ***aligned*** *discussion of the stakeholders.* ***This must be agreed and included in the List of Issues sent to the applicant.***	Thank you for your comment. However, we do not consider an adjustment of the wording to be necessary. This is to ensure for a good discussion flow and has proved to be most useful during the past JSCs.
D6.4.1 External	Matteo Scarabelli - EFPIA	16	524	*5.3 Evaluation phase*	Thank you for your comment. The minutes are for documentation

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Guidance with EMA				- *Discussion meeting (III)* *"The minutes will not be commented by HTAb"* EFPIA would like to ask the entities and experts participating in the procedure to provide their acknowledgement on the minutes, especially about whether those accurately reflect the discussions that took place, or otherwise flag that for correction. EFPIA would like to propose the following wording: *"HTA bodies will provide an accuracy check on the minutes and acknowledge them".*	purposes only. They have no direct influence on the drafting of the recommendations. The Final Written Recommendation document is the final document that an HTD can refer to in the future.
D6.4.1 External Guidance with EMA	Matteo Scarabelli - EFPIA	21	Table 1 (I)	*D +60* *"The meeting is hosted by EMA (at the moment virtually)".* EFPIA would remind the importance of face-to-face discussion meetings. Both options are used for Regulatory Scientific Advice, **according to the EMA version of the present Guidance** published on July 3, 2023. EFPIA would therefore recommend editing as follow: *"The meeting is hosted by EMA (virtually or face-to-face (F2F))".*	Thank you for your comment. For the duration of EUnetHTA 21 virtually is correct. However, we have already added the possibility of face-to-face meetings for the interim period guidance.
D6.4.1 External Guidance with EMA	Matteo Scarabelli - EFPIA	21	Table 1 (II)	*D+60* "*Tripartite session: Discussion meeting EMA and EUnetHTA 21 HTAbs with the Applicant. The meeting duration will depend on the range of issues to be*	Thank you for your comment. We consider the duration of the discussion meeting and the duration of the pre- and post-discussion to be appropriate and

Sub-deliverable	Comment from	Page number	Line/ section number	Comment and suggestion for rewording	Response Hands-on-Group
				discussed (maximum 3 h), ***with 15 minutes closed pre-, and 15 minutes closed post-discussion meeting (EMA and EUnetHTA 21)"*** EFPIA would recommend ensuring adequate duration of the discussion meeting, so as to allocate appropriate time to all the listed issues/questions. Therefore, EFPIA proposes to allocate time for pre- and post- closed discussion before and after the 3h timeframe allocated to the discussion meeting with HTD. *Cf. Comment to page 14, 458-500 on the length of the discussion meeting.*	indeed this additional time is independent from the 3 hours discussion meeting and added before and after, respectively.
D6.4.1 External Guidance with EMA	Matteo Scarabelli - EFPIA	22	541-554	*6.3. Processing of documents (entire paragraph)* EFPIA would recommend the institutions responsible for the implementation of the future framework – the European Commission and the Coordination Group of Member States – to provide the necessary visibility on the IT system for exchange of confidential information already during the transition/implementation phase. This would enable the relevant stakeholders – especially the HTD responsible for JSC requests and JCA submissions – to prepare in view of the application of the HTAR as of 2025. Moreover, EFPIA would recommend the HTA bodies involved in the Interim model – 2023 and 2024 – to remain consistent with the use of the current system (Eudralink).	Thank you for your comment. This will be taken into consideration.

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D6.4.1 External Guidance with EMA	Matteo Scarabelli - EFPIA	22	559-560	*6.4 Briefing document for Parallel EMA/EUnetHTA 21 Joint Scientific Consultation* *«Questions related to health economics are possible and should be directed to HTAbs only».* EFPIA recommends keeping the focus of parallel consultations (involving both Regulators and HTAb) and of JSCs on the clinical aspects only. Moreover, considering the scope of the HTA Regulation, EFPIA believes that the focus of the JSC should be to inform the generation of evidence that would support the JCA. (Cf General comment to the Briefing Book Template) Health economic assessment questions should naturally be addressed in a dedicated discussion with HTA bodies and payers within more appropriate framework such as national advice procedures, as those are better suited to discuss local specific economic modeling requirements and considerations. Therefore, sections related to the health economic model questions should not be part of the BB.	Thank you for your comment. Health economic assessments, that are not part of a JCA, are considered relevant for many HTAbs and the advice in this regard is based on a voluntary basis according to Article 23 of the EU HTA Regulation.
D6.4.1 External Guidance with EMA	Matteo Scarabelli - EFPIA	22	560-562	*6.4 Briefing document for Parallel EMA/EUnetHTA 21 Joint Scientific Consultation* *"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".*	Thank you very much for your comment. However, we believe that it should be possible to provide answers from the HTA perspective when relevant.

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				As per previous comment, EFPIA would therefore recommend amending with the following wording: *"The labelling of questions is a guide but does not prevent interested bodies **commenting on** questions deemed also relevant and of interest although originally raised to the other entity".*	
D6.4 Procedural Guidance JSC	Matteo Scarabelli - EFPIA	23	572-576	*7.1 Advice format (entire paragraph)* *- (EunetHTA 21 final written recommendation)* EFPIA would like to submit the following recommendations: • The discussion should result in actionable actions addressing evidence generation uncertainty. • The JSC is of greatest value when it is actionable and HTA bodies can align on a consolidated recommendation which allow the HTD to leverage the recommendation to adapt the CDP before the start of the pivotal trials as well as explore alternative approaches to generate relevant evidence beyond the main pivotal trial programme. • Making sure that the patients' views is elaborated and reflected in all final written recommendations. • Including in the output both the consolidated as well as relevant details of each HTA agency's	Thank you for your comment. We agree with your statements and would like to emphasise that this is already common practice.

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				advice, so that the company can get an holistic picture of the evidence needs . The advice needs to reflect EU level feedback considering the views of the CG.	
D6.4 Procedural Guidance JSC	Matteo Scarabelli - EFPIA	23	578-579	*7.2 Follow-up procedures* *"A follow-up procedure is not foreseen".* As per previous comments, EFPIA recommends that the future JSC model under the HTAR will benefit from the opportunity of follow-up advice, as it is routinely available in the regulatory space, where follow-up is allowed to get further advice on the technology. The options for follow-up advice or "late" consultation should be open for HTD both at EU HTA level and national level. The objective of these options is to ensure that HTDs can receive the best quality advice and that innovation has the best chance to reach the patients. Should additional advice be needed and to complement the EU level JSC, both the option of follow-up JSC as well as the option of national advice procedure should be preserved to address specific local requirements for example specific economic points or local implementation challenges. The national discussions could include additional national level stakeholders, such as a patient organizations or medical societies as the focus is to inform the national pricing &	Thank you for your comment. The regulation clearly states that a JSC should provide advice on the planning of a pivotal study. As this demand is considered relevant, further discussions on this topic will take place in the JSC subgroup, but also other relevant subgroups and the HTACG..

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				reimbursement decisions.	
D6.2.1 Briefing Document Template	Matias Olsen, EUCOPE	general		While the document provides "recommendations", it would be good to also propose sections for the anticipated evidence related to the PICO(s), e.g. data sources, feasibility etc. In addition, the document seems to be restricted to the current "clinical development program" and does not really bring in the reality of the HTA situation which heavily relies on SLR + ITC&MAIC, other data sources, and scanning through upcoming potential new treatments that will be needed to address all HTA questions. The structure of the document will also be problematic in that context and it should not be structured to restrict the discussions only to the current clinical study(ies). The regulatory requirements for designing a clinical trial will typically take precedence over HTA requirements, which requires more external data sources. In the joint EMA/EUnetHTA scenario, please also consider alignment on the unmet medical need definitions.	Thank you for your comment. This will be taken into account for future considerations.
D6.2.1 Briefing Document Template	Matias Olsen, EUCOPE	5	59-61	We suggest to clarify this sentence. Add: "Evolution of treatment **options** should be discussed, including current standard therapy (referencing relevant guidelines and variations between the countries) and referring to relevant publications as well as any current unmet need(s)."	Thank you for your comment. The sentence has been adjusted accordingly.

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D6.2.1 Briefing Document Template	Matias Olsen, EUCOPE	5	65-66	For new treatments that are in advanced stages of development, there is no definitive evidence yet. For some indications in particular, such as diabetes, it is difficult to have an overview of all product developments.	Thank you for your comment. The HTD is expected to represent this to the best of his knowledge and ability.
D6.2.1 Briefing Document Template	Matias Olsen, EUCOPE	5	81	There might be conflicts with regards to the remit of the PDCO. We recommend clarifying this. Replace "[Chemical/biological product; orphan product; advanced therapy medicinal product;…" With: "[Chemical/biological product;~~orphan product~~ **Orphan Medicinal Product and medical products used in paediatric populations**; advanced therapy medicinal product;…"	Thank you, "medicinal products for paediatric populations" has been added.
D6.2.1 Briefing Document Template	Matias Olsen, EUCOPE	6	106-107	The Applicant is asked to inform if scientific advice has been sought, but it would also be useful to know the details. The current guidance does not ask for details or reference documents.	Thanks, changed to: "If scientific consultation has been previously requested from national HTA bodies or EUnetHTA (21). If yes, please include the full advice documents for the <u>European procedures</u> as an annex to the <u>briefing document</u>."
D6.2.1 Briefing Document Template	Matias Olsen, EUCOPE	6	115-117	A synopsis should also be sufficient, as a consultation should take place before the finalisation of the protocol. See also lines 358-359.	Thank you for your comment. We adjusted the sentence.
D6.2.1 Briefing	Matias Olsen, EUCOPE	6-7	118-120	The requirement is not clearly stated.	Thank you for your comment. A request for a literature review on

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Document Template				Delete: "Explain the choice of PROs and patient reported outcome measures (PROMs) ~~including a literature review of existing PROs~~ in the disease along with justification of the appropriateness of the questionnaire(s) chosen and the frequency of collection of this data.	existing PROs is considered reasonable.
D6.2.1 Briefing Document Template	Matias Olsen, EUCOPE	7	137-139	Should the rationale that is to be provided for justifying the request for seeking parallel consultation be more aligned with the criteria in draft EUnetHTA21 guidance D6.4 *"External Guidance with EMA"* under the section "CSCQ JSC selection criteria, scope and coordination"?	Thank you for your comment. The rationale for requesting a JSC by the HTD is independent of the selection criteria applied by the CSCQ JSC.
D6.2.1 Briefing Document Template	Matias Olsen, EUCOPE	8	152-154	Are open questions possible? Please define the requirements for the questions (see also lines 167-168). Does a question always have to be addressed to a either EMA or HTA bodies? (see draft EUnetHTA 21 deliverable D6.4 *"External Guidance with EMA"* line 407: "…consider whether the questions are appropriately addressed to HTAbs, Regulators or both.".	Thank you. We added the option to address a question to both entities, this is a common practice in reality.
D6.2.1 Briefing Document Template	Matias Olsen, EUCOPE	8	161-162	Please clarify which dossier is meant here.	Thank you for your comment. Amended to "briefing document".
D6.2.1 Briefing Document Template	Matias Olsen, EUCOPE	12	312-313	Please clarify: Where do the requested data from pivotal studies come from in the situation when the hea52lth technology developer is only planning the pivotal studies at the time of application? Since JSC is meant to inform the design of the clinical trials, PLEG cannot be contextualised with data from studies that have not yet been initiated.	Thank you for your comment. Added "[…] clinical data <u>expected</u> from pivotal (phase II/III) studies."

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D6.4.1 External Guidance with EMA	Matias Olsen, EUCOPE	general		While the roles and remits of the agencies should remain clearly separated, it could be helpful to align the timing for sharing the LOI with the health technology developer. EMA and EUnetHTA each prepare their own LOI and forward it to the health technology developer at different time points within the process (day 40 for EMA; day 35 for EUnetHTA). The deadlines for the response to the LOI also differ between EMA (5 working days before the meeting week) and EUnetHTA (12 working days before the discussion meeting). To make this process more efficient, the timings should be consolidated so that the health technology developer receives and submits the information, at the same time.	Thank you, we will look into possibilities for further alignment here.
D6.4.1 External Guidance with EMA	Matias Olsen, EUCOPE	6	113-115	As “important” is not clearly defined, we suggest to delete it from the sentence. Delete: “Thus, a strong interaction between Regulators and HTAbs/other relevant stakeholders is critical to facilitate patients’ access to ~~important~~ new medicines with added value and hence the overall benefit of public health.”.	Thank you for your comment. We agree and have amended the sentence accordingly.
D6.4.1 External Guidance with EMA	Matias Olsen, EUCOPE	8	162, 168-170	Within the context of a JSC, confidentiality should also apply to academically confident information. Any commercially confidential information should also be maintained confidential after authorisatoin of the product, in accordance with EUnetHTA 21 deliverable *D7.1.3 “process for commercially confidential information”*.	Thank you for your comment. As described in D7.1.3, the handling of academic-in-confidence data has been excluded from the guideline as results or data in assessment reports published by health technology assessment

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					agencies, medical regulatory authorities, medical device regulatory authorities or other regulatory authorities are not considered duplicate publications. Furthermore, the statements follow those of the guideline D7.1.3 regarding JSC.
D6.4.1 External Guidance with EMA	Matias Olsen, EUCOPE	10	284-285	The parallel consultation with EUnetHTA 21 and EMA is an early consultation. As such, it takes place before the pivotal trials are initiated. Due to the length of the clinical trials and the time needed for the statistical analysis of the data, sometimes multiple years may pass between the consultation and the start of the assessment. This poses the risk that the recommendations from the consultation may be out-dated. Therefore, it is vital that every pharmaceutical company has the opportunity for a Joint Scientific Consultation before the Joint Clinical Assessment begins.	Thank you for your comment. The regulation clearly states that a JSC should provide advice on the planning of a pivotal study. As this demand is considered relevant, further discussions on this topic will take place in the JSC subgroup.
D6.4.1 External Guidance with EMA	Matias Olsen, EUCOPE	10	286-288	When the JSC Secretariat provides the outcome of the call, will they also provide the rationale why the health technology developer may not have been selected for Joint Scientific Consultation? That feedback would be extremely useful for the Applicant.	Thank you for your comment. Yes, the applicant was informed of the reasons for the rejection.
D6.4.1 External Guidance with EMA	Matias Olsen, EUCOPE	10	291-292	Early dialogue is a crucial step in the evaluation of a medicinal product in order to align on the relevant methodologies for the assessment and the evidence to include in the dossier, and a robust submission is in the best interest of all stakeholders involved, including HTA bodies, payers and patients. In line with the importance of early dialogue, which has also been stressed in the draft document, it is crucial that all developers be given	Thank you for your comment. With regard to future consultations, it is up to the JSC subgroup and the HTACG to develop an appropriate system under the HTA Regulation, also in terms of the available resources.

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				the opportunity to receive Joint Scientific Consultations. In order to meet the high demand for Joint Scientific Consultation, adequate EU funding must be allocated.	
D6.4.1 External Guidance with EMA	Matias Olsen, EUCOPE	11	319-321	This must be formulated more strongly. Replace: "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." With: "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~~ **reaching an agreement**."	Thank you for your comment. The attempt to reach consensus is seen as correct, as it would be presumptuous to assume that there would never be dissenting views. Efforts are always maximised to find alignment. To clarify this, we added: "whenever possible."
D6.4.1 External Guidance with EMA	Matias Olsen, EUCOPE	14	430-437	The Regulator's draft of List of issues (LOI) is supposed to be produced approximately by day 40. EUnetHTA shares their LOI with the health technology developer around day 35. It would be desirable to have a streamlined process with the same timelines for all involved parties. Providing different deadlines may be inefficient and confusing (see general comment).	Thank you, we will look into possibilities for further alignment here.
D6.4.1 External Guidance with EMA	Matias Olsen, EUCOPE	14	438-447	The paragraph describes the exchange between EMA and HTA bodies. The way this paragraph is phrased makes it seem like	Thank you for your comment. The exchange of the List of Issues takes place once they are finalised. It is important to point

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				the interaction between EMA and HTA bodies and the exchange of their respective LOI takes place after the LOI has been sent to the health technology developer. Harmonising the timing for receiving the documents, with the consultation meeting with EMA and HTA bodies taking place at the same time, would help to streamline the whole process and increase efficiency (see general comment).	out once again that both remits are distinct and that both LOIs are the respective responsibility of EMA and HTA bodies, respectively. A detailed exchange between the 2 entities take place approx. 1 week prior to the discussion meeting to prepare for the exchange with the HTD and to be clear about agreement or diverging positions.
D6.4.1 External Guidance with EMA	Matias Olsen, EUCOPE	14	445-446	This should be formulated more strongly. Replace: “Potential solutions that could facilitate one trial, or at least one development plan, could be discussed in advance of the discussion meeting.” With: “Potential solutions ~~that could facilitate~~ **to achieve** one trial, or at least one development plan, ~~could~~ **should** be discussed in advance of the discussion meeting.”	Thank you for your comment. It is not the responsibility of the EMA or the HTA bodies to offer direct solutions, but to draw the attention of the HTD to aspects that are considered critical. It is our aim to provide most useful advice to the HTD that will inform an appropriate trial design to generate relevant data.
D6.4.1 External Guidance with EMA	Matias Olsen, EUCOPE	14	451-454	It would be desirable to have a streamlined process with the same timelines for all involved parties. Providing different deadlines may be inefficient and confusing (see general comment).	Thank you, please refer to the response above.
D6.4.1 External Guidance with EMA	Matias Olsen, EUCOPE	15	479-480	This seems inconsistent with lines 519-524 where minutes are regarded as an Applicant’s record of the meeting and not supplied by EMA and/or EUnetHTA. If minutes are provided for the meeting, they should be	Thank you for your comment. The minutes are for documentation purposes only. They have no direct influence on the drafting of

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				officially recognised.	the recommendations. The Final Written Recommendation document is the final document that an HTD can refer to in the future.
D6.4.1 External Guidance with EMA	Matias Olsen, EUCOPE	15	497-501	While it would be positive to aim for more meetings to take place, and allow for more slots for Joint Scientific Consultations by potentially shortening meetings whenever a longer meeting is not needed, the health technology developer should be consulted on the need for a longer or shorter meeting. Replace: "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." With: "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~~ **consulted** about the **need for a longer or shorter** ~~length of the~~ discussion meeting ~~in due~~ **ahead of** time."	Thank you for your comment. The regular meeting time is set at a maximum of 3 hours. However, in a few cases, consideration has been given to shortening the discussion time due to limited discussion content. However, this would only apply in exceptional and reasonable cases.

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D6.4.1 External Guidance with EMA	Matias Olsen, EUCOPE	16	519-524	If minutes are provided for the meeting, they should be officially recognised. If EMA and/or EUnetHTA 21 do not want to endorse the minutes written by the health technology developer, official minutes should be supplied by EMA and/or EUnetHTA instead.	Thank you for your comment. The minutes are for documentation purposes only. They have no direct influence on the drafting of the recommendations. The Final Written Recommendation document is the final document that an HTD can refer to in the future.
D6.2.1 Briefing Document Template	EFSPI	general	---	EFSPI would welcome an update of the current template to better accommodate HTA needs. This includes its general structure (please see below) as well as changes to specific sections. While the document provides “recommendations”, it would be good to also propose sections for the anticipated evidence related to the PICOs (data sources, feasibility…). In addition, the document seems to be restricted to the current “clinical development program” and does not really bring in the reality of the HTA situation which heavily relies on SLR + ITC & MAIC, other data sources, and scanning through upcoming potential new treatments that will be needed to address all HTA questions. The structure of the document will also be problematic in that context. It should not be structured only to restrict the discussions to the current clinical study(ies). The overall regulatory requirements for designing a clinical trial will always prevail on the HTA requirements, which, by nature, requires more external data sources.	Thank you for your comment. This will be taken into account for future considerations.

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D6.2.1 Briefing Document Template	EFSPI	general	---	As JCA will potentially include multiple PICO, if health economic assessment (not mandatory) is addressed in the briefing document, it is fair to expect a clearer articulation between PICO set in JCA and the health economic assessment parameters as Population and Comparators. Are Population/Comparators for JCA expected to be the ones selected for the health economic assessment?	Thank you for your comment. Health economic assessments, that are not part of a JCA, are considered relevant for many HTAbs and the advice in this regard is based on a voluntary basis according to Article 23 of the EU HTA Regulation. However, no universal statement can be made on individual health economic parameters.
D6.2.1 Briefing Document Template	EFSPI	5	59-61	EFSPI proposes updating the following sentence to clarify that there might be more than one treatment. **Current wording:** "Evolution of treatment should be discussed, including current standard therapy (referencing relevant guidelines and variations between the countries) and referring to relevant publications as well as any current unmet need(s)." **Proposed wording:** "Evolution of treatment <u>options</u> should be discussed, including current standard therapy (referencing relevant guidelines and variations between the countries) and referring to relevant publications as well as any current unmet need(s)."	Thank you for your comment. The sentence has been adjusted accordingly.
D6.2.1 Briefing Document Template	EFSPI	5	58-68	We suggest being more specific about the description of the disease in terms of subpopulations as it is unclear whether the current wording expects a description of subpopulations which may be important for HTA and may also vary across local guidelines. In addition, it would be important to link standard therapies to corresponding subpopulations.	Thank you. It is the responsibility of the HTD to provide the necessary information to adequately answer the HTD's questions. With regard to subpopulations, however, subpopulations that are relevant

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				Similar to what is mentioned in lines 65-66 about screening of new therapies in advanced stages, we further suggest including also screening of draft local guidelines, as updates of subpopulations in local guidelines could be expected which are not yet available within the current final versions.	for HTA or EMA are defined if necessary, irrespective of the elaborations of the HTD.
D6.2.1 Briefing Document Template	EFSPI	6	92-94	EFSPI suggests providing more guidance in this Section on the scope, when it is needed, and which kind of details are expected.	Thank you for your comment. The definition of the scope is considered sufficient as it is the HTD's responsibility to provide the relevant information to allow the questions raised to be adequately answered.
D6.2.1 Briefing Document Template	EFSPI	6	96-98	EFSPI suggests providing more guidance in this Section on the scope, when it is needed, and which kind of details are expected.	Thank you for your comment. The definition of the scope is considered sufficient as it is the HTD's responsibility to provide the relevant information to allow the questions raised to be adequately answered.
D6.2.1 Briefing Document Template	EFSPI	6	106-109	Since it is not requested to submit advice documents from scientific regulatory advice, for equity reason it should also not be an obligation to submit HTA advice documents. This should be at the discretion of the applicant if it is needed for JSC. **Current wording:** "If scientific consultation has been previously requested from national HTA bodies or EUnetHTA (21). If yes, please include the full advice documents as an annex to your briefing document." **Proposed wording:** "If scientific consultation has been	Thank you, changed to: "If scientific consultation has been previously requested from national HTA bodies or EUnetHTA (21). If yes, please include the full advice documents for the European procedures as an annex to the briefing document."

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				previously requested from national HTA bodies or EUnetHTA (21)."	
D6.2.1 Briefing Document Template	EFSPI	6	115-117	**Current wording:** "Present the study protocol that is the subject of the Parallel EMA/EUnetHTA 21 JSC (study design, inclusion and exclusion criteria, comparator, endpoints, patient reported outcomes (PRO), sample size estimation, statistical analyses, etc.)." **Proposed wording:** "Present the study protocol that is the subject of the Parallel EMA/EUnetHTA 21 JSC (study design, inclusion and exclusion criteria, comparator, endpoints, patient reported outcomes (PRO), sample size estimation, statistical analyses, multiplicity, etc.)."	Thank you, multiplicity has been added.
D6.2.1 Briefing Document Template	EFSPI	6-7	118-121	EFSPI suggests adding information about minimal important difference (MID). Furthermore, we suggest being more specific about the 'appropriateness of questionnaire(s)'. What kind of information should the applicant provide (aspects of a validation study)?	Thank you for this comment. It is the responsibility of the HTD to provide the necessary information to adequately answer the HTD's questions as these concepts are highly specific to the scope of the JSC..
D6.2.1 Briefing Document Template	EFSPI	7	136-139	Should the rationale to be provided for justifying the request for parallel consultation be more aligned with the criteria further illustrated in the process document in the section "CSCQ JSC selection criteria"?	Thank you for your comment. The rationale for requesting a JSC by the HTD is independent of the selection criteria applied by the CSCQ JSC.
D6.2.1 Briefing Document Template	EFSPI	8	158-160	EFSPI considers the discussion of Unmet Medical Need a key dimension of HTA. Therefore, this topic should be part of any BB for JSC. **Current wording:** "Furthermore, as the existence of a medical need is included in the Committee for Scientific	Thank you for this comment. It had been assumed that a potential medical need had been sufficiently described by the HTD in the Application form for a JSC to fulfil the selection criteria

Sub-deliverable	Comment from	Page number	Line/ section number	Comment and suggestion for rewording	Response Hands-on-Group
				Consistency and Quality (CSCQ) eligibility assessment for parallel EMA/EUnetHTA 21 JSC, related questions are out of the scope of parallel EMA/EUnetHTA 21 JSC." **Proposed wording:** We suggest removing this sentence.	applied during EUnetHTA 21. Therefore, discussing unmet medical need is not a priority. However, if the HTD wishes to do so due to a complex treatment setting or multiple competitors in the development stage, this can still be addressed during a JSC. Adjusted to "related questions do not seem a priority topic for the Parallel EMA/EUnetHTA 21 JSC, but can be addressed if needed.".
D6.2.1 Briefing Document Template	EFSPI	9	209-210	EFSPI suggests being more specific about the nature of extrapolation as it may e.g., refer to survival extrapolation or to maintenance/waning of treatment. **Current wording:** "Population, including potential deviation between study population vs targeted indication, biomarkers, subgroups, extrapolation, generalizability;" **Proposed wording #1:** "Population, including potential deviation between study population vs targeted indication, biomarkers, subgroups, extrapolation <u>of effects beyond trial observed period</u>, generalizability;" **Proposed wording #2:** "Population, including potential deviation between study population vs targeted indication, biomarkers, subgroups, <u>time</u> extrapolation <u>of effects</u>, generalizability;"	Thank you for your comment. The reference to extrapolation should remain openly formulated not to give rise to any restrictions.
D6.2.1 Briefing	EFSPI	15	404	**Current wording:** "<Other relevant statistical issues (e.g. stratification)>,"	Thank you for your comment. "Multiplicity" has been added.

Sub-deliverable	Comment from	Page number	Line/ section number	Comment and suggestion for rewording	Response Hands-on-Group
Document Template				**Proposed wording:** "<Other relevant statistical issues (e.g. stratification, multiplicity)>,"	
D6.4.1 External Guidance with EMA	EFSPI		General	**Capacity building** For development of new drugs and early patient access it is critical that every new clinical development program is tailored to the needs of regulators and HTAbs. Therefore it is essential that for every new medicine JSC can be undertaken to inform appropriate evidence generation. In this context EFSPI would like to emphasize the importance of adequate ressources and capacities within the designated JSC subgroup of the future HTAR to meet this demand so that every request for JSC can be accommodated at any time throughout the product lifecycle.	Thank you for your comment. It is the responsibility of the HTACG and the respective JSC subgroup to adapt the guidance document to the structure and procedural workflow under the HTA Regulation. This will also take into account capacities and request periods, etc.
D6.4.1 External Guidance with EMA	EFSPI		General	**Inclusive approach** To ensure a lean and efficient process with respect to the subsequent scoping phase and JCA production EFSPI would welcome that in the future HTAR system the designated subgroup for JSC aspire to incorporate the view of every member state HTAbs or at least of as many member states HTAbs as possible. Involvement by the member states at this early timepoint can establish a strong link between JSC and JCA and facilitate a fit for purpose clinical program.	Thank you for your comment. It is the responsibility of the HTACG and the respective JSC subgroup to adapt the guidance document to the structure and procedural workflow under the HTA Regulation. As stipulated by the HTA Regulation the final JSC output document is adopted by the HTACG and inclusiveness is a clear goal.
D6.4.1 External Guidance with EMA	EFSPI		General	**Sustainable and workable JSC output** EFSPI appreciates the approach of the guidance to create opportunities for mutual understanding between regulators and HTAbs and potential solutions that could facilitate one pivotal trial serving both needs. For this purpose EFSPI would like to recommend that	Thank you for your comment. While we share your opinion on the value of mutual understanding between regulators and HTA, it is important to recognise that these are two different remits and

Sub-deliverable	Comment from	Page number	Line/ section number	Comment and suggestion for rewording	Response Hands-on-Group
				under the new HTAR framework the output of the joint scientific consultation outcome document should be actionable in a sense that the required evidence can be generated reasonably considering context specific evidence generation uncertainty and that the advice is consolidated and consensus is reached to the best possible extent between regulators and HTAbs and among HTAbs as well with the ultimate goal of one development plan.	essentially different research questions are being addressed. The HTA body's attempt to reach consensus is seen as essential, but it would be presumptuous to assume that there would never be dissenting opinions. Efforts are always maximised to find alignment and provide comprehensive advice.
D6.4.1 External Guidance with EMA	EFSPI	6	95	This guidance refers several times to post license evidence generation without providing a precise definition of it. EFSPI would recommend to add a section of definitions where such terminology is explained to create a common understanding between authors and readers of this document.	Thank you for this comment. PLEG is not further defined in this guidance as we did not want to introduce any limitations in this regard.
D6.4.1 External Guidance with EMA	EFSPI	7/8	159-171	In this section it is not detailed how confidentiality is ensured in the case of withdrawal or stop of JSC procedure. Thus, from our perspective a specification would be helpful that confidentiality encompasses these circumstances as well.	Thank you for your comment. As described in the confidentiality agreement form linked in the guidance, there is no time limit on the validity of confidentiality, so the termination of the consultation does not affect the confidentiality assurance.
D6.4.1 External Guidance with EMA	EFSPI	8	222	The guidance doesn't state how the contact sheet will be sent from EMA to EUnetHTA 21 JSC secretariat, a clarification at this point would be helpful.	Thank you for your comment.
D6.4.1 External	EFSPI	8	222-224	*EMA sends an EMA contact sheet to the EUnetHTA 21 JSC Secretariat including all details for regulator participants (i.e. SAWP Rapporteurs, EMA Scientific*	Thank you for your comment. This falls within the remit of EMA. Since the identification of EMA staff

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Guidance with EMA				*Officer, assistant and other contacts, if applicable) as soon as available.* The timing as soon as available seems vague, EFSPI would suggest more clarity by specifying a concrete timepoint aligned with the timelines of Table 1.	takes some time and might differ between procedures, it is not possible to give a more precise time frame. In the past this has never had a relevant impact on the timeline of a procedure. Sentence was adjusted.
D6.4.1 External Guidance with EMA	EFSPI	9/10	230-233/ 268-271	It seems that the scope of advice is defined slightly different between Regulators and HTAbs. We endorse the EMA approach that enables advice at any stage of the product lifecycle adopting a broad scope whereas the EUnetHTA 21 and HTAbs scope is more restricted with regard to timepoint and type of evidence. In accordance with the HTAR the EFSPI would recommend that in the future HTAR framework JSC can be sought at at any stage of the product lifecycle without restriction with respect to the type of evidence.	Thank you for your comment. The regulation clearly states that a JSC should provide advice on the planning of a pivotal study. Exploring the possibilities of consulting at another point in the development process is, however, the responsibility of the HTACG and the JSC subgroup.
D6.4.1 External Guidance with EMA	EFSPI	9	245	The EFSPI welcomes the aspiration to reach consensus by mediation to consolidate the final JSC output as far as possible. With respect to the new HTAR framework EFSPI would like to recommend to establish a process for how mediation can take place in the designated subgroup to reach consensus and how disagreement will be handled.	Thank you for your comment. With regard to future consultations, it is up to the JSC subgroup and the HTACG to develop an appropriate process to reach consensus between HTA bodies.
D6.4.1 External Guidance with EMA	EFSPI	10	274-292	EUnetHTA21 JSC pilots have shown significant challenges related to the open call system. For a robust and sustainable working model within the new HTAR framework such an approach seams to be inappropriate. For a seamless and continuous opportunity of JSC at any stage of the products lifecycle the EFSPI would like to suggest to replace the open call system by a rolling	Thank you for your comment. It is the responsibility of the HTACG and the respective JSC subgroup to adapt the guidance document to the structure and procedural workflow under the HTA Regulation. This will also take into account capacities and request

Sub-deliverable	Comment from	Page number	Line/ section number	Comment and suggestion for rewording	Response Hands-on-Group
				submission model. This would enhance the planning certainty and flexibility for the HTD to seek advice at any given time to serve the overarching goal of robust evidence generation and early patient access. In this context EFSPI welcomes that the Federal Joint Committees guidance for parallel consultations by EMA and HTA agencies for the interim period provides a rolling submission system which should be carried forward and implemented within the future HTAR, too.	periods, etc. For further details, please refer to the related response above.
D6.4.1 External Guidance with EMA	EFSPI	10	286-290	For the time being under the current operating system it would be helpful if the EUnetHTA 21 JSC Secretariat not only communicates the decision but provides further details in case of rejection of the rationale lying behind it. For this purpose EFSPI suggest to add the following sentence: *For those request that have been rejected EUnetHTA 21 JSC Secretariat provides the underlying rationale for the reasons of declining the request.*	Thank you for your comment. During EUnetHTA 21 HTDs have been informed about the reasoning of declined requests. Sentence added to emphasise this: For those request that have been rejected EUnetHTA 21 JSC Secretariat provides the underlying rationale for the HTD on the reasons of declining the request.
D6.4.1 External Guidance with EMA	EFSPI	11	299-304	For the time being under the current operation system it is unclear regarding the selection criteria - especially the first three aspects - if these should be assessed for the CSCQ member states or the HOG member states only or for all member states? For the meanwhile it should be made clear to which member states the selection criteria are being applied.	Thank you for your comment. As described in the guidance (p.10), the full CSCQ JSC discussed the applicability of the selection criteria and the selection of a product for a JSC.
D6.4.1 External Guidance with EMA	EFSPI	11/12	333-363	For a comprehensive approach the EFSPI would welcome the inclusion of other stakeholders such as statistical experts so that beyond clinical and patient centered aspects methodological and biometric expertise and consultation is incorporated, too.	Thank you for your comment. In alignment with the Guidance D7.2/3 we have included a sentence: “Other experts with specific expertise may also be

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					involved if there is an explicit need."
D6.4.1 External Guidance with EMA	EFSPI	12	353-354	The former version comprised a tiered approach by EUnetHTA 21 to enhance expert (patient and/or HCP) involvement. Whereas the previous version still was aiming at experts involvement with respect to specific questions and reviewing the draft LoI this is not the case anymore. Although we acknowledge that expert involvement in its entirety may not always be possible we would still encourage any effort to maximizing experts involvement including their perspective on specific questions and LoI, too.	Thank you for your comment. The basic concepts of expert involvement are set out in D7.2/3 and were intensively discussed during the development of the document.
D6.4.1 External Guidance with EMA	EFSPI	13	403-409	*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 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.* We welcome comments on the draft briefing package. However to meet the specific need of JSC the scope should be set and driven by the HTD´s questions for which parallel advice is sought. Thus, any clarifying question is appreciated but it goes beyond the intention of the HTAR if additional questions are added that were	Thank you for your comment. We consider it good practice to draw the HTD's attention to aspects that they themselves have not considered. However, we agree that this should not be the default case. The formulation seems appropriate to cover such cases.

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				not submitted by the HTD. Thus, we would suggest to modify the passage as follows*:* *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 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*.	
D6.4.1 External Guidance with EMA	EFSPI	14	438-447	In the former version it was proposed that EMA and SAWP Rapporteurs take part in a closed meeting with the EUnetHTA 21 JSC Secretariat, EUnetHTA 21 Assessor and Co-Assessor before finalizing each LoI and sending them to the HTD, respectively. To increase alignment and avoid overlapping or contradictory LoI EFSPI would like to advocate that this possibility is still preserved so that each LoI are finalized and shared with the HTD only after such a pre-meeting has taken place.	Thank you for your comment. The exchange of the LOI takes place before submission to the HTD. However, it is important to point out once again that both remits are to be separated and that both LOIs are the respective responsibility of EMA and HTA bodies respectively. A detailed exchange between the 2 entities take place approx. 1 week prior to the discussion meeting to prepare for the exchange with the HTD and to be clear about agreement or diverging positions.
D6.4.1 External	EFSPI	16	519-524	EFSPI appreciates HTD involvement by providing minutes of the discussion meeting. However, it is	Thank you for your comment. The minutes are for documentation

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Guidance with EMA				unclear how the minutes are routed to EMA and if they will be commented by EMA. To have clarity and to increase the level of alignment, EFSPI would like to recommend that first it is specified how the HTD sends the minutes in and second that the meeting minutes provided by the applicant shall be endorsed by EMA and the HTAbs to ensure there is consensus about having captured adequately the opinions of all stakeholders.	purposes only. They have no direct influence on the drafting of the recommendations. The Final Written Recommendation document is the final document that an HTD can refer to in the future.
D6.4.1 External Guidance with EMA	EFSPI	18/19	Table	From the displayed timeline it is not clear how day 0 is defined; presumably day 0 refers to the receipt of the final briefing package. However, to avoid speculation and since all timelines are anchored around day 0 EPFSI would like to suggest to include day 0 and its definition in the timeline.	Thank you for your comment. Yes, that is correct, D 0 was added to the table to clarify this.
D6.4.1 External Guidance with EMA	EFSPI	21	Table 1	In national HTA advice procedures it has proven very helpful and reasonable that a preliminary version of the advice is sent to the HTD for annotation purpose. By giving the HTD the possibility to comment on the preliminary version possible ambiguities can be clarified and taken into account before issuing the final advice. Thus, with respect to the new HTAR framework EFSPI would recommend the incorporation of such a feedback loop to ensure a clear and common understanding of all parties of the final advice.	Thank you for your comment. However, it is understood that at this stage of the consultation all relevant information has been provided by the HTD through various interactions during the procedure and foremost during the discussion meeting. The Final Written Recommendations is the validated output document of the HTAb side and the creation of a further feedback/response loop is not considered appropriate.
D6.4.1 External	EFSPI	21	Table 1	For a maximum gain from the parallel procedure within the future HTAR system there should also be dedicated post discussion meeting between Regulators and HTAbs where the discussion meeting and positions on the HTD´s questions are reflected to align mutual needs	Thank you for your comment. A debriefing meeting between EMA and HTA is already established and common practice and serves the stated purpose.

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Guidance with EMA				on the clinical development of EMA and HTAbs as far as possible.	
D6.4.1 External Guidance with EMA	EFSPI	21	Table 1	We acknowledge that the timing of some important milestones was already further harmonized and streamlined between EMA and EunetHTA 21. However, there is still a temporal misalignment between the final EMA advice letter (d 70) and the EunetHTA 21 final written recommendations (d 82) and from our point of view it would be desirable to harmonize this deliverable as well by bringing down the timing of the HTA output to the same timing of the EMA.	Thank you for your comment. Procedural steps such as final confirmation by the CSCQ JSC and medical editing do not allow for a shorter period of time. However, we will look into possibilities for further alignment here.
D6.2.1 Briefing Document Template	Marjorie Morrison, Lymphoma Coalition	General		In addition to clinical development information, the integration of patient reported outcomes (PROs) and patient reported outcome measures (PROMs) are critical to support research of new treatments and therapies. The document proposes that full methodology should be given “if patient preference data are planned to be collected alongside clinical development.” As patient preference data that addresses the complexities and implications of health-related quality of life patients experience and priorities are essential and influential in decision-making, we support language that reflects the integration of PROs and PROMs wherever feasible and relevant. Further, as real-world evidence and real-world data sources are positioned to provide complimentary data where collection of evidence and data are lacking in relation to innovative therapeutics or medicines, additional language, greater clarity, and consideration	Thank you for your comment. This will be taken into account for future considerations.

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				in this respect might also be beneficial.	
D6.2.1 Briefing Document Template	Marjorie Morrison, Lymphoma Coalition	5	59	Regarding the provision of background information, the document indicates information on the disease to be treated, in addition to specifics regarding the evolution of disease symptoms and burden are all considered main features of the disease. Other features noted include the evolution of treatment, current unmet needs, and availability of treatment alternatives for the treatment of the pathology. Given the complexity and comprehensive nature of burden in the context of disease symptoms, it may be beneficial to further clarify what is meant by burden of disease symptoms while considering other factors such as burden measurement or assessment. For further clarity and understanding, it may also be beneficial to define the inclusion or exclusion of underlying disease conditions or chronic disease issues that may affect or impact patient health related quality-of-life in relation to burden and the health technology or intervention.	Thank you for your comment. This will be taken into account for future considerations. For now, it is the responsibility of the HTD to present this information in a meaningful way.
D6.2.1 Briefing Document Template	Marjorie Morrison, Lymphoma Coalition	General		Consistency in language, shared understanding, and resources to ensure interpretation of information and propose are essential. With respect to therapeutic indications, the European Medicines Agency document (dated 21 October 2019) provides assessors of centralised applications with a supplementary guide to support a consistent approach “in the process of defining Therapeutic Indications during the assessment of centralised applications for new active substances or new indications.” Wording of therapeutic indication - guide for assessors (europa.eu) As a practical suggestion, it may be valuable to	Thank you for your comment. This will be taken into account for future considerations.

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				consider the inclusion of content in relation to therapeutic indications and/or the timely provision of supplementary resources that address therapeutic indications to support universal understanding of common processes, criteria, and terminology amongst diverse stakeholders.	
D6.4.1 External Guidance with EMA	Marjorie Morrison, Lymphoma Coalition	6	89-90	The Committee for Scientific Consistency and Quality for Joint Scientific Consultation (CSCQ JSC) and formerly the Early Dialogue Working Party (EDWP) is currently comprised of 11 countries, namely: Spain, Italy, Germany, France, Portugal, Belgium, Ireland, Hungary, Norway, Sweden, and the Netherlands. Within the framework, the criteria for the CSCQ JSC appointment and/or relevant terms should remain transparent and accessible to the public given the role of the CSCQ. At present, it appears that while the role of the CSCQ is defined sparingly with limited information about the aspects the CSCQ considers prior to endorsement by the Consortium Executive Board (CEB), the criteria or terms are not easily or readily available. This should be considered as a best practice to promote knowledge sharing and increase broader stakeholder understanding and appreciation of the role of the CSCQ JSC.	Thank you for your comment. CSCQ and CEB are solely defined for the EUnetHTA 21 project. Respective information can be found on the EUnetHTA 21 website. Also, both project entities have a Standard Operating Procedure (SOP).
D6.4.1 External Guidance with EMA	Marjorie Morrison, Lymphoma Coalition	8	163-164	Transparency promotes a culture and environment of trust and plays a significant role in helping to ensure robust understanding of protocols, best practices, and compliance. As EMA and associated regulatory experts are bound by the EMA Code of Conduct and Confidentiality Agreements (Policy/0043), it is important for processes to ensure that any actions in relation to the policy (and/or related to compliance and/or	Thank you for your comment. It is taken note of.

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				decisions regarding issues of conflict that arise) are disclosed and/or made available to interested stakeholders.	
D6.4.1 External Guidance with EMA	Marjorie Morrison, Lymphoma Coalition	8	196	To avoid duplication and support robust participatory and engagement protocols, there is an understanding that applicants ensure consecutive use in consultation methodologies when there is a variance and/or difference in consultation formats. The different consultation formats (for instance, those defined in the document as regulatory advice before parallel JSC) must be strictly held to the same standards of criteria and validation regardless of the determined consultation format. This does not appear to be addressed in the document at present and for consistency, the aforementioned should be integrated into the document to ensure understanding and compliance.	Thank you for your comment. The statement in the guidance document points out that questions that have already been asked recently in a separate EMA scientific advice should not be asked again in a JSC, as EMA has already commented on them and no divergent answer is to be expected.
D6.4.1 External Guidance with EMA	Marjorie Morrison, Lymphoma Coalition	8	202-203	There may be circumstances or “exceptional cases where consultation may not be achieved”. As outlined in the document, these cases require “a heads-up as early as possible to both EMA and EUnetHTA 21” as a mandatory requirement. The introduction of a mandatory requirement such as this must also be accompanied by a definition of timelines to provide unbiased and consistent guidelines. This is not supported or attainable when language (“early as possible”) is applied. Additionally, clarification regarding the point at which it is too late to cease and/or revise the continuation of a process (once it has been initiated) is also an important consideration that does not appear to be addressed within the	Thank you for your comment. Terminating an ongoing consultation at any point in the process is problematic; on the other hand, there is no logical reason why an HTD should be forced to continue a consultation if they see no benefit in it. Therefore, setting a specific time when a consultation can or cannot be terminated is considered pointless. The goal of all involved parties should be to ensure that a JSC that has been started is also completed.

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				document at present.	
D6.4.1 External Guidance with EMA	Marjorie Morrison, Lymphoma Coalition	10	207	The role of the Scientific Advice Working Party (SAWP) as an EMA standing working party is to "remit of providing scientific advice and protocol assistance to applications, advising on the conduct of the various tests and trials necessary to demonstrate the quality, safety, and efficacy of medicinal products." The EMA has a clear commitment to full transparency of member representatives and alternates, as evident on the scope and depth of information on the EMA website. As a practical suggestion, those who wish to view the declaration of interests, nominating authority and curriculum vitae of SAWP members need to search out the information in the comprehensive EMA European Experts Listing by name only. It would be beneficial to include, for example, the country of country of origin (alongside the member names of the SAWP) to provide more than one search avenue or option, as well as easily identify geographical representation and support a more seamless search approach that is less time consuming and more user friendly.	Thank you for your comment. This will be taken into account for future considerations.
D6.4.1 External Guidance with EMA	Marjorie Morrison, Lymphoma Coalition	General		From a practical perspective, it is essential that an automated acknowledgement process of all applications received for review by the CSCQ JSC is implemented as an essential step in the process. Presently, it may be unclear as to whether an automated acknowledgement is integrated at the time an application is initially received, or at later stages in the application.	Thank you for your comment. During the EUnetHTA 21 project phase this was done manually by the JSC Secretariat staff. This point will be taken into account for future considerations.
D6.4.1 External	Marjorie Morrison, Lymphoma Coalition	17	526	With respect to Table 1: Outline of actions for Applicant, EMA and EUnetHTA 21 in Parallel EMA/EUnetHTA 2 JSCs, D-15, Feedback on draft: the table indicates that	Thank you for your comment. Regarding EUnetHTA 21, the involvement of experts is

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Guidance with EMA				additional experts/patient representatives are identified and shared with EUnetHTA21 JSC Secretariat. The engagement of experts and patient representatives at critical junctures is key. It may be value to further clarify how patient representatives are defined in this context to promote increased understanding of the process and criteria. While this is addressed in other corresponding documents or documentation, it may also be relevant to provide clarity and details within the document for consistency.	described in detail in the guidance document D7.2/3.
D6.2.1 Briefing Document Template	Dr.Dr. Ch.-Markos Dintsios Bayer	6	118	Specify the literature review (target or systematic)	Thank you for your comment. Added “systematic”.
	Dr.Dr. Ch.-Markos Dintsios Bayer	7	134	Add CAT classification of ATMP if applicable	Thank you for your comment. Added “and Committee for Advanced Therapies (CAT) classification for Advanced Therapy Medicinal Products (ATMPs), if applicable.”
D6.4.1 External Guidance with EMA	Dr.Dr. Ch.-Markos Dintsios Bayer	general		It is not clear why the Guidance Document provided for the future Process under EU HTA Regulation is named EMA/EUnetHTA 21 Joint Scientific Consultation, as the EunetHTA21 consortium will cease operation. Please name the correct HTA body replacing the EUnetHTA 21 in this process	Thank you for your comment. The document is intended to describe the procedure of a JSC under EUnetHTA 21 as specified in the service contract. It is the responsibility of the HTACG and the respective JSC subgroup to adapt the guidance document to the structure and procedural workflow under the HTA Regulation.
	Dr.Dr. Ch.-Markos	7	143	It is not enough to reach mutual understanding between	Thank you for your comment. It is

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	Dintsios Bayer			EMA and HTA bodies. With the EU HTA Regulation coming to action, a closer harmonization on the relevant research question between EMA approval and HTA JCA is needed because both assessments will rely on the same body of evidence; therefore, alignment of both authorities on PICO requirements during a JSC is mandatory because it guides planning of pivotal clinical phase. If the HTD cannot rely on the recommendations given in a JSC, they eventually fail to deliver meaningful studies, rendering the whole construct of JCA futile.	important to recognise that HTA and EMA cover two different remits and essentially address different research questions that are not necessarily based on the same body of evidence. Furthermore, the HTA bodies attempt to reach consensus is considered essential, but it would be presumptuous to assume that there would never be dissenting opinions.
	Dr.Dr. Ch.-Markos Dintsios Bayer	8	182	Although not legally binding, it is crucial that the HTD can rely on the advice to build his clinical study program e.g., in regard of comparative therapy	Thank you for your comment. We agree, but it is the responsibility of HTD to recognise changes in the therapeutic landscape of current medical standards that can quickly render previously given advice obsolete.
	Dr.Dr. Ch.-Markos Dintsios Bayer	10	275	It does not become clear if the advice requests are placed via open call or on a rolling basis. How many open calls and respective JSC slots per year are planned? A rolling basis as offered during interim phase by GBA is strongly recommended in order to facilitate the advice meetings as needed.	Thank you for your comment. It is the responsibility of the HTACG and the respective JSC subgroup to adapt the guidance document to the structure and procedural workflow under the HTA Regulation. This will also takes into account capacities and request periods, etc. See responses above for further details.
	Dr.Dr. Ch.-Markos Dintsios Bayer	10	293	There should be no selection for advice as any eligible request should be accommodated following an application on rolling basis; every product has its	Thank you for your comment. It is the responsibility of the HTACG and the respective JSC subgroup

Sub-deliverable	Comment from	Page number	Line/ section number	Comment and suggestion for rewording	Response Hands-on-Group
				specificities which should be taken into account for an advice	to adapt the guidance document to the structure and procedural workflow under the HTA Regulation. This will also takes into account capacities and request periods, etc.
	Dr.Dr. Ch.-Markos Dintsios Bayer	11	313 ff	It is not clear why the document only focuses at parallel EMA/EUnetHTA 21 JSCs within the two Open Calls in EUnetHTA21; the common understanding is that the guidance document should summarize the future process for advice	Thank you for your comment. The document is intended to describe the procedure of a JSC under EUnetHTA 21 as specified in the service contract. During EUnetHTA 21 only parallel JSCs have been performed. It is the responsibility of the HTACG and the respective JSC subgroup to adapt the guidance document to the structure and procedural workflow under the HTA Regulation.
	Dr.Dr. Ch.-Markos Dintsios Bayer	11	329	The applicant will receive a final written recommendation only at the end of the procedure; it would be of utmost importance for the applicant, however, to have a chance of prior review in case further clarifications are needed	Thank you for your comment. However, it is understood that at this stage of the consultation all relevant information has been provided by the HTD through various interactions during the procedure and foremost through the discussion meeting. The Final Written Recommendations are the responsibility of the HTA bodies and the creation of a further feedback and response loop is not considered appropriate.

Sub-deliverable	Comment from	Page number	Line/ section number	Comment and suggestion for rewording	Response Hands-on-Group
	Dr.Dr. Ch.-Markos Dintsios Bayer	12	352-53	It is not specified how JSC Secretariat coordinates European level expert recruitment; it would be recommended that experts and patients can bring in their expertise in an open format	Thank you for your comment. Regarding EUnetHTA 21, the involvement of experts is described in detail in the guidance document D7.2/3.
	Dr.Dr. Ch.-Markos Dintsios Bayer	13	401-402	Given a fixed timeline of interaction, the HTA bodies should not be allowed to contact the applicant for further clarification at any time but only once with a list of issues after the feedback on the draft has been given.	Thank you for your comment. It is considered to be in HTD's interest that HTA bodies have the opportunity to ask clarifying questions at any point in the process in order to provide the best possible advice, rather than being unable to respond or giving advice on the basis of false assumptions. Clarifications only refer to completeness of information and not a content wise exchange. During EUnetHTA 21 clarifications where asked on the basis of the draft briefing document and sometimes after the List of Issues meeting by the HTA bodies.
	Dr.Dr. Ch.-Markos Dintsios Bayer	13	422	There needs to be a confirmation of validation by both parties, otherwise the HTD cannot check if they have received the briefing package.	Thank you. EUnetHTA 21 did not introduce a formal validation step, of course all HTDs received an acknowledgement of receipt after submitting their briefing document.
	Dr.Dr. Ch.-Markos Dintsios Bayer	14	433 + 437 +451 + 453	Timelines for both list of issues of both bodies as well as the written response should be harmonized to facilitate a smooth process.	Thank you. Further harmonisation will be discussed in this regard.
	Dr.Dr. Ch.-Markos	15-16	495 +517-	There should be a clear commitment from all three	Thank you for your comment. This

Sub-deliverable	Comment from	Page number	Line/ section number	Comment and suggestion for rewording	Response Hands-on-Group
	Dintsios Bayer		518	parties that a compromise is being defined in case of divergent views of both, EMA and HTA bodies.	is not feasible. EMA and HTA have two different remits and consultations only run in parallel. As already described, Regulatory and HTA essentially ask different research questions, so that different requirements are often unavoidable.
	Dr.Dr. Ch.-Markos Dintsios Bayer	16	519-524	The meeting minutes should be commented by both EMA and HTA bodies in a coordinated process so that the HTD has one single document in the end to refer to at a later stage (e.g. during scoping and JCA).	Thank you for your comment. The minutes are for documentation purposes only. They have no direct influence on the drafting of the recommendations. The Final Written Recommendation document is the final document that an HTD can refer to in the future.
D6.2.1 Briefing Document Template	Antonella Cardone Cancer Patients Europe	General	Through the document	It seems that we are called to provide comments on a document that cannot be updated as it is already obsolete. In this public consultation, CPE would like to focus on the implementation of JSCs in the new HTAR setting as of 2025. At CPE, we would like to be given full consideration and we would like to give due consideration to the input received via the present consultation, as well as to ensure the establishment and continuation of a meaningful form of dialogue and/or consultation with relevant stakeholders over the implementation of JSCs) joint Scientific Consultations.	Thank you for your introductory comment. This final review was planned due to the EUnetHTA 21 project plan and the revised document will serve as a basis for the discussion within the JSC subgroup under the HTA Regulation. All comments received will be given due consideration also for the future JSC framework. Thank you for providing your comments.

Sub-deliverable	Comment from	Page number	Line/ section number	Comment and suggestion for rewording	Response Hands-on-Group
				The dialogue with stakeholders – and especially with patients, patient's advocates and health care providers – is essential to ensure that the advice/consultation procedure is fit for the purpose of providing the sponsors with high-quality recommendations and improving patient access to the best of new treatments and innovation.	
D6.4.1 External Guidance with EMA	Antonella Cardone Cancer Patients Europe	General	Through the document	The Guidance – originated from a document issued in September 2022 – reflects the collaboration between the EMA and EUnetHTA 21 during the 2021-2023 service contract. While welcoming the publication of the present guidance, we and its member companies look ahead through the HTAR implementation, for which further guidance will be appreciated, particularly reflecting the vision of the HTA bodies on Joint Scientific Consultation under the EU HTA Coordination Group and JSC Sub-group. In the context of the HTA Regulation, in fact, two options for joint scientific consultation co-exist: HTA-only JSC and EMA/HTA parallel JSC. The JSC procedures entirely managed by the Coordination Group / JSC subgroup are considered equally important as the JSC procedures conducted in parallel with the EMA.	Thank you for your comment. It is the responsibility of the HTACG and the respective JSC subgroup to adapt the guidance document to the structure and procedural workflow under the HTA Regulation.
D6.4.1 External Guidance with EMA	Inger-Margrethe Stavdal Paulsen, Osteogenesis Imperfecta Federation	Page 12	Line 355-356	We believe that patient representatives should represent a larger group of people if possible, and not just voice their personal opinion. They should ideally belong to the categories "individual patients with collective experiential knowledge" or "trained patient"	Thank you for your comment. The basic concepts of expert involvement are set out in D7.2/3 and were intensively discussed during the development of the

Sub-deliverable	Comment from	Page number	Line/ section number	Comment and suggestion for rewording	Response Hands-on-Group
	Europe (OIFE)			as described in the document D7.2 – GUIDANCE ON PATIENT & HEALTHCARE PROFESSIONAL INVOLVEMENT page 10 and defined in Appendix 2 – GLOSSARY ON PATIENTS (page 33-34).	document.
	Inger-Margrethe Stavdal Paulsen, Osteogenesis Imperfecta Federation Europe (OIFE)	General		We are aware that patient involvement is described in the document D7.2 – GUIDANCE ON PATIENT & HEALTHCARE PROFESSIONAL INVOLVEMENT, however, since patient involvement/patient input is mentioned several times in this document we wanted to make a general comment. We believe that patient involvement and the role of the patient representative in the process should be described and outlined in more detail also in this document. That could for instance be the patient representative's access to relevant documents, being presented with the timeline at an early stage for when input is needed and also describing the role of the patient representative in a discussion meeting.	Thank you for your comment. We have taken note of it.
D6.2.1 Briefing Document Template	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	general	general	Looking forward to applying both deliverables in the context of EUnetHTA initiatives and further actions enabling implementation of HTR (2021/2282), harmonized technology assessments across Europe to facilitate the determination of the real value of medical innovations, their reimbursement and to ensure their timely access for patients. Recently contributed to other useful reports and regulatory guidelines in relation to RWD/RWE and SATs, which might also be useful in the context of these two documents.	Thank you for your comment. The proposed addition is not considered mandatory.
	Natalia Haraszkiewicz-Birkemeier, BioPharma First	1	10	European Medicines Agency Guidance for applicants seeking scientific advice and protocol assistance - EMA/798877/2022 Rev. 14 issued by Scientific	Thank you for your comment. The proposed addition is not considered mandatory.

Sub-deliverable	Comment from	Page number	Line/ section number	Comment and suggestion for rewording	Response Hands-on-Group
	Consultancy			Evidence Generation Department	
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	1	10	Insert hyperlink	Thank you for your comment. The proposed addition is not considered mandatory.
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	1	12	Insert hyperlink	Thank you for your comment. The proposed addition is not considered mandatory.
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	1	19	With the appropriate format	Thank you for your comment. The proposed addition is not considered mandatory.
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	5	64	the disease	Thank you for your comment. It has been adapted.
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	5	65/1.1	How about other non-EU countries, e.g. Japan? The European Commission and European Medicines Agency (EMA) collaborate with the Japanese Ministry of Health, Labour and Welfare (MHLW) and Japanese Pharmaceuticals and Medical Devices Agency (PMDA)	Thank you for your comment. It has been adapted.
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	5	73/1.2	Drug combinations, drug-device combination products (MD, IVMD, AI-based software as Medical Device (SaMD) see also line 82. For more information refere to: Kincsö Izsak and Apolline Terrie; Advanced Technologies for Industry – Product Watch; Artificial Intelligence based software as a Medical Device; 2020 ATI - Artificial Intelligence-based software as a medical device.pdf (europa.eu)	Thank you for the comment. For EUnetHTA 21 joint work on Medical Devices was out of scope. However, this will be considered for future JSC under the HTA Regulation.
	Natalia Haraszkiewicz-Birkemeier,	5	78/1.2	Mechanism of Action (MOA), if known	Thank you for the comment. For EUnetHTA 21 joint work on

Sub-deliverable	Comment from	Page number	Line/ section number	Comment and suggestion for rewording	Response Hands-on-Group
	BioPharma First Consultancy			Modality, general description, qualitative composition, quantitative composition (if available), e.g. excipients, pharmaceutical form Correct classification for MDs (see Article 51 and Annex VIII of Regulation (EU) 217/745 REGULATION (EU) 2017/ 745 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL - of 5 April 2017 - on medical devices, amending Directive 2001/ 83/ EC, Regulation (EC) No 178/ 2002 and Regulation (EC) No 1223/ 2009 and repealing Council Directives 90/ 385/ EEC and 93/ 42/ EEC (europa.eu) and MDCG 2021-24 Guidance on classification of medical devices; 2021 mdcg 2021-24_en_0.pdf (europa.eu), IVDs (see Article 47 and Annex VIII of Regulation (EU) 2017/746 REGULATION (EU) 2017/ 746 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL - of 5 April 2017 - on in vitro diagnostic medical devices and repealing Directive 98/ 79/ EC and Commission Decision 2010/ 227/ EU (europa.eu) and MDCG 2020-16 rev.2 Guidance on Classification Rules for in vitro Diagnostic Medical Devices under Regulation (EU) 2017/746 md_mdcg_2020_guidance_classification_ivd-md_en.pdf (europa.eu) or advanced therapies (ATMPs) (see Article 2 and Article 17 of Regulation (EC) No 1394/2007 eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32007R1394 and the adopted revised reflection paper on the classification of ATMPs Reflection paper on classification of advanced therapy medicinal products (europa.eu)	Medical Devices was out of scope. However, this will be considered for future JSC under the HTA Regulation.
	Natalia Haraszkiewicz-Birkemeier, BioPharma First	5	81/1.2	Paediatric use?	Thank you. The “target population” should be addressed by the HTD under 1.2. Indication,

Sub-deliverable	Comment from	Page number	Line/ section number	Comment and suggestion for rewording	Response Hands-on-Group
	Consultancy				"medicinal products for paediatric populations" has been added.
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	5	82/1.2	See line 73/1.2	Thank you for the comment. For EUnetHTA 21, joint work on Medical Devices was out of scope. However, this will be considered for future JSC under the HTA Regulation.
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	5	83/1.3	Risk management strategy…	"risk management strategy" already included (L.84)
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	6	94/1.4	(bio)pharmaceutical	Thank you for the comment, this has been added.
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy		94/1.4	Manufacturing and quality aspects including Quality, Chemistry, Manufacturing and Control (CMC), anticipated Quality Target Product Profile (QTPP) to ensure the quality, safety, and efficacy of a product: - dosage strength - delivery system - dosage form - container system - purity - stability and - sterility, predicted Critical Quality Attributes (CQAs), Critical Material Attributes (MAs), Critical Process Parameters (CPPs), (current) Good Manufacturing Practice ((c)GMP), drug product/drug substance specifications as described in ICH Topic Q 6 B Specifications: Test Procedures and Acceptance Criteria for	Thank you for your comment. However, this is considered too extensive for the purpose of this document.

Sub-deliverable	Comment from	Page number	Line/ section number	Comment and suggestion for rewording	Response Hands-on-Group
				Biotechnological/Biological Products; 1999 Q 6 B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products (europa.eu), proposed control strategies for product quality and process performance, Quality Management Systems (QMS) The amount of information on analytical procedures and method suitability will vary with the phase of investigation. For more information on analytical procedures and method validation refer to ICH guideline M10 on bioanalytical method validation and study sample analysis ICH guideline M10 on bioanalytical method validation Step 5 (europa.eu)	
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	6	94/1.4	In some cases, cGMP principles have to be taken into account, during early product development, related to safety concerns, e.g. for CGTPs (ATMPs) as described in Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products; 2018 2017_11_22_guidelines_gmp_for_atmps_0.pdf (europa.eu)	Thank you for your comment. However, it is HTD's responsibility to present this in a meaningful manner.
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	6	94/1.4	If a medical device/in vitro medical device is proposed, it should be described and the status of compliance with the Medical Devices Regulation (EU) 2017/745 or with the in vitro Medical Devices Regulation (EU) 2017/746 mentioned.	Thank you for the comment. For EUnetHTA 21 joint work on Medical Devices was out of scope. However, this will be considered for future JSC under the HTA Regulation.
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	6	94/1.4	Novel manufacturing approaches including: - decentralised manufacturing approaches (e.g. decentralised manufacturing approaches for cell and gene therapy (ATMPs) manufacturing as described in	Thank you for your comment. The proposed addition is not considered mandatory.

Sub-deliverable	Comment from	Page number	Line/ section number	Comment and suggestion for rewording	Response Hands-on-Group
				R. Harrison et al; Centralised versus decentralised manufacturing and the delivery of healthcare products: A United Kingdom exemplar; Cytotherapy 20 (6); 2018 Centralised versus decentralised manufacturing and the delivery of healthcare products: A United Kingdom exemplar (sciencedirectassets.com) - lean enhanced manufacturing approaches, digitalisation/automation (waste minimization, productivity enhancement and continuous improvement) - applications of innovative technologies such as nanomaterials or genome editing should be described.	
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	6	98/1.5	If applicable, information about Pharmacology, Pharmacokinetics, Pharmacodynamics and Toxicology studies should be provided. In some cases full absorption, distribution, metabolism, and excretion" (ADME) programs for pharmacological characteristics are not applicable. As recommended by S. Ylä-Herttuala STED parameters should be considered in pre-clinical studies: Pharmacology of Gene Therapy 25; 2017 https://doi.org/10.1016/j.ymthe.2017.07.007 Compliance with GLP principles should be assessed, as described in L. Navas et al; Stem Cells Transl Med. 11; 2022 10.1093/stcltm/szac046	Thank you for your comment. It is HTD's responsibility to present this in a meaningful manner.

Sub-deliverable	Comment from	Page number	Line/ section number	Comment and suggestion for rewording	Response Hands-on-Group
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	6	108/1.6	Within the framework of EUnetHTA as highlighted in HTA NETWORK REFLECTION PAPER ON "REUSE OF JOINT WORK IN NATIONAL HTA ACTIVITIES" adopted by the HTA network in April 2015 reuse_jointwork_national_hta_activities_en_0.pdf (europa.eu) and EUnetHTA 21 to build a future EU HTA system under the HTA regulation 2021/2282. For more information refer to the relevant EMA website. It is worthwhile to note, however, that Scientific and / or regulatory advice related to early dialog during early clinical development stages (e.g. Phase 1 – 2) which can be received by national competent authorities (NCAs), HTA and reimbursement aspects are currently excluded as indicated in Guidance for applicants on Simultaneous National Scientific Advice (SNSA) phase 2 pilot (from October 2022) – Optimized process	Thank you for your comment. The proposed addition is not considered mandatory.
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	6	112/1.6	Applicants can request scientific advice from EMA in preparation of a Paediatric Investigation Plan (PIP), which is free of charge for questions relating to the development of paediatric medicines.	Thank you for your comment. The proposed addition is not considered mandatory.
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	6	115/1.6	Clinical trials characteristics (Randomized Clinical Trials (RCTs)), vs Single Arm Trials (SAT), Adaptive CTs and further patients' population, comparators, the potential use of RWD/RWE, registries (rare diseases) and biomarkers (prognostic, predictive) as surrogate end-points. Applicable guidelines: EMA Guideline on Clinical Trials in Small Populations; 2007, EMA Guideline on Registry based Study; 2021, Qualification of Novel Methodologies for Drug Development: guideline for applicants; 2020, Essential Considerations for successful qualification of novel methodologies; EMA; 2017	Thank you for your comment. The proposed addition is not considered mandatory.

Sub-deliverable	Comment from	Page number	Line/ section number	Comment and suggestion for rewording	Response Hands-on-Group
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	7	130/1.7	For more information about timelines and standard Centralized Procedure refer to European Medicines Agency pre-authorisation procedural advice for users of the centralised procedure	Thank you for your comment. The proposed addition is not considered mandatory.
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	7	134/1.7	Detailed EMA Priority Medicines Scheme (PRIME) eligibility criteria and timelines are described on the appropriate EMA website As indicated in the scientific paper authored by G. Detela and A. Lodge ,EU Regulatory Pathways for ATMPs: Standard, Accelerated and Adaptive Pathways to Marketing Authorisation; Molecular Therapy Methods and Clinical Development 13; 2019 EU Regulatory Pathways for ATMPs: Standard, Accelerated and Adaptive Pathways to Marketing Authorisation (cell.com) the type of MA applied for depends on the extent of clinical data obtained during development and/or whether the medicine addresses an unmet medical need. Two timetables are possible for Advanced Therapies (ATMPs: standard assessment and accelerated assessment. For more details refer to Procedural advice on the evaluation of advanced therapy medicinal product in accordance with Article 8 of Regulation (EC) No 1394/2007	Thank you for your comment. The proposed addition is not considered mandatory.
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	8	147/2	As indicated in the European Medicines Agency Guidance for Applicants seeking scientific advice and protocol assistance issued by Scientific Evidence Generation Department in October 2022; EMA/4260/2001 Rev. 14	Thank you for your comment. The relevant guidance is already sufficiently quoted.
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	8	159/2	The Committee for Scientific Consistency and Quality (CSCQ) eligibility assessment	Thank you for your comment. The link included leads to the relevant EUnetHTA 21 website with all relevant information.
	Natalia Haraszkiewicz-	9	206/2.5	**A general overview of the clinical development**	Thank you for your comment.

Sub-deliverable	Comment from	Page number	Line/ section number	Comment and suggestion for rewording	Response Hands-on-Group
	Birkemeier, BioPharma First Consultancy			**program should be provided emphasising: Clinical pharmacology, Pharmacokinetics, Pharmacodynamics, Clinical efficacy and safety. Supportive and pivotal clinical studies and any (statistic) analyses performed across trials (pooled and meta-analysis) should be subjected. The discussion should identify the most important findings and challenges in the clinical development program, and its compliance with appropriate legal requirements.**	However, it is HTD's responsibility to present this in a meaningful manner.
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	9	210/2.5	Generalizability (external validity)	Thank you for your comment. "Generalizability" is considered sufficient.
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	10	215/2.5	Including randomization (if applicable), single arm studies (SET), the use of external comparators and their types (RWD/RWE, registries). For additional information refer to line 115/1.6 on page 6	Thank you for your comment. The proposed addition is not considered mandatory.
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	11	254/2.5.3	The content of section 2.5 and 2.6.3 is repeated. …As indicated in section 2.5	Thank you for your comment. Section 2.5.3 refers to questions specific to HTA that relate to the elements set out in Section 2.5.
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	12	293/2.5.4	A significant benefit relates to the clinically relevant advantage or a major contribution to the patient care if such an advantage or contribution benefits a substantial part of the target population in the context of orphan medicines addressing unmet medical needs. For more details refer to European Medicines Agency Guidance for Applicants seeking scientific advice and protocol assistance issued by Scientific Evidence Generation Department (EMA/4260/2001 Rev. 12) (Rev. 14 of the document in preparation) For novel proposals on orphan legislation refer to	Thank you for your comment. The relevant guidance is already sufficiently quoted.

Sub-deliverable	Comment from	Page number	Line/ section number	Comment and suggestion for rewording	Response Hands-on-Group
				Proposal for a DIRECTIVE OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on the Union code relating to medicinal products for human use, and repealing Directive 2001/83/EC and Directive 2009/35/EC	
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	12	296/2.5.4	… to the Committee for Orphan Medicinal Products (COMP)	Thank you for your comment. The relevant guidance, which also describes the responsible committee, has already been sufficiently cited.
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	12	309/2.6	Which excel version is compatible with REQueST tool? Do all links work properly?	Thank you. The link is functional. REQueST tool tested successfully with MS Office Professional 2019.
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	13	321/3	relevant systematic	Thank you for your comment.
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	13 - 14	331 – 355/3	Should background information be included in first sections (line 77/1.3)?	Thank you for this comment. The sections target: Background information on the product vs. the development.
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	15	396/3.4	E.g., in a cost effectiveness model for ATMPs, axicabtagene ciloleucel used against B-cell Lymphoma is compared with chemotherapy and the same advanced cell therapy used in populations suffering from B-ALL is compared to Clofarabine. Later this information could be relevant to assess total discounted costs, total life years or total QALYs in order to calculate ICER. Also, in some cases comparators based on RWD/RWE are used based on natural patients history, e.g. observational, retrospective CTs.	Thank you for your comment. The template for the briefing document should not contain any concrete examples.
	Natalia Haraszkiewicz-	15	399/3.4.1	Network Meta-analysis (NMA) B. Rouse et al; Network	Thank you for your comment.

Sub-deliverable	Comment from	Page number	Line/ section number	Comment and suggestion for rewording	Response Hands-on-Group
	Birkemeier, BioPharma First Consultancy			meta-analysis: an introduction for clinicians. Intern Emerg Med. 12 (1); 2017	Network Meta-analysis added to the abbreviation NMA.
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	15	405/3.4.1	health-related quality of life (HRQOL), Quality-adjusted life year (QALY) or total life years	Thank you for your comment. Referring to health-related quality of life as a general consideration is seen as sufficient.
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	15	406/3.4.1	Post-authorisation efficacy studies (PAESs)	Thank you for your comment. Full text of the abbreviation was added.
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	16	416/4	Are non-clinical HTA assessments (health economics, economic evaluation) not based on clinical outcomes?	Thank you for your comment. As stated in the briefing document, the scope of a joint scientific consultation and a joint clinical assessment is clearly defined in the Regulation on HTA.
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	16	417/4	HTA can cover both clinical and non-clinical aspects of a health technology. Examination of the technical characteristics of the health technology under assessment is linked to its relative safety, and its relative clinical effectiveness. A non-clinical assessment relies on cost and economic evaluation of a health technology, and its ethical, organisational, social and legal aspects. HTA is used to well informed decisions in relation to establishing the pricing or reimbursement levels of health technologies. Voluntary cooperation between Member States (MS) on HTA relates to examples summarized in Section 4 Article 23 of the Regulation (EU) 2021/2282 ('HTA Regulation').	Thank you for your comment. The voluntary cooperation described in Article 23 of the Regulation on HTA is already referred to in Section 4 of the briefing document.
	Natalia Haraszkiewicz-Birkemeier, BioPharma First	17	448/4.2.1	External validity and internal validity?	Thank you for your comment. "Internal validity" has been added.

Sub-deliverable	Comment from	Page number	Line/ section number	Comment and suggestion for rewording	Response Hands-on-Group
	Consultancy				
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	17	453/4.2.1	Meta-analysis (MTC)	Thank you for your comment. The full abbreviation to MTC (Mixed Treatment Comparisons) has been added.
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	17	455/4.2.1	Quality of life (QOL), Quality Adjusted Life Years (QALY)	Thank you for your comment. Referring to quality of life as a general consideration is seen as sufficient.
D6.4.1 External Guidance with EMA	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	5	95/1	Post-Launch Evidence generation (PLEG)	Thank you for your comment. Added the full text to the abbreviation.
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy		99/1	According to the project plan EUnetHTA-21-–-D-6.2_D6.3-templates-BB-JSC-–-Project-Plan-–-v1.0.pdf (Is the updated document available?)	Thank you for your comment. Link added. There is no more recent project plan available.
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	8	164/3.2	European Medicines Agency policy on access to documents Policy 0043	Thank you for your comment. The citation is considered sufficient.
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	8	173/3.3	European Medicines Agency policy on the handling of competing interests of scientific committees' members and experts Policy 0044	Thank you for your comment. The citation is considered sufficient.
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	8	185/3.4	any deviation	Thank you for your comment. Has been corrected.
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	8	186/3.4	European Medicines Agency Guidance for Applicants seeking scientific advice and protocol assistance (europa.eu) (EMA/4260/2001 Rev. 14) issued by Scientific Evidence Generation Department and the	Thank you for your comment. The citation is considered sufficient.

Sub-deliverable	Comment from	Page number	Line/ section number	Comment and suggestion for rewording	Response Hands-on-Group
				appropriate EMA website	
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	8	188/3.4	Recommendations reflect an evidence-based process (HTA) that will allow the competent EU and national authorities to determine the effectiveness of new or existing health technologies.	Thank you for your comment. The proposed addition is not considered mandatory.
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	8	194/4	Information on the parallel scientific advice can also be found on the EMA website and the G-BA website.	Thank you for your comment. The additions on the EMA website and the G-BA website refer to the parallel joint scientific consultations during the interim period and must not be confused with the JSCs under EUnetHTA 21 or future JSCs under the Regulation.
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	8	204/4	…re-planning will be successful	Thank you for your comment. This has been corrected.
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	9	207/4	The Scientific Advice Working Party (SAWP) is…	Thank you for your comment. Adding the link is not considered mandatory.
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	9	211/4	For general information about SAWP responsibilities refer to Mandate, objectives and rules of procedure of the Scientific Advice Working Party (SAWP) (EMEA/CHMP/SAWP/69686/04 Rev 17) document issued by Human Medicines Division	Thank you for your comment. The proposed addition is not considered mandatory.
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	9	221/4.1	The IRIS platform facilitates the exchange of regulatory and scientific information between EMA and organisations developing medicinal research products for potential use in the European Union.	Thank you for your comment. A footnote has been added.
	Natalia Haraszkiewicz-Birkemeier,	9	222/4.1	Contact sheet…	Thank you for your comment.

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	BioPharma First Consultancy				
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	9	224/4.1	As soon as available…	Thank you for your comment. This is ensured by the standardised procedures of the EMA.
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	9	226/4.1	to Article 57 (1)(n) of Regulation (EC) No 726/2004	Thank you for your comment. The citation is considered sufficient.
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	9	229/4.1	(as defined in Directive 2001/83 (as amended))	Thank you for your comment. The citation is considered sufficient.
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	9	230/4.1	The Simultaneous National Scientific Advice (SNSA) refers to (very) early advice and provides a bridge between purely national scientific advice and centralised EMA scientific advice as well as aims to support the goals of the ACT-EU initiative related to clinical trials. Currently HTA and reimbursement aspects are excluded, however restrictions may be lifted along the future development of the pilot project. For more details refer to Guidance for applicants on Simultaneous National Scientific Advice (SNSA) phase 2 pilot (from October 2022) EMA/896928/2022	Thank you for your comment. The proposed addition is not considered mandatory.
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	9	233/4.1	For recommendations on key methodological aspects that are specific to the use of patient registries by marketing authorisation applicants and holders (MAAs/MAHs) planning to conduct studies refer to Guideline on registry-based studies EMA/502388/2020 https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-registry-based-studies_en.pdf	Thank you for your comment. The proposed addition is not considered mandatory.
	Natalia Haraszkiewicz-	9	233/4.1	The Risk Minimization Plan (RMP) is related to	Thank you for your comment. The

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	Birkemeier, BioPharma First Consultancy			identification or characterisation of safety profile, adequate measurements to prevent or minimise risks including assessment of the effectiveness of those measures, post-authorisation obligations. Risk minimisation measures should guide optimal use of a medicinal product in clinical practice aiming to support the provision of the right medicine, at the right dose, at the right time, to the right patient and with the right information and monitoring. It reflects on the impact on the risk-benefit balance of the product. Long term follow-up of efficacy is required for certain medicinal products including paediatric indications and ATMPs. More insights about RMP and risk minimization can be found in the scientific paper: D. Butler et al; : Regulatory experience of handling Risk Management Plans (RMPs) for medicinal products in the EU; Expert Opinion on Drug Safety; 2021 and appropriate EMA documents including Guideline on good pharmacovigilance practices (GVP) Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators (Rev 2) EMA/204715/2012 Rev 2* and a specific guideline related to ATMPs Guideline on safety and efficacy follow-up and risk management of advanced therapy medicinal products - Scientific guideline EMEA/149995/2008. In the Summary of Risk Management (SRM) Plan for Axicabtagen ciloleucel, the most important identified risks, risk minimalization measure and additional pharmacovigilance activities are summarized. yescarta-epar-risk-management-plan-summary_en.pdf (europa.eu)	proposed addition is not considered mandatory.

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				For general documents related to the Scientific Advice Working Party (SAWP) refer to Mandate, objectives and rules of procedure of the Scientific Advice Working Party (SAWP) issued by Human Medicine Division EMEA/CHMP/SAWP/69686/04 Rev 17 and the appropriate EMA website	
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	9	235/4.2	The Committee for Scientific Consistency and Quality for Joint Scientific Consultation (CSCQ JSC) is a standing committee	Thank you for your comment. The full text of the abbreviation has already been introduced. The further addition proposed is not considered mandatory.
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	9	244/4.2	… and provide feedback	Thank you for your comment. This has been adjusted.
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	9	246-247/4.2	Repetition: The JSC Hands-on Group (JSC HOG) represents all partners involved in a specific JSC.	Thank you for your comment. This has been adjusted.
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	10	271/4.2	Is phase 3 not typically concerned as pivotal CTs, whereas phase 2/3 (small patient populations) as pivotal CTs for ATMPs?	Thank you for your comment. This is correct. Therefore, the requirements stated regarding the consultation on PLEG are considered correct.
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	10	281/4.3.1	the HTA regulation (HTAR)	Thank you for your comment. Adding the link is not considered mandatory.
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	10	286/4.3.1	after finalizing the call?	Thank you for your comment. The wording has been corrected.
	Natalia Haraszkiewicz-	10	291/4.3.1	a regular Scientific Advice procedure with EMA?	Thank you for your comment. Yes,

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	Birkemeier, BioPharma First Consultancy				if a product is not selected for a parallel EMA/EUnetHTA 21 JSC, it can still apply for a regular EMA advice.
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	10	291/4.3.1	For more information on Parallel EMA/HTA body (HTAb) Scientific Advice during Interim Period refer to the appropriate EUnetHTA 21 website	Thank you for your comment. This is out of scope of this guidance.
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	11	326/4.3.1	4,5 months?	Thanks for your comment. For clarity, this has been corrected to "four and a half months".
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	11	331/4.3.1	In the published timeline scheme	Thank you for your comment. This has been adjusted.
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy		335	How about other experts, e.g., the Committee for Advanced Therapies (CAT), statisticians when assessing ATMPs?	Thank you for your comment. In alignment with the Guidance D7.2/3 we have included a sentence: “Other experts with specific expertise may also be involved if there is an explicit need.”
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	12	341/4.4	For interaction between the EMA, patients and consumers, and their organisations (EMA/637573/2014) as indicated in the EMA document Engagement framework: European Medicines Agency and patients, consumers and their organisations (europa.eu) EMA/649909/2021 and Mandate, objectives and composition of the Patients and Consumers Working Party (PCWP) EMA/563123/2018 Rev. 4 issued by Stakeholders and Communication Division	Thank you for your comment. The proposed addition is not considered mandatory.

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	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	12	345/4.4	EMA exchanges information?	Thank you for your comment. Sentence has been corrected.
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	12	348/4.4	to involving experts, patients and representatives as well as HCPs	Thank you for your comment. Patient expert and clinical expert are the comprehensive terms.
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	12	362/4.4	exchanges information with EMA	Thank you for your comment. This has been adjusted.
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	12	370/5.1	the IRIS platform	Thank you for your comment. The footnote has been included earlier in the document.
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	12	372/5.1	Pre-submission Teleconference (TC)	Thank you for your comment. This has been adjusted.
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	12	373/5.1	Is it not ca. 20 working days (4 weeks) starting from the application submission (no preparatory meeting) till SAWP1 (start procedure)? How about the summer period?	Thank you for your comment. Timelines need to be adjusted to SAWP meeting weeks, summer breaks etc. Therefore, only a rough estimation of the timeline can be provided. The concrete JSC timeline is shared with the HTD several weeks before the submission of the draft briefing document.
	Natalia Haraszkiewicz-Birkemeier,	12	374/5.1	Is it not ca. 48 days (10 weeks) starting from the SAWP1 (start procedure) till SAWP3 (discussion	Thank you, please refer to the response above.

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	BioPharma First Consultancy			meeting)? How about the summer period?	
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	12	380/5.1	day 40	Thank you for your comment. As correctly stated in the guidance, it is day -40 (minus forty).
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	13	383/5.2	the IRIS platform	Thank you for your comment. The footnote has been included earlier in the document.
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	13	389/5.2	What is considered as the starting point in the 40- and 70- working (?) days procedure? How is the length established?	Thank you for your comment. The deadlines are set according to the standard EMA procedure. The days are calculated back from D0, i.e. from the acceptance of the final briefing package.
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	13	399-400/5.2	Within 15 working days? What is the starting point? Maybe it could be useful to include 2 schemes with timelines (one for internal use, the other one for TDs? Maybe schemes presented in the Microsoft Word - FINAL Revision December 2008 - Time allowed to Aplicants to Answer LoQ-LoOIs .doc (europa.eu) and the publication EU Regulatory Pathways for ATMPs: Standard, Accelerated and Adaptive Pathways to Marketing Authorisation (cell.com) could be helpful?	Thank you for your comment. As stated in the guidance document, the EMA and HTA submit comments on the draft submission documents within 15 days of receipt of the draft.
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	13	418/5.2	the IRIS platform	Thank you for your comment. The footnote has been included earlier in the document.
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	14	424/5.2	(SAWP1 always takes place between Monday and Thursday)	Thank you for your comment. As correctly stated in the guidance, the documents must be submitted by Wednesday of the previous

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					week.
	Natalia Haraszkiewicz-Birkemeier, BioPharma First Consultancy	14	428-437/5.3	Maybe schemes presented in the Microsoft Word - FINAL Revision December 2008 - Time allowed to Aplicants to Answer LoQ-LoOIs .doc (europa.eu) and the publication EU Regulatory Pathways for ATMPs: Standard, Accelerated and Adaptive Pathways to Marketing Authorisation (cell.com) could be helpful?	Thank you for your comment. This will be taken into future consideration.