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The professional society for health economics and outcomes research

Improving healthcare decisions

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April 20, 2021

Dear EUnetHTA:

ISPOR – the professional society for health economics and outcomes research - is pleased to respond on behalf of its membership to your consultation entitled "**EUnetHTA WP1: A future model of HTA cooperation**."

ISPOR is a scientific and educational society with many of its members engaged in evaluation of health technologies, including pharmaceuticals, medical devices, and other interventions. We have a large membership living and working in 110 countries globally, across a range of disciplines, including health economics, epidemiology, public health, pharmaceutical administration, psychology, statistics, medicine, and more, from a variety of stakeholder perspectives, such as the life sciences industry, academia, research organizations, payers, patient groups, government (including some from European regulatory agencies), and health technology assessment bodies. The research and educational offerings presented at our conferences and in our journals are relevant to many of the issues and questions raised in this request for information.

The response to this consultation was led by the Policy Outlook Committee of our most senior advisory body, the Health Science Policy Council. To engage our membership, we consulted with interested members of our HTA, Institutional (ie, industry and consulting), and Patient Councils. We focused especially on section 4, which covered the primary tenets of your white paper. The attached spreadsheets are a synthesis of their comments. We hope they prove useful.

ISPOR would be happy to answer any questions about our response, as well as to participate in any follow-up consultations on the relevant program items mentioned within the report.

Sincerely,

Nancy S. Berg
CEO & Executive Director
ISPOR

Section	line(s)	Comments
1	260 - 264	It would be important to understand not only the extent and type of changes required at the country level for this collaboration to work but also how feasible is for them to take place. For those changes deemed feasible, it is relevant to estimate the timeframe required for these changes to occur in each country.
2	302-305	The EUnetHTA joint collaboration initiative (JA3) has grown to 81 organisations from 29 countries. As such, individuals HTA needs, concerns/willingness to participate, and expectations related to this voluntary HTA cooperation project are likely to differ greatly between mature and less mature HTA organisations. In this context, it would be very useful to have a better understanding of the individual responses to this prioritisation exercise in order to identify areas of shared unmet need versus those areas with divergent results. The latter category will necessitate further discussion and alignment to minimize the risk of acting as barriers challenging the sustainability of this exercise. This information could inform a more pragmatic, progressive and time-bound implementation strategy.
4.1	377-397	While we recognize that this consultation is focused on process aspects of HTA cooperation, ISPOR's stakeholders feel it is important to recognize some broader goals of HTA coordination as well, both for context and because they may inform process aspects. These broader goals should include: • enabling earlier access to therapies across the region due to efficiencies in assessment and minimizing local duplication of effort • more systematic addressing of unmet healthcare needs • achieving uniformly high scientific standards and systematic use of best practices in assessment • better information sharing with the general public about product evaluation and innovation • transparency about the existence and nature of dissenting opinions or non-alignment with the conclusions of the assessment • more consistent, predictable assessment results across countries • a commitment by participating countries to use the assessment results in their decision-making or to provide a rationale for not using them.

4.1	376 – 397	There would be value in trying to differentiate Joint Collaboration versus Alignment goals and the resultant (and likely different) associated activities. Most proposed objectives in this section seem to support a Collaboration goal. The exception probably being objective # 6 which seems to pursue an Alignment goal. As an example, Early Dialogues are likely to constitute a very useful joint exercise in itself. The challenge would be to aim for full alignment on the outputs of these dialogues. As such, it would be very important to be clear between Joint Collaboration and Alignment purposes/inputs/processes/outputs at every stage of the process in order to carefully assess feasibility and upstream/downstream implications. Efforts aimed at optimising collaboration between EU HTA agencies are likely to be a more efficient, effective and realistic endeavour vis-a-vis Alignment goals – at least in the short-term -. This is mainly due to high heterogeneity across HTA agencies in term of a) Core procedural and resourcing areas including their remit, scope, legal framework, capacity and technical capability and b) Country-specific Economic, Societal, Cultural and Ethical factors driving the evolution of Pricing, Reimbursement and/or HTA processes These differences explain to a great extent discrepancies on how value is defined, identified, assessed and ultimately rewarded – even if only the clinical component of it. Consequently, and in the context of this effort being a voluntary one, collaboration activities (which are more likely to flow from more established HTA agencies to those less so) could be more easily endorsed/implemented in the short term. Furthermore, a stepwise approach (collaboration --> alignment) might also assuage concerns (from HTA agencies and other stakeholders) about additional processes, incremental workload and the potential diversion of already limited human and financial resources.
4.1	381	Being completely unbiased may be difficult to achieve in every case due to participant affiliations, a factor which was recognized in the discussions around the new definition of HTA that was endorsed by EUnetHTA. A more realistic objective may be to minimize bias and strive for objectivity in the assessment process. Also, the term "ethical" belongs in this definition.
4.1	383	Is the phrase "as much as possible" necessary here? Seems like "suppprt" makes the intent clear enough without it.
4.1	390-391	Suggested additions in italics. "The mechanism of HTA cooperation should be one that participants *understand clearly*, want to and are able to engage in, and benefit from."
4.1	395-397	Suggested additions in italics. "HTA cooperation should have sufficient flexibility to adapt and be adapted to differing and changing healthcare systems, *objectives, stakeholders* and decision-making *frameworks*, and evolution in the HTA landscape."

4.2	398-496	We were pleased to see the inclusion of the PLEG component as most HTA collaborations to date have focused on early dialogue and joint/collaborative assessments. Taking this approach will allow for participating countries to collaborate in the output(s) of most imporatnce to their individual needs thereby supporting the voluntary nature of this HTA collaborative model. It is also nice to see that there will be other areas of focus for future collaboration such as horizon scanning and information exchange as described in section 4.3.
4.2	406-407	HTA may not only inform resource allocation decisions - evidence produced for HTA, particularly PLEG, may be used for market authorizations in the future
4.2.1	413-447	Excellent description of the purpose of early dialogue with sponsors, including the menu of ED opportunities (single HTA, multi-HTA, joint with EMA, drugs or devices, etc.). It would also be interesting to see joint ED with established Scientific Advice programs outside of Europe in the future (NICE, CADTH, PBAC, etc.)
4.2.1	413-447	ED might be especially useful to set up evidence generation requirements if the product definition goes beyond a single health technology (MD+drug, MD+AI software, etc)
4.2.1	413-447	The comments are factually correct, however potentially missing an opportunity. Early dialogues have been a key success of EUnetHTA. HTA advice was a concept in early development prior to the EUnetHTA collaboration, which EUnetHTA JA1 adopted, developed, and now owns. There is a clear desire for multi and parallel advice from companies, and the growing demand demonstrates it is delivering value, which works through the entire stakeholder chain, delivering better evidence for decision makers, and therefore supporting appropriate access for patients. However – Limited /restricted capacity is an issue. Suggested addition: The report should make a case for increasing capacity in this key activity that all stakeholders see value in.
4.2.1	413 – 447	It would be important to identify efficiencies/synergies between these two processes as well as how conflicting requests/feedback amongs EMA and HTA bodies and between HTA bodies are handled/discussed/priortised/reported. This would ensure outputs from these consultations provide unambiguous, realistic, harmonised and implementable guidance to manufacturers. An exercise aimed at satisfiying the needs of various HTA bodies could benefit from identifying and distilling core evidence requirements shared by HTA agencies from those evidence needs arising from HTA-specific perspectives on key areas including but not limited to handling of uncertainty, evidence networks, treatment switching, OS extrapolation). Reporting Early Dialogues outputs in such a discriminative fashion is likely to help manufacturers who would benefit from a harmonised and aligned set of core evidence requirements from EU HTA agencies. At the same time, reporting areas of heterogeneity/discrepancy in terms of HTA evidence needs would provide useful information for manuracturers and could also signal areas where greater alignment can be explored.

4.2.1	414	If ED outcomes are not binding, what ensures that it is worthwhile for manufacturers and HTA bodies to engage in the dialog? We understand that it is infeasible for them to be completely binding given current uncertainties and the potential for changing circumstances in the future, and that the principal intent of ED is to reduce - but not eliminate - mutual uncertainty about the evidence that should be and will be produced. However, some symmetry of accountability also seems reasonable. If sponsors are judged by whether they followed the guidance, and are expected to explain deviations from it, HTA agencies should be held similarly accountable if the guidance is followed.
4.2.1	415- 416	Suggested change in italics. "… appropriateness of data *collected and* evidence produced …"
4.2.1	421	replace "relevant outcomes" by "patient-relevant and clinically meaningful outcomes"
4.2.1	422	Would encourage the allowance of dialogues on the economic evidence generation plan. Currently, this is written as 'possibly', and leaves it unclear whether the option rests with EUNETHTA, the applicant, or others.
4.2.1	424	replace "could be developed to fulfil HTA requirements across multiple countries." by "could be developed to address patient unmet needs and fulfil HTA requirements across multiple countries."
4.2.1	425	Will these procedures cover IVD and digital technologies in the future ?
4.2.1	429	Will this apply to medical device procedures (multi-HTA?)
4.2.1	434-435	replace "Consultations allow medicine developers to obtain feedback from regulators and HTA bodies on their development plans" by "Consultations allow medicine developers to obtain feedback from regulators and HTA bodies, as well as patient organisations and advocates, on their development plans"
4.2.1	442	replace "obtain simultaneous feedback on their development plans from multiple HTA bodies" by "obtain simultaneous feedback on their development plans from multiple HTA bodies with the input of patient organisations and advocates"
4.2.1	442-443	replace "generate optimal and strong evidence that satisfies the needs of both regulators and HTA bodies." by "generate optimal and robust evidence that both satisfies the needs of regulators and HTA bodies and matter to patients."
4.2.2	448 –470	A joint assessment of the relative effectiveness of a technology which aims to feed into national HTA procedures is likely to be one of the most challenging steps in a PTJA. In consequence, a thorough, transparent and detailed evaluation of how REAs identify, handle and report common and different HTA value paradigms and evidence/methodological needs is a fundamental and valuable requirement for all stakeholders.
4.2.2	448-470	The differences between a JA and a CA are not fully clear in the paper; however, we would expect that the companion documents would provide further detail. Future expansion of JA/CA could perhaps focus on collaborative approaches for components of HTA beyond those included in the REA (largely just the effectiveness and safety). For example, could there also be collaboration in patient engagement, ethics review, etc.

4.2.2	455	Please clarify – this section identifies that Collaborative Assessments are only produced for (non-drug) Other Technologies (OT). It elaborates that these are usually not single technologies, and not restricted to a specific time point in a regulatory pathway. Suggested addition: To clarify for those developing the framework of the future collaboration, the report should emphasis that the JA process discussed in lines 449-454 has been designed specifically with the EMA regulatory process for pharmaceuticals in mind.
4.2.2	458	For Other Technologies (OT): "Dialogues with industry are optional" - we understand that there are a multitude of device and 'other' technologies, but optionality to go/no-go with CA should be collaboratively decided.
4.2.2	468-469	For those OTJA and OTCA that are multiple technology assessments, collaboration across all relevant stakeholders should be allowable and industry optionality to include or not include may be considered.
4.2.2	470	Is there a timeline being described for JA/CA?
4.2.2	470	Also, the guidelines and recommendations for the HTA outcomes' implementation on a country level is missing especially for those jurisdictions that were not part of JA/CA process
4.2.3	471-496	This is an area of growing importance involving the collection and analysis of RWE, and the conduct of reassessments. Collaboration in these areas will be critical to the evolution of HTA if we are to promote patient access to technologies that have significant uncertainty following market approval by the EMA.
4.2.3	471 – 496	**1. Product-specific PLEG projects** Greater clarity on what “compiling” means in the context of Product-specific PLEG projects would be useful. The comments below assume that Compilation is defined as: operations performed on data to derive new information according to a given set of rules. • A decision to compile local evidence needs to be preceded by a transparent discussion and a robust evaluation of key evidence areas that HTA agencies deem relevant and appropriate to benefit from a common data set analysis (es) (e.g. safety and PROs) given intrinsic differences across healthcare systems and HTA agencies (as previously discussed). • Subsequently, differences in timelines for issuing guidance across HTA bodies (e.g. coverage with evidence development decisions) need to be factored to ensure the availability of timely analysis outputs. **2. Registry PLEG projects** Aligned data collection procedures and quality assurance principles for local data sources deemed eligible for compilation need to be in place. This will ensure that, at the local level, there is a robust and integrated system for collecting, cleaning, storing, monitoring, reviewing, and reporting on data—which will determine the utility of compiling data for meeting the ultimate goals of Product-specific PLEG projects In general, It is of great importance to set up the list of "must to be met" standards/checklists to ensure the balance between governance for data rigidity and flexibility for setting specific limitations on data use.

4.2.3	474	Please add how PLEG can help address conditional approval scenarios, esp for rare oncology conditions, where there are no approved treatments prior to conditional approval and RCT is not possible since it would be unethical to deny patient conditionally approved treatment. PLEG may provide an option for full approval. Please consider adding language that allows EMA/EUnetHTA parallel HTA route in such a scenario.
4.2.3	480-483	As with early dialogue, we would encourage symmetry of accountability for sponsors and HTA agencies here
4.2.3	480-483	Leveraging registries and existing infrastructure for dual-purposes should be encouraged, where feasible. EUnetHTA should coordinate with EMA to proactively create registries beneficial and sufficient for both agencies' purposes.
4.2.3	484	Just for clarity, it may be useful to provide a description or reference as to what is included in the term "registry"
4.3	497-554	It is excellent to see the inclusion of future areas amenable to HTA collaboration. ISPOR would be pleased to work with EU participating nations on developing joint and collaborative approaches to these additional areas of cooperation. An additional area to be considered is to establish a framework for continuous collaboration on the methodological advancements especially with respect to new types of health technologies and encourage countries to establish "shortcuts" for innovation
4.3.1	504-510	For the areas listed as outside of scope, it is unclear the degree to which they may be mandatory/expected/optional. Some clarification would be helpful here.
4.3.1	511-523	It would be good to see the POP and EVIDENT databases become publicly accessible, to the extent confidentiality concerns allow, with perhaps an opportunity for countries outside of the EU contributing data.
4.3.1	522	Areas of expansion included in Table 4.4. seem reasonable and appropriate. Greater clarity on each of these areas (including the source, type and level of information included in Prices and pricing strategies) would be important when available
4.3.2	524 - 532	Areas of expansion included in Table 4.5. seem reasonable and appropriate. Greater clarity on each of these areas, including confidentiality considerations, would be important when available
4.3.3	533-547	While each of these area of assessment have some potential for collaboration, perhaps some on a global basis, they each involve complexities beyond basic REA that are related to differences in healthcare systems, etc., and would necessitate much, much more discussion. Given that it is a "speculative" section, it seems out of place here.
4.3.4	548-555	Expertise early in the process is often associated with potential conflicts of interest. Flexibility in navigating and mitigating these potential conflicts to allow for high-quality scientific outputs should be encouraged.

4.3.4	548 - 555	It would be fundamental to ensure participation from all relevant stakeholders in key areas including a) defining scope for each activity, b) identifying experts and ensuring there is an appropriate representation of HTA experiences, c) agreeing on target audiences. Greater clarity on each of these areas would be important when available.
4.3.4	548-555	When judgements about fact and value conflict, you need both expert and stakeholder perspectives, so the way that expertise is characterized is too narrow. There are both stakeholder and technical perspectives that may need to be considered: • Stakeholder perspectives: Patient(s), Public, Providers of care, Payers, Producers and innovators of technology, Principal investigators in research, Policy makers • Technical perspectives: experts and specialists in: Medicine, Law, Ethics, Economics, Epidemiology, Patient and Public Involvement and Engagement, Innovation and commercialization, Medical devices (e.g., bioengineering)
4.3.4	548-555	Sharing of expertise across regions would be particularly helpful in assessing technologies for rare and ultra rare diseases, and for truly innovative technologies at product launch.
4.4	556-570	It is excellent to see the inclusion of these three sets of principles. These will be subject to debate and reconsideration, so ISPOR would recommend re-visiting these principles at set intervals.
	556-564	The report could highlight that the optimal format of the output of Joint Assessments that would facilitate uptake by Member States should be defined.
4.4	565	1. Recommend removal of the term "unbiased" in principle #1. Free from COI is sufficient. That said, expertise early in the process is often associated with potential conflicts of interest. Flexibility in navigating and mitigating these potential conflicts to allow for high-quality scientific outputs should be encouraged. Also, it must be recognized that often the HTA agency as such has financial interests with any decision they take.
4.4	565	1. Greater alignment on the definition of COI and the required reporting processes is needed when it comes to HTA processes across EU juridictions See example by following the link: https://tools.eunethta.be/glossary/www.eunethta.be/glossary/index1cd2.html?q=taxonomy/term/81
4.4	565	5-7. Ensuring timely availability of relevant, meaningful and robust information to meet the needs of HTA bodies whilst reducing unnecessary duplication and workload is likely to foster sustained HTA cooperation. As stated previously, there is value in trying to differentiate joint Collaboration/Cooperation goals versus Alignment goals and the resultant (and likely different) associated activities.

4.4	565	10. The notion of HTA being conducted too early necessitates to be discussed carefully. EMA remains committed to accelerate patients' access to medicines that address unmet medical needs via accelerated assessments and conditional marketing authorisations. These types of regulatory approvals are often based on more limited evidence (in terms of, for example, sample size, length of follow up, or use of controlled study design). Concomitantly, HTA agencies are increasingly aiming to issue guidance on health interventions shortly after market authorization to ensure timely patient access. In this context, HTA agencies, entrusted with a different remit, often face a limited time to address uncertainties (i.e. input uncertainty) arising from existing evidence. EMA remains committed to accelerate patients' access to medicines that address unmet medical needs via accelerated assessments and conditional marketing authorisations. These types of regulatory approvals are often based on more limited evidence (in terms of, for example, sample size, length of follow up, or use of controlled study design). Concomitantly, HTA agencies are increasingly aiming to issue guidance on health interventions shortly after market authorization to ensure timely patient access. In this context, HTA agencies, entrusted with a different remit, often face a limited time to address uncertainties (i.e. input uncertainty) arising from existing evidence.
4.4	565	12. Cooperation must remain relevant: while cooperating agencies and bodies may locally contextualize the EU-wide output, they should be helping to unify health care technology access across Europe. In short, contribution and collaboration within the EUNETHTA collaborative process should be encouraged to highly inform local decisions and towards the aims of JA3: Access, Efficiency, and predictability. To that end, accountability of the cooperating planning agencies in their planning and scoping opinions should be encouraged and help to foster predictability of usage of the HTA output.
4.4	568	These are very comprehensive. We are pleased to see the comment about using the "best available evidence to ensure a timely and adequate response", and that the output allows for independent contextualization and decision-making at the national level. These principles will foster participation. However, there are a few specific concerns, listed below.
4.4	568	1-2. Gaining alignment on what outcomes (PICO) are deemed relevant and appropriate across EU HTA agencies at the time of conducting and issuing guidance highlights some potential challenges and exemplifies the importance of trying to differentiate joint Collaboration/Cooperation goals versus Alignment goals. This distinction could inform decisions on what type of activities can be implemented and when this implementation seems more appropriate/realistic.
4.4	568	8-9.Publication without any redaction is likely to create challenges, especially in terms of meeting GDPR requirements, and ensuring patient privacy. There would need to be some flexibility to this.
4.4	568	9. We have concerns about the sharing of all data and analyses with all parties, especially if the submitted data package has to meet th e requirements of all the member states. For example, different member states request different types of subgroup analyses, some of which would not be pre- specified or considered statistically robust. Submitting a suite of different analyses to meet all needs and to share these broadly risk s multiplicity of testing, sub-groups which may be underpowered or may not follow randomization or may show spurious association, and inappropriate interpretation of results.

4.4	568	9. Complete data without redaction and without confidentiality will also make industry hesitant to fully participate. Some confidentiality to protect academic publishing interests, subjects personal information confidentiality concerns, etc. are relevant. For IP protection, submitters (pharmaceutical companies/device mfgs) should be able to redact confidential/sensitive/high uncertainty information. The distinct remit, timing, process and related evidence/data requirements between a single regulatory agency (EMA) and EU HTA agencies needs to be considered for the purpose of sharing specific regulatory data.
4.4	569	Excellent principles that will promote transparency by internal and external participants. It would be nice to see a principle promoting international participation and cooperation beyond the EU.
4.4	569	We would encourage more explicit consideration of the use of deliberative processes in your plan for external participation. Table 4-1 the term "participation" but then characterizes this as expert "contribution" and "input", including "input from technology developers would argue that in order for processes to be truly participatory, it needs to go beyond "input" or "consultation" and actually allow fo exchange of views for the purpose of mutual understanding. An ISPOR task force that's reporting out this June (https://www.ispor.org/member-groups/task-forces/joint-htai---ispor-deliberative-processes-for-hta) is working to develop a consens definition for a deliberative process from an HTA perspective and internationally recognized good practice recommendations on the u deliberative processes in HTA that highlights the need for participation and the exchange of perspectives. We would hope that this re be useful in this respect as the plan for EU HTA collaboration progresses.
4.4	569	Table 4-10: Suggested addition – Consider new Principle – Relevance/value/format of outputs of HTA cooperation (specifically (JAs) to intended member State users is important.
4.4	569	Table 4-10: Suggested addition - Confidence in other contributors across the network to HTA activities is important.
4.4	569	6. Replace "While HTA is a scientific and technical exercise, it must be understood by a wide variety of stakeholders" by "While HTA is a scientific and technical exercise, it must be understood by a wide variety of stakeholders, including consumers and patients"
5	611	5.2 Lessons Learned: This is a good summary. However suggested addition: Please make a comment on requirements for JAs to replace, and not be just adiditonal information to local HTA activity.
5	698	5.4 Recommendations for Future Work – Section 5 recognises that different HTA agencies have different potocols outlining engagement with industry. For a future collaboration to engage stakeholders meaningfully to be sucessful in improving efficiency and reducing local duplication, it will need to reflect best practice of stakeholder engagement from Member States, not the lowest common practice. With this in mind, we would suggest adding after Line 702; Stakeholder engagement in specific HTA activities (eg scoping of an assessment) should reflect the best engagement practices within member states.
6.1	709	Unclear from the document if this is the case, but if not - the standing scientific oversight committee should have a representative on the executive board. (this may already be the case through the subgroups)

6.1	738	Confidentiality agreement: many of the experts involved in HTA may have an interest in publication of the HTA process, findings, or produce similar research in parallel. Policies and safe harbor to ensure expertise without hampering scientific development independent to EUNETHTA would be beneficial to ensure expertise is available.
6.2	756	Access to expert knowledge: many of the experts EUNETHTA may call upon are independent of EUNETHTA. Such independence is beneficial, but developing governance policies to provide meaningful benefits for the experts beyond financial reimbursment should be explored (citations, recognition, grants, etc.)
6.3	792	Declaration of interest should be flexible to allow for, and appropriately compartmentalize and moderate potential conflicts of interest while engaging in the collaborative process. Many experts will have potential conflicts of interest and EUNETHTA should consider the balance between informed experts and these conflicts. It is likely that the benefits of expertise outweigh those of conflicts, and that these conflicts can be managed.
6.4	802	N/A - Agree that definition of the expert groups is needed, and policiies beneficial to the maintainence of these expert groups when engaging in EUNETHTA collaboration should be explored to ensure that EUNETHTA participation doesn't dilute these expert groups or pressure their capacity to serve EUNETHTA.
7	821	Should read „work package leads“.
7	825	Figure 7-1 does not best illustrate management of support function, there should be a clear destinction between Secretariat and work packages and which areas each supports on its own or in combination.
7	881	Should read “Some centralised support structures…”
7	888	Should read „Define the roles, remits and scope of each of the support functions...“
8	891	The recommendations seem sound as their next step would be to look at the feasibility of having common IT tools rather than an implementation of them.
8	927	Table 8-3 JA3 IT tools: The Core model is an excellent conceptual tool for HTA, explaining the core and additional domains. However it was also developed (previously) into a tactical tool, to assist report compilation. Unfortunately it is now an example of tool development within eunethta without thinking of the intended end user. During JA2 it was dropped as a tactical tool for being too complex and unwieldy, even for the report authors. Whilst this may seem a minor point, it is a KEY LEARNING, if the expectation is for outputs of the HTA cooperation to replace local HTA activity. The outputs must be designed with the end-user in mind, not just from the ease of the report producers.

8	959	Section 8.3: Recommendations for a future model of HTA Cooperation: Suggested Addition: - This section would benefit from including a recognition that and IT design should be undertaken with the End User in mind, especially if they are outside the HTA community (see pt 10 above for example).
9	1162	Add: Communication platform/rules to facilitate timely decision.
9	1168	Establishing rules for reactive topic identifications to effectively accomodate identification by different stakeholders: patient groups, professional groups.
10	1244	The Early dialogues should not form part of the evidence package for joint assessment, because 1.This may bias the intrepretation of the results, 2. The evidence package may be publically available and this advice is confidential.
10	1264 – 1277	We welcome the pragmatic proposals around reviewing and updating guidance, however at present it is not clear how these would / could be operationalised within the HTA cooperation framework. This has not been part of the process so far and will be an important area for consideration, and stakeholder input during the finalisation of processes. We should seek to avoid unnecessary re-assessment, whilst also using the most recent data. The way the outputs are used by the members states, and therefore what the outcome means in practice will be key in determining when it is, or is not approporiuate to review, and how we develop alternatives way to ensure the most up to date data/evidence are easily used
10	1282	Suggested Addition: 10.4 Recommendations for future work: this should include designing a format of the output that will faciliate local uptake (and non-duplication) by member states.
11	1335	In the listed experience there is nowhere HEOR experience requested.
11	1393	Here it is mentioned staff needs to have the appropriate experience, but this experience is not defined. Defining what is required to do good HTA would be a future task.
12	1419	It is excellent that they have included this section in the document because it is very easy for a project to miss deadlines, get lost or derailed, and to be very inefficient if there is not good project management. Most HTA agencies have learned this through trial and error and have developed project management teams and procedures that have been embedded within their project work.
12	1419	ISPOR is very supportive of the recommended approach to activity management as described in the document. Establishing sound and efficient procedures for managing both centralised and decentralised projects will be critical to the success of HTA Cooperation in the EU.
12	1431	Excellent: There is a clearly defined process for conflict resolution.
12	1440	Table 12-2 provides a detailed list of activity management processes to support ED, JA/CA, and PLEG. The list is comprehensive, sensible, appears efficient, and was developed based on lessons learned during JA3.
12	1478-80	Extremely important concept – strongly support this approach of early involvement of groups providing insight and approval. This should extend to external scientific organizations and societies such as ISPOR.

12	1580	ISPOR recommends the development of a detailed and publicly accessible procedural manual to fully describe the activity management processes.
13	1581	Whilst we recognise the scope should be set by the reviewers, Suggest adding that Companies should have input into the development of the scope, as they were key in developing the research programme identifying the original intended patient population, indication, comparator choice and expected outcomes. Whilst the final decision rests with the authors, companies should have a voice to justify their development plan, rather than simply being told what the PICO will be, without consultation.
13	1561	it is important to understand regulatory scenario for oncology products or areas of higher unmet need where PRIME, BTD, fast-tracked or orphan desginations enjoy regulatory path that needs to be appropriately appreciated by EUnetHTA. Many countries do.
13	1591	feedback box: can this be further standardized in the PICO format? How binding can this be made to gain some teeth?
14	1600	replace "of patients or patient experts" by "patients, patient group representatives or patient experts"
14	1625	there isn't enough clarity in which typology of "patients" we are considering in each HTA process: which stakeholder do we seek to involve to gain patient input: (1) patients (naïve or non expert), (2) expert patients or (3) representatives of patient organisations or is it that patient engagement is understood as any of the above? The type of input will vary from one category to the other and it is important to clarify "Who" and "identification and recruitment"
16	1784	Another thing to consider here: how the collaboration between regulators and HTA agencies is to ensure faster & more equal access to treatment across jurisdictions (what kind of potential deliverables of regulatory/HTA are to be expected in that respect)
16	1784	And another thing to consider: how the data sharing should be channeled to strike the balance between the transparency of HTA/regulatory collaboration and data confidentiality to ensure public interests and manufacturers' right to confidentiality
16	1784	Are there any differences in the collaboration between regulators and HTA agencies per types of health technologies?
16	1849	The dialog with respect to specifically ED and PLEG is a very important pillar of collaboration between regulators and HTA bodies should be perhaps further reinforced
16	1851	The need to promote the best possible evidence development plans seems a bit unclear
16	1860	The notion of confidentiality framework should be very welcomed but requires further details.
17	1960	17.4 Recommendations for Future Work – Suggest adding a recommendation to ensure the templates for future JA outputs are designed with the end-user in mind, not just from the ease of the report producers. This will assist local uptake, and reduce local duplication, a key objective of any future HTA Cooperation