



# eunetha

EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

**WORK PACKAGE 5 JOINT ACTION:  
RELATIVE EFFECTIVENESS ASSESSMENT OF PHARMACEUTICALS**

**HTA Core Model® for Rapid Relative Effectiveness Assessment of Pharmaceuticals**

**Public consultation: List with comments and responses**

**February 2013**

### Public consultation of WP5 HTA Core Model for Rapid Relative Effectiveness Assessment of Pharmaceuticals

The draft HTA Core Model for Rapid Relative Effectiveness Assessment of Pharmaceutical under production by Work Package 5 Joint Action 1 was open for public consultation from 1 October 2012 to 30 November 2012.

### Objective of the Model

It is the objective of work package 5 (WP5) to develop HTA tools and methods for relative effectiveness assessment (REA) of pharmaceuticals. For this purpose the HTA Core Model was adapted into a version that specifically aims at REA of pharmaceuticals: the HTA Core Model for Rapid Relative Effectiveness Assessment of Pharmaceuticals.

### List with commentators

The list below provides the contact information of all the organisations that properly submitted contributions as part of the public consultation.

	Comments provided by	Abbreviation
1.	Association of the European Self-Medication Industry George Yiangou (g.yiangou@aesgp.eu) 7 avenue de Tervuren, 1040 Brussels, Belgium Tel: +3227355130	AESGP
2.	EuropaBio Aleksandra Krygiel-Nael ( <a href="mailto:a.krygiel@europabio.org">a.krygiel@europabio.org</a> ) Avenue de l'Armée 6, 1040 Brussels Belgium Tel : +32 2 739 11 82	EuropaBio
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4.	Novartis Jennifer Cain Birkmose (Jennifer.cain@novartis.com) Novartis Campus, Forum 1, CH 4051, Switzerland Tel: +41797857397	Novartis
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6.	Healthcare Improvement Scotland Heather McIntosh (heather.mcintosh1@nhs.net) Delta House, 50 West Nile St, Glasgow, G1 2PN, Scotland, UK Tel: +441412256980	HIS

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Relative Effectiveness Assessment (REA) of Pharmaceuticals

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1.	AESGP	General comments	AESGP welcomes the public consultation on the HTA Core Model for Rapid Relative Effectiveness Assessment of Pharmaceuticals. As some issues have already been raised and addressed within the Stakeholder Advisory Group, we would like to use this occasion to take note of the following: The objectives set by WP5 with regard to the rapid REA Core Model are to a great extent successfully met with this document. A challenge lies ahead with the application of the rapid REA Core Model in different pilot assessments in the second Joint Action of EUnetHTA. This will allow for a concrete assessment on whether the model can be broadly applied and help identify areas where modifications or improvements may be required for the delivery of results in a timely, transparent, efficient and replicable manner.	Thank you for this comment. And, indeed the Model will be further improved, based on the experiences from the pilots.
2.	EuropaBio	General	We would appreciate that the guidelines also include a specific decision-making framework. HTA is best understood as tool to inform and enable consistent decision making about the adoption of a health technology within a specific healthcare system and its associated financing system. In the absence of such a context it is difficult to assess the likely utility of the guidelines or core model.	It has been a deliberate choice not to include decision making frameworks in the model. This is because the aim of the model is to assist in defining and producing core information which can be utilized by the HTA organisations of all Member States when they develop their local HTA with local guidance on decisions. That is why the guidance in the Model targets at scientific rigor, and not clear guidance for decision making.
3.	EuropaBio	General	It is appropriate that REAs be sponsor submission driven.	Thank you for the comment.
4.	EuropaBio	General	The HTA Rapid REA Model v2.3 needs some additional clarity about the nature of the data sources to be used in the assessment process. The focus of the current version is upon two key data sources that are to be the manufacturer's submission and the EPAR [e.g. page 7, lines 42-46]. However, the document indicates that the rapid assessment may relate to either a new pharmaceutical launched onto the market or a pharmaceutical for a new indication or with new relevant data [page 7, lines 17-20], the focus of the rapid model pilots will be on assessment of new pharmaceuticals in parallel with the marketing authorisation process of the EMA. Although this is not specified in the document, it is implied that the assessment will occur prior to the generation of any 'real-world' data and that it will thus be limited to assessment of RCT data. This creates a fundamental problem with the document as these two different processes (pre-authorisation rapid assessment vs. post-authorisation rapid assessment) are mixed into the	The pilot assessments in WP5 JA2 will not be limited to only new pharmaceuticals at the time of market authorization. The Model should be useful for a new pharmaceutical launched onto the market or a pharmaceutical for a new indication or with new relevant data. The pilots in WP5 JA2 should show whether the Model is suitable for both purposes and whether further specifications are required.

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			descriptions of the assessment methodologies. It would be very beneficial to separate the two processes and, considering the focus of the pilots in 2013, to focus only on rapid assessment of new pharmaceuticals prior to market authorisation at the EMA.	
5.	EuropaBio	General	In the context of new pharmaceuticals being assessed prior to the EU Commission Decision, it is important to note that the EPAR will not be available until up to 15 days after the Commission Decision. It may be possible for the rapid REA assessment to use the CHMP Assessment Report which contains the key information regarding safety and efficacy required by the EUnetHTA process. However under the current EMA process, the CHMP Assessment Report will contain commercially confidential information as well as internally confidential information (e.g. names of reviewers) and is not as complete as the full EPAR. At Day 45 post the CHMP positive opinion the first draft of the EPAR is formally adopted by the CHMP and at this stage the confidentiality issues should have been identified and resolved. Therefore, the information available from the EMA for rapid assessment needs further clarification including detail about the proposed information exchange between the EMA and the EUnetHTA reviewers.	For pilots in WP5 JA2 that start pre-market authorisation it is indeed the intention to work with the CHMP assessment report (to be provided by the manufacturer as this is not publicly available). Once the final EPAR is available, a check will be made by comparing the EPAR with the content of the draft assessment.
6.	EuropaBio	General	While we recognise that a template for the manufacturer's submission is to be developed under Joint Action 2, it is clear that the rapid REA will be reliant on this submission and so there should be more explicit focus in the model about what exactly the manufacturer will be providing for all four domains. It is unclear whether the manufacturer will be required to provide information about differences in standard of care, usage or dosage patterns of comparators across the EU Member States. In addition, there needs to be a description of the mechanism by which the assessors can request clarifications from the manufacturer during the review process and how the manufacturer can have the opportunity to review the rapid REA assessment so as to ensure that their submission has been correctly interpreted.	These are good suggestions for harmonizing submission file and the Model, and being explicit what is required for a submission file from the point of view of HTA. This is an activity that will proceed during JA2. We have stored these suggestions for future use. It should be noted that the Model is a tool for producing rigor HTA information. Details on for example reviewing mechanisms may better be described in a procedure manual. A procedure manual for doing the pilots in WP5 JA2 will be produced in the early phase of JA2.
7.	EuropaBio	General	It is fundamental to the understanding of the rapid REA model that the process by which the assessment will be conducted is made explicit. Unfortunately, in version 2.3 of the model, very limited information about the process is provided. The process description is limited to a statement that the review will be limited to two authoring agencies that will review the product across all of the domains of the model followed by an in-depth review by 'several' agencies	Describing the process has not been included in the original HTA Core Model as the Model is a tool for producing rigor HTA information. Details on the process may be better described in a procedure manual. A procedure manual for doing the pilots in WP5 JA2 will be

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			(Page 71, lines 34-35, plus p72, lines 1-2). In a slide presentation by the WP5 leaders (W. Goettsch and S. Kleijnen, October 11, 2012) more detail on the planned process with respect to the forthcoming rapid REA pilots is provided. These slides make it very clear that the process is envisaged to commence with dual submission to the EMA for Regulatory approval and to the EUnetHTA process with submission of a concept file with the REA process commencing at the time of the CHMP positive opinion. It would have been helpful for this information to have been included into the rapid REA model and we recommend that this information is built into the next version of the model.	produced in the early phase of JA2. This procedure manual will be based on discussions with WP5 members and industry and will also be subject to consultation by the Stakeholder Advisory Group (SAG). Based on the experience gained in the pilots in WP5 JA2 the procedure manual will be further improved.
8.	EuropaBio	General	The document indicates that there will be two authoring agencies followed by multi-agency review. It would be helpful to expand upon this. Is the intention to follow a rapporteur/co-rapporteur model with a reviewing CHMP-style HTA committee? A clear description of the assessment process is required including specification as to which agencies will be selected as rapporteurs and co-rapporteurs. Different possibilities can be envisaged such as where a 'mature' agency will be the lead author with a 'weaker' agency joining them to help build experience; alternatively the two agencies might be selected based upon capturing diversity of systems. Secondly, how will the review be conducted? Will this be done separately by agencies or together in the form of a committee? How will conflicting opinions be resolved? How will additional information be requested, if at all, and at what stage? Thirdly, there is considerable focus on the issue of industry bias, however how will assessor bias be evaluated? Such biases may occur due to the nature of that agencies HTA system and how that agencies weights risks and benefits, or due to a local need for cost containment that may lead to more stringent reviews of products perceived to have a high budget impact.	Thank you for the suggestions for the process of REA. They will be considered for the procedure manual to be developed for the pilots in WP5 JA2. See also previous response (no 7). In addition, we would like to mention that the way of collaborating in the pilots will not be fixed in order to explore what works well. The selection of the authoring/co-authoring agencies will mainly be based on the interest of the agencies to participate in a specific topic as well as on their experience in doing these assessments.
9.	EuropaBio	General	There needs to be further clarity in the model as to how the rapid REA process will interact with the EMA regulatory approval process. The draft process from the Goettsch/Kleijnen presentation indicates that T=0 is the day of the CHMP positive opinion with steps related to scoping and manufacturer preparation of the submission file occurring prior to that date. This would require at minimum notification from the CHMP and possibly also the provision of either the CHMP Assessment Report and/or the draft EPAR at day 45. Either way there will also be a	Thank you for the suggestions for the process of REA. They will be considered for the procedure manual to be developed for the pilots in WP5 JA2. See also response to comment 7.

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			requirement for interaction prior to T=0 in order to determine the likely label that will be authorised as this will have a direct impact on the manufacturer's submission.	
10.	EuropaBio	General	The manufacture's submission will be the key document upon which the rapid REA will be conducted. As such it will be critical to build into the process the opportunity for the assessors to request clarification from the manufacturer and also for the manufacturer to have the ability to review the assessment prior to its finalisation and thus have the opportunity to provide feedback or dispute findings that they may consider inappropriate. At this stage there should also be consideration of a process for arbitration in order to resolve differences in opinion. This might also apply where there are differences between the reviewing agencies that cannot be readily resolved.	Thank you for the suggestions for the process of REA. They will be considered for the procedure manual to be developed for the pilots in WP5 JA2. See also response to comment 7.
11.	EuropaBio	General	We think that it will be important to explain how EUnetHTA propose to understand the value of this report to the Member States and we suggest that EUnetHTA consider including a mechanism to learn from and refine the process after reviewing the extent of adoption by Member States.	Mechanisms to monitor the use of the model and maximising the user experiences in Model development is an important issue and it is built in the EUnetHTA structure already. WP8 in EUnetHTA JA2 is responsible for coordinating the overall Core Model development and WP5 feeds in that process by updating the REA Model (including the process) based on the experiences from the JA2 REA-projects.
12.	EuropaBio	General	While we recognise that due to the difference in HTA and reimbursement systems at the Member State level some aspects of the findings in the report may be more or less useful for individual agencies, it is of critical importance to industry – and to the ultimate success of the model itself – that those agencies that do use some or all of the rapid assessment reports do so in a <i>consistent</i> manner. Therefore, we recommend that EUnetHTA establish a scorecard to track the dissemination and use of the rapid reports, this will also help EUnetHTA learn from their "customers" – the Member States, about the value of the report (as mentioned above).	Monitoring the use of REA model and the pilot assessments, as well as the national HTA reports prepared based on the pilot assessments is important and is already taken into consideration in the Core Model development in general. In addition, WP5 and WP3 of JA2 will put efforts in monitoring these type of data as well. However, it should be noted that actual decision making is a national competence.
13.	EuropaBio	General	It is stated the MA holder should "preferably" be consulted. This should be changed to "must be consulted", e.g. in formal scoping workshops conducted by the well-established agencies. Manufacturers have typically the deepest insights into their technologies, trial designs, populations studied, etc and their input will contribute to delivering best results.	The tools developed by EUnetHTA are guidelines and recommendations on best practices. They can not enforce behaviour such as consulting the manufacturer although we do think this is preferred way of working.

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14.	EuropaBio	General	The term "Manufacturers Submission Files" should relate to a product's HTA submission file and not the Marketing Authorisation submission. However this is not always clear in the current guidelines. The language should be therefore reviewed and clarified as appropriate.	Thank you for the comment, this has been improved.
15.	EuropaBio	General	There is a potential duplication of efficacy and safety assessments that are performed by Regulatory. –Regulatory assessments should not be duplicated by the EUnetHTA process.	The duplication of work will be controlled better in the upcoming rapid REA projects of WP5 due to the changes made in the Model and the process. In addition, the 10 pilots can provide further inside in possible reduction of overlap. The aim of the safety assessment as part of the REA is to assess the relative safety compared to products already on the market.
16.	EuropaBio	Section 3.1, page 25-30	Multiple sources are cited but not the manufacturer's submission. Pragmatically, the manufacturer's submission would constitute a significant part of this section and should be included.	Manufacturer's submission file is added as a source in most of the elements of the HPCU domain.
17.	EuropaBio	Section 3.1, page 25-30 & 3.2, page 31-34	There is in general a lack of specificity in the recommendations regarding production of the HPCU (3.1) and DCT (3.2) sections. Granted, the objective is in most cases to produce a "descriptive summary," but recommending the use of an extremely broad list of sources (see page 16), to include "Google" and "other internet search engines," is of questionable value. It would be beneficial to work towards a consistent approach to at least some of the elements in these sections, even if the selected approaches/sources are not necessarily authoritative, they should have a high degree of validity and reliability.	The value of these sources is indicated as "additional". "Additional sources may be useful to find domain-specific information" referring to table 1 with all the possible information sources..
18.	EuropaBio	Section 3.3, page 35-38 & 3.4, page 39-42	The guidance appears to call for redundant work in the safety section (3.3) and effectiveness (3.4) domains relative to what can be found in the EPAR. The focus should be beyond the scope of regulatory documents (element C0008, for example, which calls for a <u>comparative</u> safety assessment)? There is a potential duplication of efficacy and safety assessment that is performed by Regulatory. We would like to underline that regulatory assessments should not be duplicated.	The point is taken about avoiding duplicate efforts. We agree that the focus is to produce information about the balance of benefits and harms. The 10 pilots in WP5 can provide further inside in possible reduction of overlap.
19.	EuropaBio	Section 3.3,	It appears that the assessors of the REA are being asked to make judgments on safety issues. Use of the term "harms" is new within the EUnetHTA guideline. For example, would there be a	The authors of safety domain encountered the varied use of safety concepts. Moreover, in the context of



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		page 35-38	<p>consistent understanding of the difference between harm vs. ADE vs. ADR vs. serious or severe ADR. It may be inappropriate in this context and appears to come from a negative point of view.</p> <p>Some additional examples and issues are:</p> <ul style="list-style-type: none"> <li>• CTs determine relative frequencies of adverse events and suspected ADRs. How is this to be used by EUnetHTA?</li> <li>• Adverse events/suspected ADRs can be frequent and severe (e.g. a headache is frequent but not necessarily important from a safety perspective. How will these be weighed against one another? Some are more of a tolerability issue rather than an ADR.)</li> <li>• Very rare cases of hepatic effects would be of greater clinical concern. Are HTA assessors trained to make this judgement call?</li> </ul>	<p>pharmaceuticals assessment there are even more specific uses of words. The text represents the current use of safety terms by several EUnetHTA partner organisations. We are aware that there are still inconsistencies and the guidance to authors could be improved. Based on the experiences from the pilots we hope to further refine the safety guideline and the consistency of the safety reporting in the assessments.</p>
20.	EuropaBio	Page 7, line 45-46	<p>The section cites the call for a full systematic literature search in reference databases. In what circumstances is it envisaged that this would be needed?</p>	<p>We changed the text to state that “a systematic literature search in reference databases is only performed if the submission file appears to be incomplete or relevant new information is likely to be available”</p>
21.	EuropaBio	Page 8, line 22-24	<p><i>In addition, the focus of the evaluation of relative effectiveness is to determine the magnitude of health benefits and harms or, in other words, of the net benefit (benefits minus harms) of an intervention and the certainty of the evidence.</i></p> <p>We suggest that “to determine magnitude of health benefits and harms” be replaced by “to assess the incremental benefit of a technology relative to current standards of care, including consideration of harms.”</p> <p><i>“in other words, of the net benefit (benefits minus harms) of an intervention”</i></p> <p>It is rare that in the absence of an economics component that benefits and harms will be measured on a single scale (e.g. by use of a utility measure) that would permit a quantitative assessment of net benefit. At best in an assessment that confines itself to a consideration of</p>	<p>The paragraph defining the assessment of relative effectiveness is modified using the commenter’s notions: “When assessing the relative effectiveness of pharmaceuticals the focus is on determining the magnitude of the health benefits and harms of a (new) pharmaceutical compared with existing pharmaceuticals or some other technology. As stated in the principles on relative effectiveness (HLPF 2008b), a REA should include a comparison with the most appropriate healthcare intervention(s). The assessment should primarily focus on data derived from usual circumstances of health care practice, although these</p>



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			clinical effectiveness, only a qualitative assessment will be permitted.  <i>"and the certainty of the evidence"</i> Care should be used with the terms "certainty" and "uncertainty" throughout the document as they are not semantically symmetrical from a decision maker's perspective. It is important also to point out the difference between statistical, qualitative, and structural uncertainty and provide advice as efforts to address these might be presented.	are usually not available right after marketing authorisation. Additionally, the assessment should present the uncertainties affecting interpretation of reliability and clinical relevance of the results.."
22.	EuropaBio	Page 8, lines 25-26	As an illustration of the above point it states that data on results under usual circumstances of health care are often not available at a first launch but then the guidelines go on to discuss implications of using additional data for assessment of relative effectiveness. The guidelines should clarify what data are expected under at least two unique circumstances: (1) a first launch for the product, or (2) when the product has been approved and launched elsewhere such that additional "real world" information is available. "Finally, the evaluation should be about the results under the usual circumstances of health care practice. However, often these data are not (yet) available soon after marketing authorisation"  There is some confusion throughout the document about the preference for RCT level evidence vs. so-called real world evidence. On Page 8 a preference is expressed for the latter, whilst further on (page .20) in the body of the document the stated preference is for systematic reviews or RCTs due to the lack of generalisability of pragmatic trials or observational datasets (not to mention that many mature HTA agencies around the world still regard "observational datasets" as unreliable for the purposes of assessing effectiveness due to unresolved methodological challenges in controlling for unobserved confounding variables.) This inconsistency should be addressed.	The Model should be useful for new pharmaceutical launched onto the market or a pharmaceutical for a new indication or with new relevant data. The pilots in WP5 JA2 should show whether the Model is suitable for both purposes and whether further specifications are required.  The evidence requirements or criteria for study-designs in various contexts seems to be an area where there is variation in perceptions and practices across national HTA organisations. Evidence requirements of individual organisations will be further investigated as part of WP7 JA2 (development of submission file template for rapid assessments). This may lead to further refinement of the guidance.
23.	EuropaBio	Page 9, line 8	The guidelines request data on the patterns of use of the technology but these data are unlikely to be available unless the product has been launched elsewhere in the world (see comments above).	The Model does not request data but instead, suggests issues to be dealt with in the report. The authors select from the list of Assessment Elements those elements which are pertinent, and where there is data available.
24.	EuropaBio	Page 9, line 22-24	<i>"Anticipated problems in the technology's use, e.g. inappropriate extension of indications (off-label use), bad compliance and misuse are to be discussed."</i>  In order to make the language clearer, please consider replacing with:	Thank you, we have modified the sentence into: <i>"Potential problems with the use of a technology within a health system should be identified: examples include, risk of use beyond the authorized marketing label,</i>

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			<i>"Potential problems with the use of a technology within a health system should be identified upfront. Examples include: risk of use beyond the authorized marketing label or reimbursed indication; compliance challenges; and the misuse or diversion of the product. Sponsors should be provided with the opportunity to present approaches to minimize such problems."</i>	<i>compliance challenges, and the misuse or diversion of the product."</i>
25.	EuropaBio	Page 10, line 14	The guidelines do not state <i>how</i> safety should be compared for and against a comparator.	A more through guidance for methods is presented in the Safety Guideline document (Endpoints used in REA of pharmaceuticals – Safety)
26.	EuropaBio	Page 11, line 7-8	<p><i>"The assessment of health benefits should primarily consider <u>clinically meaningful endpoints</u> such as mortality, morbidity, and quality of life."</i></p> <p>Consider replacing with "<u>patient relevant endpoints</u>" as many surrogate endpoints, especially those used to treat chronic and progressive conditions, are regarded as both clinically meaningful and significant within routine medical practice.</p> <p>Acknowledgement should also be given for why surrogate endpoints are often selected as the primary endpoint for clinical trials, including consideration of adequate statistical powering and baseline event frequency.</p> <p>Validation of surrogate endpoints should be considered pragmatically for decision making purposes. Validation requirements should not result in an unreasonable burden of proof. Various policy option and incentives might be introduced to encourage surrogate validation research without delaying access to medicines (e.g. CED).</p>	<p>We keep the word 'clinically meaningful' as it matches better the current Guideline document (Endpoints used in REA of pharmaceuticals- clinical endpoints). Specifics on surrogate outcomes are dealt with in the guideline 'Endpoints used in REA of pharmaceuticals-surrogate endpoints'.</p>
27.	EuropaBio	Page 11, line 11	Who determines, and how, whether surrogate end-points are appropriately validated. What if there is disagreement between Regulatory and HTA?	This is discussed in the guidelines on surrogate endpoints: If surrogate endpoints are used for REA, they should be adequately validated: the surrogate-final endpoint relationship must have been demonstrated based on biological plausibility and empirical evidence. The level of evidence, the uncertainties associated and the limits of their use should be explicitly explained.

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				Complete validation data should always be provided. For adequately validated surrogate endpoints, a second validation for REA purposes will not be necessary. For more detailed guidance on the use and relevance of surrogate endpoints see the guideline on surrogate endpoints. HTA and regulatory assessment have a different purpose. Therefore it is possible that a specific surrogate outcome is accepted for regulatory purposes but not for HTA purposes.
28.	EuropaBio	Page 12 , section 2.2 Scoping	It appears the manufacturer needs to submit a file PRIOR to scoping occurring. Shouldn't the scoping come before the submission in order that the appropriate data are contained in the submission, e.g. choice of comparator	For the pilot assessment we will test the following approach: a draft submission file will be submitted by the (future) marketing authorisation holder; this will be followed by a scoping meeting with the (future) marketing authorisation holder. After the scoping meeting the (future) marketing authorisation holder will receive comments on the draft submission file after which the (future) marketing authorisation holder is asked to submit a final submission file. The pilot assessments will show whether this is the optimal way of working.
29.	EuropaBio	Page 13, Line 24	The guidelines should give additional clarification on what is meant by "usually", perhaps choose a different term, or request for information. For example, if "usually" is the standard, are there any notable exceptions?	There might be cases in which the off-label use of a new pharmaceutical (for instance in first-line treatment instead of second-line according to the label) is obvious because similar treatment patterns were observed for the comparators with a similar label. We would assume that in general the assessments would be restricted to the label.
30.	EuropaBio	Page 13, lines 44-49	The possibility for variable practice across Europe means the choice of a single comparator based on " <i>current clinical practice</i> " will be difficult if there are not clear guidelines on how to do this for current clinical practice and in which countries. The choice of comparators needs further explanation, given that treatment practice and reimbursements varies between countries in the EU. From this paragraph " <i>the number of comparators should be limited and thus the most</i>	Thank you for sharing these considerations.

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			<p><i>meaningful comparator will be current clinical practice because this will be most informative and relevant."</i></p> <p><i>"In the rapid relative assessment context, i.e. the assessment of the effectiveness of a new technology relative to existing technologies, the number of comparators should be limited and thus the most meaningful comparator will be current clinical practice because this will be most informative and relevant."</i></p> <p>In the context of any HTA being conducted to inform a decision to adopt a technology, it is vital to have a well-defined and consistently applied policy of comparator selection to prevent gaming from both payers and sponsors alike.</p> <p>Various considerations follow:</p> <ul style="list-style-type: none"> <li>• From a static economics perspective the comparator should be that product which the new technology will most likely displace in the market. This is broadly aligned with the comments in the guidelines. From a dynamic economics perspective care should be taken to how this might be translated into any subsequent pricing and reimbursement decision, as it will disincentise bringing to market new technologies where considerable time has passed since the current standard of care was introduced.</li> <li>• In the application of any comparator selection policy consideration should, however, also be given to the quality and standard of evidence available. Older products may be underpinned by poorer quality trial design making comparisons difficult (e.g. through lack of exchangeability) and the size of any incremental benefits uncertain. Standards of care may also have changed since a clinical development program involving a head to head trial was finalised making assessments against the new standard of care, e.g. through 2 step indirect comparisons, more uncertain.</li> <li>• It is important that the selected comparator is registered and marketed for the</li> </ul>	

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			indication in the applicable jurisdiction.	
31.	EuropaBio	Page 14, line 25	<p><i>Checklist for potential ethical, organisational, social and legal aspects'</i></p> <p>Ethical and legal considerations often influence what is possible to demonstrate by constraining clinical trial design, often to the detriment of the sponsor of the new technology. The clearest example of this is the ethical requirement to permit early crossover to the active treatment arm in oncology trials for those whose cancer progresses. Such crossover biases the results towards the null hypothesis, resulting in a systematic underestimation of the actual treatment effect. A number of techniques are now employed to partially correct for this bias but these are generally acknowledged as not ideal.</p> <p>It is important that the effects of such ethical and legal constraints are well understood by HTA agencies, and the implications fairly acknowledged and accounted for in decision making. Reducing such considerations to an additional checklist is unlikely to ensure this.</p>	This is an important general issue. As the proposed checklist for eth/org/soc/legal issues will be tested in the upcoming REA projects of WP5 we probably encounter the potential benefits and drawbacks of the check list as a tool.
32.	EuropaBio	Page 14, lines 1-3 Comparison(s)	A request is made for data on current treatment pathways from as many member states as possible are requested. Who will generate this data?	We feel that it is primary the responsibility of the (future) marketing authorization holder to provide this information from the European countries. These data will be checked in the upcoming rapid REA projects by participating countries (authors and dedicated reviewers). Additionally the result cards structure allows easy amendments: so in principle this information can be added later on too by countries that use the REA report.
33.	EuropaBio	Page 15, section 2.3 and line 11: "Original Studies"	It is not clear what is being requested in this part of the document. Is it the Clinical Study Report?	Bullet point is removed as the missing information is already covered in the first bullet point.

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34.	EuropaBio	Page 16, Table 1	We believe that this table should be more focused on sources of high quality evidence. Many of the websites listed do not seem to be appropriate sources for REA, (i.e. national health services websites, etc). It is vital that HTA agencies are transparent about the methodologies that they use and apply to any data that they require from sponsors and they consult carefully with sponsors on the use and interpretation of such data. Sponsors are best positioned to understand the data and this should be acknowledged.	Table 1 has been originally developed for the full HTA Core Model. Some adjustments were made during REA model development but refining further this table is probably appropriate in the next update of the Model. Your comment is taken forward to the REA model developers.
35.	EuropaBio	Page 17, Line 10-11	Is there a requirement that the manufacturer provide updates over time to their HTA Core Model Submission – if so at what frequency and how should the updates be provided?	No policy on (the frequency of) updates has been established yet. This may be more appropriate after the experience gained WP5 JA2.
36.	EuropaBio	Page 19, Line 18	It is not clear what is meant by " <i>artificial</i> " relevance. Clarification would be appreciated.	The following sentence has been deleted: Assessing relevance is not straightforward: As all issues can have some relevance for someone in some time, judgment is required to weigh their relative relevance, without rejecting them too easily as irrelevant either.
37.	EuropaBio	Page 20, Line 1	Is there a suggested template or format for the manufacturers to use?	There is not yet any template made for the manufacturers to use. A submission file template will be developed in WP7 JA2. In principle, after the REA Model is published, the tools it includes can be used, taking into account the terms of use <a href="http://www.eunetha.eu/outputs/hta-core-model-terms-use">http://www.eunetha.eu/outputs/hta-core-model-terms-use</a> .
38.	EuropaBio	Page 20, Line 7-12	We suggest that the sentence: " <i>unsystematic gathering of information from ...the internet can be considered</i> " – is either removed or the context is clarified* so that the approach will make for the basis of a robust scientific review.  <i>*perhaps this refers to the gathering of the "background" information such as burden of disease and epidemiology, but this needs to be clarified</i>  Also this paragraph does not seem to be aligned with the rest of the document (i.e. it implies that a systematic review from the MA holder is not mandatory).	This paragraph is removed.

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39.	EuropaBio	Page 20, Line number 11-12	Does the entire regulatory submission to the EMEA need to be submitted?	The section was referring to an HTA submission file. However, the paragraph is removed (see comment 38)
40.	EuropaBio	Page 20, line 30	General point for this section – perhaps worth including here the relevance of meta-analysis and where it lies within the levels of evidence.	The following sentence has been added: A (well conducted) meta-analysis of the results of more than one RCT would provide the highest level of evidence.
41.	EuropaBio	Page 20, Line number 52	What does full assessment mean here?	The paragraph is removed and the previous paragraph amended with the information of rarity of pragmatic trials just after marketing authorization.
42.	EuropaBio	Page 21, Line 17-18	<p>The reference to "truth" is inappropriate and misleading language. We believe that the paragraph should refer simply for the need to assess for bias when considering the internal validity of the evidence.</p> <p>In respect to assessment of bias, it is imperative that this be undertaken in a structured and transparent manner that minimises subjectivity on behalf of the assessor. More consideration is required as to how this should be done to avoid exclusion of meaningful evidence.</p>	<p>The sentence has been slightly reworded according to rewording in the final version of the guideline: 'Internal validity describes the extent to which the (treatment) difference observed in a trial (or a meta-analysis) is likely to reflect the 'true' effect within the trial (or in the trial population) by considering methodological quality criteria'</p> <p>We do not think the sentence is misleading as this appropriately addressed in the next sentence: 'Because the 'truth' can never be assessed, it is more appropriate to speak of the potential for or risk of bias.'</p> <p>We think that the recommendations in the guideline provide sufficient guidance for a structured and transparent manner of assessing bias.</p> <p>In WP7 JA2 the guideline on internal validity will be extended to observational studies.</p>
43.	EuropaBio	Page 21, Line 25-28	Of the three options listed for assessing bias in clinical effectiveness data – which is preferred?	There is no preference presented on purpose. We are in an initial phase of European Collaboration where we can only list the methodological solutions that all can approve. In later stages we are probably able to end up with recommending one solution over the others.
44.	EuropaBio	Page 23, Line 38-40	Whilst it is important to acknowledge that statistical significance does not translate automatically into claims of clinical significance, more guidance is required on how to set the	Some guidance is provided on page 23, lines 17-22, on estimating the clinical significance of a statistically



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			<p>parameters demarcating the latter in an objective and justified way, especially where usage of surrogates are involved.</p> <p>Medicinal products interactions in patient populations outside of the clinical trial are not likely to be known at the time of REA. Is there an expectation to provide updates on this information over time as it becomes available? This is another example of the clarity needed for a first launch vs. a follow-on launch after the product has been on the market elsewhere in the world.</p>	<p>significant difference. We assume that the commenter is concerned about objective and justified ways of estimating what is “clinically significant”. For some endpoints, such as pain measured with VAS scale, there is some published information of the threshold of clinically meaningful differences, for many other endpoints there is no such information available. But, the point is valid, and it could be useful to collect and present this information in the EUnetHTA Guidelines.</p> <p>Updating policies of rapid REAS have not been discussed yet.</p>
45.	EuropaBio	Page 24, line 6-11	The extent of medication errors are also not likely to be known at the time of a REA.	Not very likely but as they belong inherently to the assessment of pharmaceuticals we find it better to include it here.
46.	EuropaBio	Page 25, A0003	Is it expected that the manufacturer will do a literature search to identify and present prevalence of risk factors across geographic areas and subpopulations?	We think this is helpful, but feasibility should be checked. This kind of information can also be gathered collectively, which is one of the specific ideas of structuring information into assessment elements. National information can be added afterwards in the result cards by e.g. national HTA agency.
47.	EuropaBio	Page 26, A0006	Based on the sources/methods listed – incidence/prevalence/mortality should not be identified via a literature review. If national statistics are to be used, aren't these country-specific? Does the manufacturer need to try to identify country-specific numbers via these national databases across all EU member states?	<p>The sources/methods fields are written for HTA organisations. They contain the usual sources and methods used by the HTA agencies. In some pilot projects testing the Core Model the authors have made efforts to locate the information from as many countries as possible.</p> <p>The information provided in cross-border assessment should be useful to all or most of the Member States. Therefore the objective is to provide primarily EU level</p>

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				or comprehensive country level data when differences on country level are expected and seem to be relevant..
48.	EuropaBio	Page 26, A0006	Guidance on whether EU or country specific data is preferred. If this is country specific, then it should be considered how many and which countries will be involved?	See response to comment 47
49.	EuropaBio	Page 27, A0023	Does manufacturer need to identify and present the potential number of people in the target population for each of the EU member states?	The sources/methods fields are written for HTA organisations. They contain the usual sources and methods used by the HTA agencies. The information provided should be useful to all or most of the Member States. Therefore the objective is to provide primarily EU level or comprehensive country level data when differences on country level are expected and seem to be relevant..
50.	EuropaBio	Page 27, A0023	<i>"How many people belong to the target population?"</i> The clarification notes that <i>"this information is required e.g., for budget impact and other resource calculations,"</i> which are specifically called out of scope for the REA. We believe the guidance around this element should discuss the importance of this information for REA purposes, for example, increase in population exposed and greater potential for benefit/harm. It would also help to provide guidance around specific geographies to focus on (again, for REA rather than budget impact purposes).	The clarification was reworded to focus more on the non-financial aspect of the importance of knowing the size of the target population: "This information can also be used to give an idea of the resource requirements in general of implementing the pharmaceutical."
51.	EuropaBio	Table 2. Explanation of assessment element table (Transferability)	Transferability: The problem of assessing transferability occurs only when the HTA is being conducted outside a specific healthcare system. Within a healthcare system, the question is one of applicability of the presented evidence to the local situation; in the context of the core model it is a subjective assessment of whether the evidence is generically transferrable to multiple jurisdictions, without articulating specifically the requirements of those systems. This is an insurmountable problem that will only introduce significant bias to the assessment.	This is in the root of the idea of Core Model. We know that there are pieces of information that can be shared and those should be produced jointly using the Core Model structure. When we intend to make a tailored document for decision making in our own jurisdiction we need something additional. So, we need to be able to separate the transferable or partly transferable information from the non-transferable and do only the transferable together. A Rapid REA does not have the aim to be the document which is used in all decision making settings, but it is rather a document which all countries can use when they prepare their documents

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				for their own decision making setting.
52.	EuropaBio	Page 33, B004 and B005	We could not determine who administers this and in what level of care it is administered and it will vary by country – Is it assumed this is consistent across the EU as a whole? This may not be a valid assumption.	The response to this question could be as follows: the first paragraph describes the administration issues which are common to all. Then, it will be followed by country specific paragraphs describing the nuances in different countries. The examples from other countries may be useful for others to see too. As mentioned earlier, these clarifications have been written for HTA organisations.
53.	EuropaBio	Page 34, B0011	<i>"What kind of registry is needed to monitor the use of the technology and comparator?"</i> This strikes us as fundamentally a regulatory concern. Is it proposed that both the EMA and a central HTA agency make this determination independently? Per earlier comments, this is not an appropriate issue for the HTA agency as it has at best the potential for redundancy and, at worst, the potential for conflict and confusion.	There is a trend that new technologies become available on conditional basis (conditional approval and/or conditional reimbursement). During this period of conditional availability often additional data are requested from the MAH. For these data collection, registries are used. If this is relevant it should be checked that requirements for additional data collection from regulators and reimbursers/HTA agencies should be aligned as much as possible.
54.	EuropaBio	Page 36, C002	The concept of dose relationship is introduced here. If this has been established in CTs, then it would have been taken into account in the approval process and the final recommended doses which would seek to optimise benefit risk...presumably doses which would tip the B/R into the marginal or negative would not be approved; similarly doses where the therapeutic index is so marginal .....if there were implications for training and organisation, then that would be covered in the conditions of approval with respect to the risk and covered in the RMP ...a publically available summary will be published.	The pilots in WP5 JA2 should provide further information on how relevant this element is for rapid assessment of pharmaceuticals.
55.	EuropaBio	Page 36, C004	It is difficult to see how this information will be available from controlled CTs...also it is in the remit of risk management and regulators and not HTA.	The pilots in WP5 JA2 should provide further information on how relevant this element is for rapid assessment of pharmaceuticals.
56.	EuropaBio	Page 36, C005	If these subgroups have been identified, then that it actually a positive point as it can help make appropriate mitigation.	Thank you for the comment. In addition it may be relevant in a REA in order to identify differences in prescribing possibilities versus comparator

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57.	EuropaBio	Page 37, C008	This is a clinical judgement that may fit more with the regulators rather than the HTA agencies.	This question is essential for providing an assessment of the relative effectiveness of the pharmaceutical. The focus is on the 'relative safety' vs comparator.
58.	EuropaBio	Page 39 General comment on section 3.4 Clinical effectiveness elements	General comment on the example clinical effectiveness elements:  The sources listed for the Clinical effectiveness data are very broad especially if this needs to be applied to the selected comparators (observational data, registries are listed). Could the data sources listed be more focused and selective? Would the issue best be handled by a systematic review of RCT data and, if so, who should do it?	The sources fields could indeed be more specific for rapid assessment of pharmaceuticals in some issues. Based on the input from the pilots in JA2 this may be further specified.
59.	EuropaBio	Page 42, D0016, D0012, & D0013	We suggest that clarification is needed here. The guideline proposes to report the results in absolute terms and relative to the comparator. Please clarify whether this means quantitatively relative to the comparator (i.e., an indirect meta-analysis)?	This is further specified in the guideline for clinical endpoints: Outcomes can be summarised and presented in absolute or relative terms. Absolute measures are useful to clinicians as they provide a quantification of treatment effect that is meaningful for treatment evaluation and prognosis. However, due to the dependence of absolute measures on baseline risk, relative measures are more generalisable across studies. The manner in which clinical outcomes are presented leaves significant scope for misleading conclusions to be supported. Every attempt should be made to provide both absolute and relative measures in tandem.
60.	EuropaBio	Page 42, D0017	<i>"Was the use of the technology worthwhile?"</i> The clarification here calls for information on patients' perceptions of value and satisfaction. These are two very different issues, and we would propose that neither answers the question of whether a technology is worthwhile. We would suggest rephrasing this issue as <i>"What is the effect of the technology on patient satisfaction?"</i> and perhaps having another separate issue <i>"What is the effect of the technology on patient perceptions of value?"</i> to include data from contingent valuations, etc.	We agree that satisfaction and perception of value are two different things and would thus deserve two different questions (issues). On the other hand Core Model has been criticised of being too split and including too many assessment elements. Therefore we rather keep the issue as one. Additionally, the current clarification guides the authors to report satisfaction and value perception separately.

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61.	EuropaBio	Page 56, Template5	We assume that it would not be expected that this be completed for comparators and that we would report abbreviated data on comparators?	The use of data extraction tables or evidence tables is a new feature in the upcoming rapid-REA-projects of WP5. These projects will test the feasibility the templates proposed by the current version of the REA Model and they will be very likely further adjusted for optimal use. The idea has been until now to produce templates for the use of HTA organisations. There has not yet been any discussions how should the templates be adjusted to manufactures' requirements. A submission file template for the marketing authorisation holder will be developed in WP7 JA2.
62.	EuropaBio	Page 75, 76 Appendix 5	The specificity of these guidelines will be key to the implementation of this Core Model.	Thank you for this comment.
63.	EFPIA	General	<p>The document makes frequent reference to the methodological guidelines that are currently being finalized based on the input received during various public consultations. We refer to the EFPIA comments submitted in the framework of these public consultations.</p> <p>In general we welcome the fact that the core model acknowledges that rapid REA will base on a manufacturer submission and look forward to discussing with EMA the need for a template submission format. We also welcome that the rapid REA will base on the EPAR as a source of information, which will enable to build on knowledge developed in the regulatory process. The interface to the EMA remains an important matter on which further clarification is needed, in order to avoid redundancy and/or inconsistency in the assessment of some domains, particularly the Safety parameters.</p> <p>The involvement of stakeholders in the Rapid REA should be further defined, in particular with respect to Clinical Experts and Patients representatives.</p>	<p>Thank you for this comment.</p> <p>Thank you for this comment. This will also be further tested in the pilots in WP5 JA2.</p> <p>Your point of hearing clinical experts and patients, as well as the suggestions for the scoping phase will be discussed within WP5 of EUnetHTA JA2 when designing the process of rapid REAs, including the procedural details. The Model itself is not intended as a procedural document.</p>

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			<p>We consider that the MAH should be systematically and directly involved in the Rapid REA scoping process. That joint scoping phase should take place as early as possible in the development process, preferably before the start of phase III pivotal studies. It could be complemented by a second scoping before the start of the preparation of the Rapid REA submission dossier.</p> <p>The selection of relevant comparators (and selection criteria) for the Rapid REA is of critical importance, as is the interpretation at launch of efficacy results in terms of effectiveness (Rapid REA). We to our comments on the guidelines on these specific points.</p> <p>Further clarification on the exact procedure for a joint rapid REA would be useful, such as whom to contact and procedural rights of applicants, the status of the assessment in the European context, the impact of the joint REA on national decision-making, and what EUnetHTA intends to do to avoid any duplication between European and national activities.</p> <p>At a number of points in the document the terminology shifts from Rapid REA to HTA or Core HTA. The aim should be to focus attention on a Rapid REA, The main value of a Rapid REA will be at or around the launch of a new medicine. More could be done to slim down some of the draft to ensure that the focus is on the kinds of data which are likely to be available at launch.</p>	<p>For the pilots in WP5 JA2 involvement of the MAH in the scoping phase is intended. The scoping should indeed start timely however it is not likely to do this before the start of the phase III pivotal studies as WP5 JA2 is only a three year project.</p> <p>OK</p> <p>The Model itself is not intended as a procedural document. The procedure for the WP5 JA2 pilots will be described in a procedure manual to be developed for this purpose at the beginning of JA2.</p> <p>There may be still remnants of terminology from the HTA Core Model, which are more suitable for full HTA of established technologies. The text will be checked for these in the next updated version of the REA model. In addition, possible further selection of assessment elements will be done based on the input from the pilots in WP5 JA2.</p>
64.	EFPIA	p. 7, l. 24	<p>Please refer to Directive 89/105/EEC relating to the transparency of measures regulating the pricing of medicinal products for human use and their inclusion within the scope of national health insurance systems (commonly referred to as the Transparency Directive).</p> <p>The Transparency Directive mandates timelines for pricing and reimbursement decisions. This means that any rapid assessment of REA, to the extent that it might be used in national P&amp;R decision, should be made within these timelines, and therefore will be shorter than these timelines.</p> <p>The reference to the Transparency Directive implies that EUnetHTA is working towards Rapid REA as a tool to be used in national reimbursement decisions of pharmaceuticals. It might be</p>	<p>Reference amended as suggested.</p> <p>The role of REA model in national reimbursement decisions will be defined by the voluntary uptake of the Model and of the cross-border produced rapid REAs in the work of national/regional HTA organizations. There will not be any obligation to use the tool or the products. However, to increase the likelihood of national uptake of cross-border assessments in countries it is the aim to fit</p>

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			relevant to clarify this situation further in the EUnetHTA mandate moving forward.	within the timelines of the Directive.
65.	EFPIA	p. 7, l. 42	We welcome the fact that the REA will be conducted on the basis of a manufacturer submission file. It would be interesting to clarify the submission template that manufacturers should work on moving forward in the context of EUnetHTA activities.	Thank you for this comment. The submission template will be developed in WP7 JA2 in close collaboration with WP5 JA2.
66.	EFPIA	p. 7, l. 51	The new structure for the joint REA seems indeed more practicable. Questions arise regarding the mode for selection of the rapporteur and co-rapporteur, in particular regarding the level of capacity of the given HTA agency, whether some therapeutic specialisation will be sought across countries, and what the role of the manufacturer will be in this process. It should also be carefully considered how to ensure sufficient buy-in from the other EUnetHTA members (i.e. those who are not rapporteur and co-rapporteur) in order to ensure that the outcomes of the joint REA are used in national decision-making, as otherwise it would lead to duplication and unnecessary waste of resources.	Requirements for capacity or specialisation of the HTA organisations that are about to perform assessment using Core Model (and hence also REA Model) has been recently discussed in relation to formulating the policies for the use of the HTA Core Model. The Policies for the use of the Core Model do not contain details of the assessment process, which means that manufacturer involvement in specific phases of the project needs to be defined by REA model users; in this case WP5 of JA2 who coordinates the rapid REAs of pharmaceuticals. Your point of ensuring the use of the rapid REA project's results by countries other than the ones involved is an important point to take forward.
67.	EFPIA	p. 8 section 1.2	This section is useful and fully in line with the outcomes of the High Level Pharmaceutical Forum. Since the core model is about a rapid assessment at launch when real life data is not yet available (as acknowledged in Page 20 line 50-53), more explicit acknowledgement of the need for models and inferred data and real world impacts would help. ..	There is also the potential to use the Model in rapid assessment of not-new pharmaceuticals, as mentioned in the introduction, page 7: <i>"It may assess a new pharmaceutical launched onto the market, or (re)assess a pharmaceutical for a new indication or when new relevant data are available"</i> .
68.	EFPIA	p. 9, figure 1	We welcome the focus of the model for rapid REA on the first four domains of the core model, as these are the most transferrable across countries.	Thank you for the comment
69.	EFPIA	p. 9, l. 22-24	Off-label or other inappropriate use is important for potential comparators currently established in medical practice, but speculation on potential off-label use of the new medicine or other technology seems inappropriate here. The wording on p. 13 21-24 is better. Discussing potential	The sentence is edited to the form: ". Potential problems with the use of a technology within a health system should be identified: examples include risk of use



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			off-label uses is more speculative than a core part of any rapid relative effectiveness assessment. Consideration of this topic is probably best done by regulatory agencies.	beyond the authorized marketing label or reimbursed indication, compliance challenges, and the misuse or diversion of the product." Information about off-label use has been considered potentially relevant information for decision making and it is therefore included as part of the Assessment Element number A0001.
70.	EFPIA	p. 10, section 1.3.3	The interface and respective roles of EMA and EUnetHTA in the assessment of safety should be clearly defined to avoid redundant work and diverging interpretations of the same data. We refer to the EFPIA comments submitted on the safety guideline.	Thank you for this comment and the comments to safety guideline. We agree that minimizing overlapping in safety assessment is important and this will be further tested in the pilots in WP5 JA2.
71.	EFPIA	p. 11, l. 1-5	In case the assessment body requires a different comparator from that used in the clinical trial, indirect comparisons are an important tool to ensure that manufacturers can meet the requirements of the assessment and regulatory authorities.  There is a commitment from industry and other stakeholders to improving the availability of the right information at the time of launch (such as through the IMI project on 'Incorporating real-life clinical data into drug development', see topic text available online at <a href="http://www.imi.europa.eu/sites/default/files/uploads/documents/7th_Call/Call7_FinalCallText.pdf">http://www.imi.europa.eu/sites/default/files/uploads/documents/7th_Call/Call7_FinalCallText.pdf</a> ) and this could be referred to and acknowledged in the documents.  We refer to the EFPIA comments on the guidelines related to endpoints to complement our comments to this section.	Indirect comparisons are referred to in the section 2.5.4. (Extrapolation of efficacy to give relative effectiveness data)
72.	EFPIA	p.12, l.9: "Preferably the marketing authorization holder should be consulted regarding the scope"	Delete "Preferably". We suggest that the MAH be systematically and directly involved in scoping, well ahead of the REA submission. That joint scoping phase should take place as early as possible in the development process, preferably before the start of phase III pivotal studies. Please clarify how clinical experts and patient organization representatives will be involved. We would like to reiterate the importance and value added of including the perspectives of also these stakeholders in the REA process.	The tools developed by EUnetHTA are guidelines and recommendations on best practices. They can not enforce behaviour such as consulting the manufacturer although we do think this is preferred way of working. The involvement of other stakeholders will also be explored in WP5 JA2 pilots.
73.	EFPIA	p. 13, l. 11-13	It needs to be carefully considered how subgroups and sub-indications are defined. Ideally	We agree with your comment, this should be considered

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			these should be agreed at the stage of trial design, as otherwise trials would not be powered enough for statistically meaningful sub-group analyses.	carefully.
74.	EFPIA	p. 13, l. 14	We would suggest to remove 'preferably' (see comment above)	See response to comment 72
75.	EFPIA	p. 13, l. 24	We would suggest to remove 'usually' (see comment above)	See response to comment 29
76.	EFPIA	p. 13, l. 27	We would suggest to remove 'in general'	We have not removed general as it sometimes happen that the population for the REA slightly differs (e.g. more narrow population) from the patient population for which it received market authorisation.
77.	EFPIA	p. 14, l. 1-3 Comparison(s)	A request is made for data on current treatment pathways from as many member states as possible are requested. Who will generate this data?	See response to comment 32.
78.	EFPIA	p. 15, l. 1 first bullet	<p>Whilst it is true indeed that available HTA reports will be a valuable source of information, it poses the question of the place of the rapid REA and the interface with national assessments and decision-making. If the intention of the rapid REA is to be conducted at the time of marketing authorisation, to support subsequent national decision-making, then probably there will be no HTA reports available at that time. It would be interesting to better understand the role of the rapid REA in supporting access to innovative pharmaceuticals.</p> <p>Furthermore, if existing HTA reports are referenced, it would be interesting to clarify what exactly will be used from these reports. i.e. facts and evidence are transferrable, but judgments and conclusions might not be.</p>	<p>National HTA reports may be available when doing a rapid assessment of an already available pharmaceutical (for e.g. new indication) which is the other potential use of the REA Model.</p> <p>If existing HTA reports are referenced it is likely that mainly the facts and evidence that is presented in the reports will be used.</p>
79.	EFPIA	p. 15, l. 1, second bullet and l. 17	We consider that industry can be a trustworthy partner in the process and will work to avoid any bias.	The aim of this sentence is not to question the trustworthiness but remind the authors of the importance of critical appraisal of every phase of the assessment.
80.	EFPIA	Page 15, section 2.3 and line 11: "Original	It is not clear what document is being requested here. Is it the Clinical Study Report?	Bullet point is rewritten to indicate what kind of additional information could be taken into account.

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		Studies"		
81.	EFPIA	p. 16, Table 1	General: this table needs to be more focused on sources of high quality evidence. – many of the websites listed do not seem to be appropriate sources for REA	The recommended sources could indeed be more specific for rapid REA. The current complete set of sources derives from the "full Core Model" which was the starting point for the REA model developers. It should be checked throughout the Model. This feedback is taken to the Model developers. But, as the current version states: "Additional sources may be useful to find domain-specific information" referring to table 1 with all the possible information sources, we think that the value of these sources is indicated as "additional".
82.	EFPIA	p. 17, l. 10-11	Is there a requirement that the manufacturer provide updates over time to their REA Core Model Submission – if so at what frequency and how should the updates be provided?	See response to comment 35.
83.	EFPIA	p. 18 footnote 1	We welcome the indication that EUnetHTA will continue updating the core model following learning following further piloting and look forward to contributing to this discussion with EUnetHTA.	We look forward to collaborating.
84.	EFPIA	p. 19, l. 18	It is not clear what is meant by "artificial" relevance – Please clarify	The following sentence has been deleted: Assessing relevance is not straightforward: As ll issues can have some relevance for someone in some time, judgment is required to weigh their relative relevance, without rejecting them too easily as irrelevant either.
85.	EFPIA	p. 20, l. 1	Is there a suggested template or format for the manufacturers to use?	See response to comment 37.
86.	EFPIA	p. 20, l. 7-12	Suggest that the sentence: "unsystematic gathering of information from ...the internet can be considered" – is either removed or the context is clarified* or as this approach will not make for the basis of a robust scientific review. <i>*perhaps this refers to the gathering of the "background" information such as burden of disease and epidemiology, but this needs to be clarified</i> Also this paragraph does not seem to be aligned with the rest of the document.= (i.e. it implies that a systematic review from the MA holder is not mandatory)	See response to comment 38.
87.	EFPIA	p. 20, l. 12	And at the time of marketing authorisation is probably the most relevant source.	The paragraph is removed and the previous paragraph

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				amended with the information of rarity of pragmatic trials just after marketing authorisation.
88.	EFPIA	p. 20, l. 52	What does full assessment mean here?	See response to comment 41.
89.	EFPIA	p. 21, l. 25-28	Of the three options listed for assessing bias in clinical effectiveness data – which is preferred?	See response to comment 43..
90.	EFPIA	p. 22, l. 16	The process of “transformation” (referred) to here is a very critical one in the context of the Rapid REA at launch and would certainly deserve a comprehensive presentation and discussion in the context of this guideline on surrogate endpoints. We refer to the EFPIA comments to this guideline for further details.	Thank you for providing these comments. Individuals responses to these comments will be answered as part of the guideline development process.
91.	EFPIA	p. 22, l. 21-27	We strongly support a pragmatic approach that makes use of indirect comparisons and robust models. Rapid REA will not be possible without a willingness to accept the realities of data availability at launch.	These lines also support the use of indirect comparison where evidence from direct comparison is insufficient.
92.	EFPIA	p. 22, l. 34	Replace “Core HTA” with “Rapid REA”	Done
93.	EFPIA	p. 22, l. 41	Replace “HTA reports” with “Rapid REA reports”	Done
94.	EFPIA	p. 22, l. 45	Replace “HTA report” with “Rapid REA report”	Done
95.	EFPIA	p. 23, l. 3-5	It is interesting to see that collaboration with the EMA resulted in this table. Would more information be available on other outcomes of collaboration between EUnetHTA and EMA?	The collaboration with EMA was started with the collaboration on the EPAR. This also led to preparation of the template of the table. It is foreseen that parts of the work on the EPAR will published in the near future. Other outcomes of collaboration between EMA and EUnetHTA will be shared with the Stakeholder Forum
96.	EFPIA	p. 23, l. 29	Replace “HTAs” with “relative effectiveness assessments”	HTA replaced by REA
97.	EFPIA	p. 23, l. 38-40	Drug interactions in patient populations outside of the clinical trial are not likely to be known at the time of REA. Is there an expectation to provide updates on this information over time as it becomes available? This is another example of the clarity needed for a first launch vs. a follow-on launch after the product has been on the market elsewhere in the world.	See response to comment 35.
98.	EFPIA	p. 24, l. 8-9	“difficulties of reading handwriting that lead to mistakes by the patient or professional” may be	Specific practical concerns of e.g. administration of a

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			an important factor in general medicines use, but is not appropriate for a consideration in a Rapid REA. We agree it is the remit of the marketing authorisation agencies.	drug, are important information for implementing decisions, as they may require added attention to organisational issues. Therefore these issues are covered in Assessment Element C0007. Further testing in the WP5 JA2 pilots will show whether some elements can be regarded as redundant for performing a rapid REA.
99.	EFPIA	p. 25-30, Section 3.1	Multiple sources are cited but not the manufacturer's submission. Pragmatically, the manufacturer's submission would constitute a significant part of this section and should be included.	Added in the source fields of several assessment elements.
100.	EFPIA	Section 3.1, page 25-30 & 3.2, page 31-34	There is in general a lack of specificity in the recommendations regarding production of the HPCU (3.1) and DCT (3.2) sections. Granted, the objective is in most cases to produce a "descriptive summary," but recommending the use of an extremely broad list of sources (see page 16), to include "Google" and "other internet search engines," is of questionable value. It would be beneficial to work towards a consistent approach to at least some of the elements in these sections, even if the selected approaches/sources are not necessarily authoritative, they should have a high degree of validity and reliability.	See response to comment 17.
101.	EFPIA	p. 30, A0021	It does not seem appropriate to grade reimbursement status as completely transferrable. Reimbursement is a decision that will build on the results of a REA, taking into account priorities of a given healthcare system. Reimbursement status is not an assessment element and it is therefore questionable that it should be part of the core model for REA.	The reimbursement status of a certain country is considered completely transferrable information because it is a fact that does not change depending on the view of the reader and it can be used for guiding reimburse decisions in other countries (which may be of course different). Not all assessment elements require truly "assessment": this holds also for prevalence data.
102.	EFPIA	p. 31, B0002	Should it not be 'expected' benefit rather than 'claimed' benefit?	The expectations are mentioned in the clarification.
103.	EFPIA	P. 32, B0003	The concept of 'truly novel/innovative' technology is difficult to understand: the Rapid REA will be about determining the relative efficacy or effectiveness of the technology. We refer to the three dimensions of value outlined by the High Level Pharmaceutical Forum.	Sometimes this information is relevant even in rapid assessment. The phase of development –information helps the decision maker to place the new product in context which may affect e.g. purchase decisions. The word 'truly' has been deleted.

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104.	EFPIA	p. 34, B0011	We welcome the reference to various schemes for additional data collection and encourage further action to ensure alignment between these various mechanisms.	Thank you for the comment.
105.	EFPIA	Section 3.3, page 35-38 & 3.4, page 39-42	The guidance appears to call for redundant work in the safety section (3.3) and effectiveness (3.4) domains relative to what can be found in the EPAR. The focus should be beyond the scope of regulatory documents (element C0008, for example, which calls for a <u>comparative</u> safety assessment)? There is a potential duplication of efficacy and safety assessment that is performed by Regulatory –Regulatory assessments should not be duplicated.	See response to comment 18
106.	EFPIA	Section 3.3, page 35-38	It appears that the assessors of the REA are being asked to make judgments on safety issues. Use of the term “harms” is new within the EUnetHTA guideline. For example, would there be a consistent understanding of the difference between harm vs. ADE vs. ADR vs. serious or severe ADR. It may be inappropriate in this context and appears to come from a negative point of view. Some additional examples and issues are: <ul style="list-style-type: none"> <li>• CTs determine relative frequencies of adverse events and suspected ADRs. How is this to be used by EUnetHTA?</li> <li>• Adverse events/suspected ADRs can be frequent and severe (e.g. a headache is frequent but not necessarily important from a safety perspective. How will these be weighed against one another? Some are more of a tolerability issue rather than an ADR.</li> <li>• Very rare cases of hepatic effects would be of greater clinical concern. Are HTA assessors trained to make this judgement call</li> </ul>	See response to comment 19
107.	EFPIA	p. 49, l. 8	This list is useful but could be complemented by other sources of information. Furthermore it might be relevant to classify the various guidelines they are referring to (guidelines by professional organizations, by HTA agencies...)	We are open for suggestions for complementing the list.
108.	EFPIA	p. 49, l. 12	See comment on p. 30, A0021	See response to comment 101. .
109.	EFPIA	p. 52, template 2	Whilst it is useful to provide examples for a better understanding of the concepts presented,	We would be grateful to have the unclarities specified. The format and content of the templates will be further

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			some of these are not totally clear.	tested in the WP5 JA2 pilots.
110.	EFPIA	p. 56, template 5	By whom will this table be used moving forward?	This table may be used in the WP5 JA2 pilots. Feasibility of the use of this table will be checked.
111.	EFPIA	p. 70, l. 5	The overview on the process leading to the development of the core model is very useful. It would be interesting to getting more information on the Member States that will collaborate on joint assessments moving forward.	Information about participating organisations will be available in the first months of 2013.
112.	EFPIA	p. 71, l. 26	Please refer to Directive 89/105/EEC relating to the transparency of measures regulating the pricing of medicinal products for human use and their inclusion within the scope of national health insurance systems (commonly referred to as the Transparency Directive). The Transparency Directive mandates timelines for pricing and reimbursement decisions for <u>all</u> EU Member States. This means that any rapid assessment of REA, to the extent that it is used in national P&R decision, should be made within these timelines, and therefore will be shorter than these timelines. The reference to the Transparency Directive implies that EUnetHTA is working towards Rapid REA as a tool to be used in national reimbursement decisions of pharmaceuticals. It might be relevant to clarify this situation further in the EUnetHTA mandate moving forward.	See response to comment 64
113.	EFPIA	p. 75, appendix 5	We refer to the EFPIA comments to the various guidelines listed in the appendix	Thank you, those comments will be considered for the production of the final version of the guidelines.
114.	Novartis	Overall comments on EUnetHTA core model	We would like to thank you for the opportunity to comment on the proposed core model for rapid REA. EUnetHTA commitment to involving industry as a partner is very much appreciated. As in our previous comments on proposed EUnetHTA methodologies, we would like to emphasize stakeholder engagement in the HTA processes, specifically, the essential role of patients, health care professionals, clinical experts, and clinicians in health technology assessment as well as in the formation of such guidelines and models for future European relative efficacy assessments. It is our hope that these stakeholders are involved in developing the core model and will have a voice in future assessments.	Thank you for this comment.  Your point of hearing clinical experts and patients, as well as the suggestions for the scoping phase will be discussed within WP5 of EUnetHTA JA2 when designing the process of rapid REAs.
115.	Novartis		There is a general lack of clarity of the future that the core model holds as well as REA assessments in Europe. From a manufacturer's perspective, this lack of clarity is around: <ul style="list-style-type: none"> <li>the overall framework of decision making,</li> </ul>	Thank you for the comment. We would like to underline that the production of rapid REAs in cross-border projects using REA model does not signify European



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			<ul style="list-style-type: none"> <li>• when such European assessments would be taking place,</li> <li>• how REA will be deployed,</li> <li>• how decisions will be taken,</li> <li>• and whether such decisions will be binding at the Member State level and at the Member State budget holder level (e.g. national, regional, local).</li> </ul> <p>The comments that follow should have these overarching concerns in consideration as this is an area of relative uncertainty for manufacturers and for Novartis.</p>	assessment. The aim is to produce a set of sharable pieces of information which each country can use in the preparations of national documents, for their national decision making. REA reports produced within EUnetHTA are not binding and not even recommendations: they are purely a collection of research evidence and other information which is produced in order to avoid unnecessary duplication of efforts collecting this type of information.
116.	Novartis		There is a general confusion with the terminology REA. We are aware that EUnetHTA refers to "relative effectiveness assessments", however at time of launch no or very little effectiveness data is available, and that effectiveness will have in many cases to be estimated and modelled from the efficacy data obtained from clinical studies. We propose that moving forward; REA in Europe is correctly labelled as <u>"relative efficacy assessment"</u> .	This is a valid point. However, as EUnetHTA WP5 follows the recommendations (and terminology) of Pharmaceutical Forum 2008 a change of the term requires profound discussions and agreement. consideration. In addition, the model should also be suitable for assessment of new indications or when new data are available.
117.	Novartis		The interface to the EMA remains an important matter on which further clarification is needed. While agreeing to keep the EMA and the EUnetHTA respective assessments separate, we see persistent risks of redundancy and/or inconsistency in the assessment of some domains, particularly the Safety parameters. Accordingly, we aim to have any REA assessment to accept and be based on the decisions of EMA. Additionally, a standardised terminology should be adopted and consistently used between EMA and EUnetHTA. The interface and respective roles of EMA and EUnetHTA in the assessment of safety should be clearly defined to avoid redundant work and diverging interpretations of the same data.	We have notified the concern of possible overlap between the work of EMA and EUnetHTA, particularly related to safety domain. This issue will be given special attention in the upcoming rapid REA projects by WP5 of EUnetHTA JA2.
118.	Novartis		A relative efficacy assessment should not involve the assessment of costs or assignment of price. Accordingly, this is the domain of clinical experts, clinicians and patients, not of health economists.	Assessing costs will not be a part of rapid REAs by WP5 of EUnetHTA JA2.
119.	Novartis		The market access holder (manufacturer) should be systematically and directly be involved in the HTA scoping process. That joint scoping phase should take place as early as possible in the development process, preferably before the start of phase III pivotal studies. It could be complemented by a second scoping before the start of the preparation of the HTA submission dossier. This again emphasizes the close collaboration between manufacturer, EMA and	For the pilots in WP5 JA2 involvement of the MAH in the scoping phase is intended. The scoping should indeed start timely however it is not likely to do this before the start of the phase III pivotal studies as WP5 JA2 is only a three year project.

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			EUnetHTA.	
120.	Novartis		We welcome the fact that the core model acknowledges that rapid REA will be based on a manufacturer submission. We also welcome that the rapid REA will be based on the EPAR as a source of information, which will enable to build on knowledge developed and decisions taken in the regulatory process. Again as this is efficacy data that has been submitted to EMA, this REA should be a relative efficacy assessment.	Thank you for this comment. See response to comment 116.
121.	Novartis		EMA judgments and decisions of the MAH dossier should be accepted and not further challenged in the REA process.	The aim of REA is not to challenge EMA judgments but to provide national HTA organisations structured information which could be easily used for national HTA production, or even directly to decision making (on reimbursement, pricing, purchase and implementation). The added value of REA over EMAs documents is in the presentation of the balance between benefits and harms across relevant comparators, demanding clinically relevant endpoints, and providing additional pieces of information relevant for decision making
122.	Novartis		REA should be conducted by unbiased reviewers, specifically, REA should not be conducted by budget holders and payors – especially at the multi-country/European level, as assignment of price and reimbursement decisions shall be taken at the Member State level.	The rapid REAs performed in WP5 of JA2 will be performed by HTA professionals from several national or regional European HTA organisations.
123.	Novartis		As with Member State HTA assessments, European REAs should also have appeals procedures that are clear and unbiased, should disagreements arise in the assessment of a product.	The rapid REAs should be documents that contain a synthesis of the evidence available. REAs by EUnetHTA will not contain any recommendations supporting use or non-use of the technology, and they are by no means binding for Member States.
124.	Novartis		The selection of relevant and/or meaningful comparators (and selection criteria) for the Rapid REA is of critical importance. We suggest that the matter be addressed in a collaborative manner between EUnetHTA and Industry in parallel to the Joint Action 2.	For the pilots in WP5 JA2 involvement of the MAH in the scoping phase is intended.
125.	Novartis		The definition of a unique “most meaningful” comparator for the Rapid REA would not account for the fact that there are often several HTA-relevant comparators across and within National markets. So full use should be made of both direct and indirect comparisons methods in order to provide information that is relevant. Decision analytic modelling should also play a role here. We would like to suggest that this matter be further addressed in a direct collaboration between	The number of relevant comparators may indeed be large. In the upcoming rapid REAs of WP5 we will gather experiences of optimal procedures of selecting comparators. The likelihood of needing indirect comparisons will indeed increase with more

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			EUnetHTA and Industry.	comparators to be included. As for the use of decision analytic modeling techniques, this does not seem to be current practice in most Members States for relative effectiveness assessment (see results of WP5 background review). We can foresee in the future that the use of these models will be discussed between HTA agencies across Europe and might lead to recommendations on how to use these models in a REA.
126.	Novartis		The document makes frequent reference to the methodological guidelines that are currently being finalised based on the input received during various public consultations. It is thus difficult to have a clear discussion on the core model without having a clear understanding of these guidelines as well as the degree for which the use of these guidelines will be for a European-wide assessment, or are they for guidance for national Member States analysis. In this case, we refer to the Novartis' comments submitted in the framework of these public consultations to revisit our comments on the proposed methodologies.	Thank you for this comment and your comments on the methodological guidelines. It is indeed difficult to assess the whole picture of the REA model without seeing the guidelines, we are sorry for this inconvenience caused by the timelines of a three year project. It should be noted that all documents should be considered living documents that will be updated when needed.
127.	Novartis	14, 2	For transparency the justification of the comparator should not be optional but mandatory.	We agree and this is also expressed in the sentence "The choice of comparator should be justified explicitly in the report."
128.	Novartis	13, 14	Manufacturers should be involved in all scoping activities.	Increased and earlier involvement of manufacturer will be tested in the upcoming rapid REA projects and we will gather experience of this activity.
129.	Novartis	11, 7-13	Surrogates are often accepted by regulatory authorities. As registration studies are the basis for the rapid assessment the limited acceptance makes it difficult/impossible for the manufacturer to show benefits. Accordingly, in cases where EMA has accepted surrogates, these should be applied in REA.	A REA has a different purpose than an assessment in the light of a market authorisation. Therefore it is possible that different requirements are needed.
130.	Novartis	62, 13	Like in the endpoint papers it remains unclear how the decision is made about weighting of different endpoint with potential different effect directions. This is very subjective.	The methodology of balancing benefits and harms is still under construction.
131.	Novartis	52, 1-ff.	In a European assessment only very high level assessments of ethical, organisational, social and legal aspects can be made as the differences are relevant between the countries. Specifically these are domains that belong at the Member State level.	This is usually so but there are also cases where universal ethical concerns may affect the implementation of a technology, or e.g. the mode of

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				administration affects significantly the organisation of care, irrespective of the country. This table is there to help identifying these kind of issues.
132.	Novartis	66, 17-21; 15, box and line 11-12	It is mentioned that original and registration studies should be included and provided by the manufacturer. This will refer to assessments of relative efficacy.	See response to comment 116.
133.	Eli Lilly	General	The HTA Rapid REA Model v2.3 needs some additional clarity about the nature of the data sources to be used in the assessment process. The focus of the current version is upon two key data sources that are to be the manufacturer's submission and the EPAR [e.g. page 7, lines 42-46]. However, the although the document indicates that the rapid assessment may relate to either a new pharmaceutical launched onto the market or a pharmaceutical for a new indication or with new relevant data [page 7, lines 17-20], the focus of the rapid model pilots will be on assessment of new pharmaceuticals in parallel with the marketing authorisation process of the EMA. Although this is not specified in the document, it is implied that the assessment will occur prior to the generation of any 'real-world' data and that it will thus be limited to assessment of RCT data. This creates a fundamental problem with the document as these two different processes (pre-authorisation rapid assessment vs. post-authorisation rapid assessment) are mixed into the descriptions of the assessment methodologies. It would be very beneficial to separate the two processes and, considering the focus of the pilots in 2013, to focus only on rapid assessment of new pharmaceuticals prior to market authorisation at the EMA.	The Model has been developed to suit both purposes (pre-authorisation rapid assessment vs. post-authorisation rapid assessment). In future updates of the more explicit separation of the required methodology will be pursued.
134.	Eli Lilly	General	In the context of new pharmaceuticals being assessed prior to the EU Commission Decision, it is important to note that the EPAR will not be available until up to 15 days after the Commission Decision. It may be possible for the rapid REA assessment to use the CHMP Assessment Report which contains the key information regarding safety and efficacy required by the EUnetHTA process. However under the current EMA process, the CHMP Assessment Report will contain commercially confidential information as well as internally confidential information (e.g. names of reviewers) and is not as complete as the full EPAR. At Day 45 post the CHMP positive opinion the first draft of the EPAR is formally adopted by the CHMP and at this stage the confidentiality issues should have been identified and resolved. Therefore, the information available from the EMA for rapid assessment needs further clarification including detail about the proposed information exchange between the EMA and the EUnetHTA reviewers.	Agreeing on timelines and tasks between regulators and HTA community would indeed reduce duplicate efforts and facilitate keeping the timelines given in the Transparency Directive. These considerations will be taken forward for the WP5 JA2 pilots.

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135.	Eli Lily	General	While we recognise that a template for the manufacturer's submission is to be developed under Joint Action 2, it is clear that the rapid REA will be reliant on this submission and so there should be more explicit focus in the model about what exactly the manufacturer will be providing for all four domains. It is unclear whether the manufacturer will be required to provide information about differences in standard of care, usage or dosage patterns of comparators across the EU Member States. In addition, there needs to be a description of the mechanism by which the assessors can request clarifications from the manufacturer during the review process and how the manufacturer can have the opportunity to review the rapid REA assessment so as to ensure that their submission has been correctly interpreted.	These are good suggestions for harmonising submission file and the Model, and being explicit what is required for a submission file from the point of view of HTA. This is an activity that will proceed during JA2. We have stored these suggestions for future use.
136.	Eli Lily	General	It is fundamental to the understanding of the rapid REA model that the process by which the assessment will be conducted is made explicit. Unfortunately, in version 2.3 of the model, very limited information about the process is provided. The process description is limited to a statement that the review will be limited to two authoring agencies that will review the product across all of the domains of the model followed by an in-depth review by 'several' agencies (Page 71, lines 34-35, plus p72, lines 1-2). In a slide presentation by the WP5 leaders (W. Goettsch and S. Kleijnen, October 11, 2012) more detail on the planned process with respect to the forthcoming rapid REA pilots is provided. These slides make it very clear that the process is envisaged to commence with dual submission to the EMA for Regulatory approval and to the EUnetHTA process with submission of a concept file with the REA process commencing at the time of the CHMP positive opinion. It would have been helpful for this information to have been included into the rapid REA model and we recommend that this information is built into the next version of the model.	See response to comment 7.
137.	Eli Lily	General	The document indicates that there will be two authoring agencies followed by multi-agency review. It would be helpful to expand upon this. Is the intention to follow a rapporteur/co-rapporteur model with a reviewing CHMP-style HTA committee? A clear description of the assessment process is required including specification as to which agencies will be selected as rapporteurs and co-rapporteurs. Different possibilities can be envisaged such as where a 'mature' agency will be the lead author with a 'weaker' agency joining them to help build experience; alternatively the two agencies might be selected based upon capturing diversity of systems. Secondly, how will the review be conducted? Will this be done separately by agencies or together in the form of a committee? How will conflicting opinions be resolved? How will additional information be requested, if at all, and at what stage? Thirdly, there is considerable	See response to comment 8

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			focus on the issue of industry bias, however how will assessor bias be evaluated? Such biases may occur due to the nature of that agencies HTA system and how that agencies weights risks and benefits, or due to a local need for cost containment that may lead to more stringent reviews of products perceived to have a high budget impact.	
138.	Eli Lily	General	There needs to be further clarity in the model as to how the rapid REA process will interact with the EMA regulatory approval process. The draft process from the Goettsch/Kleijnen presentation indicates that T=0 is the day of the CHMP positive opinion with steps related to scoping and manufacturer preparation of the submission file occurring prior to that date. This would require at minimum notification from the CHMP and possibly also the provision of either the CHMP Assessment Report and/or the draft EPAR at day 45. Either way there will also be a requirement for interaction prior to T=0 in order to determine the likely label that will be authorised as this will have a direct impact on the manufacturer's submission.	See response to comment 9
139.	Eli Lily	General	The manufacture's submission will be the key document upon which the rapid REA will be conducted. As such it will be critical to build into the process the opportunity for the assessors to request clarification from the manufacturer and also for the manufacturer to have the ability to review the assessment prior to its finalisation and thus have the opportunity to provide feedback or dispute findings that they may consider inappropriate. At this stage there should also be consideration of a process for arbitration in order to resolve differences in opinion. This might also apply where there are differences between the reviewing agencies that cannot be readily resolved.	See response to comment 10
140.	Eli Lily	General	We think that it will be important to explain how EUnetHTA propose to understand the value of this report to the Member States and we suggest that EUnetHTA consider including a mechanism to learn from and refine the process after reviewing the extent of adoption by Member States.	See response to comment 11
141.	Eli Lily	General	While we recognise that due to the difference in HTA and reimbursement systems at the Member State level some aspects of the findings in the report may be more or less useful for individual agencies, it is of critical importance to industry – and to the ultimate success of the model itself – that those agencies that do use some or all of the rapid assessment reports do so in a <i>consistent</i> manner. Therefore, we recommend that EUnetHTA establish a scorecard to track the dissemination and use of the rapid reports, this will also help EUnetHTA learn from their "customers" – the Member States, about the value of the report (as mentioned above).	Monitoring the use of REA model and the REA reports, as well as the national HTA reports prepared based on the REA report is important and is already taken into consideration in the Core Model development in general. Concrete plans become topical when there the first actual core reports (the HTA reports that have used the Core Model) are published
142.	Eli Lily	General	The term "Manufacturers Submission Files" should relate to a product's HTA submission file	Thank you for the comment, this has been improved.

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			and not the Marketing Authorisation submission However this is not clear always clear in the current guidelines; the language should be reviewed and clarified as appropriate.	
143.	Eli Lily	General	There is a potential duplication of efficacy and safety assessments that are performed by Regulatory. –Regulatory assessments should not be duplicated by the EUnetHTA process.	This will be further tested in the pilots in WP5 JA2. .
144.	Eli Lily	Section 3.1, page 25-30	Multiple sources are cited but not the manufacturer's submission. Pragmatically, the manufacturer's submission would constitute a significant part of this section and should be included.	Manufacturer's submission file added as a source in most of the elements of the HPCU domain.
145.	Eli Lily	Section 3.1, page 25-30 & 3.2, page 31-34	There is in general a lack of specificity in the recommendations regarding production of the HPCU (3.1) and DCT (3.2) sections. Granted, the objective is in most cases to produce a "descriptive summary," but recommending the use of an extremely broad list of sources (see page 16), to include "Google" and "other internet search engines," is of questionable value. It would be beneficial to work towards a consistent approach to at least some of the elements in these sections, even if the selected approaches/sources are not necessarily authoritative, they should have a high degree of validity and reliability.	See response to comment 17.
146.	Eli Lily	Section 3.3, page 35-38 & 3.4, page 39-42	The guidance appears to call for redundant work in the safety section (3.3) and effectiveness (3.4) domains relative to what can be found in the EPAR. The focus should be beyond the scope of regulatory documents (element C0008, for example, which calls for a <u>comparative</u> safety assessment)? There is a potential duplication of efficacy and safety assessment that is performed by Regulatory –Regulatory assessments should not be duplicated.	See response to comment 18
147.	Eli Lily	Section 3.3, page 35-38	It appears that the assessors of the REA are being asked to make judgments on safety issues. Use of the term "harms" is new within the EUnetHTA guideline. For example, would there be a consistent understanding of the difference between harm vs. ADE vs. ADR vs. serious or severe ADR. It may be inappropriate in this context and appears to come from a negative point of view. Some additional examples and issues are: <ul style="list-style-type: none"> <li>• CTs determine relative frequencies of adverse events and suspected ADRs. How is this to be used by EUnetHTA?</li> <li>• Adverse events/suspected ADRs can be frequent and severe (e.g. a headache is frequent but not necessarily important from a safety perspective. How will these be weighed against one another? Some are more of a tolerability issue rather than an ADR.</li> <li>• Very rare cases of hepatic effects would be of greater clinical concern. Are HTA assessors trained to make this judgement call</li> </ul>	See response to comment 19.



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148.	Eli Lily	Page 7, line 45,46	The section cites the call for a full systematic literature search in reference databases. In what circumstances is it envisaged that this would be needed?	See response to comment 20.
149.	Eli Lily	Page 8, lines 25, 26: What is relative effectiveness?	As an illustration of the above point it states that data on results under usual circumstances of health care are often not available at a first launch but then the guidelines go on to discuss implications of using additional data for assessment of relative effectiveness. The guidelines should clarify what data are expected under at least two unique circumstances: (1) a first launch for the product, or (2) when the product has been approved and launched elsewhere such that additional "real world" information is available.	See response to comment 22.
150.	Eli Lily	Page 9, line 8	The guidelines request data on the patterns of use of the technology but these data are unlikely to be available unless the product has been launched elsewhere in the world (see above).	See response to comment 23.
151.	Eli Lily	Page 10, line 14 Safety	The guidelines do not state <i>how</i> safety should be compared for and against a comparator.	See response to comment 25.
152.	Eli Lily	Page 11, line 11 Surrogate endpoints	Who determines, and how, whether surrogate end-points are appropriately validated. What if there is disagreement between Regulatory and HTA?	See response to comment 27..
153.	Eli Lily	Page 12 , section 2.2 Scoping	It appears the manufacturer needs to submit a file PRIOR to scoping occurring. Shouldn't the scoping come before the submission in order that the appropriate data are contained in the submission, e.g. choice of comparator	See response to comment 28.
154.	Eli Lily	Page 13, Line 24	The guidelines should give additional clarification on what is meant by "usually", perhaps choose a different term, or request for information. For example, if "usually" is the standard, are there any notable exceptions?	See response to comment 29.
155.	Eli Lily	Page 13, lines 44-49, Comparison(s)	The possibility for variable practice across Europe means the choice of a single comparator based on "current clinical practice" will be difficult if there are not clear guidelines on how to do this for current clinical practice and in which countries? The choice of comparators needs further explanation, given that treatment practice and reimbursements varies between countries in the EU. From this paragraph "the number of comparators should be limited and thus the most meaningful comparator will be current clinical practice because this will be most informative and relevant."	See response to comment 30.
156.	Eli Lily	Page 14, lines 1-3 Comparison(s)	A request is made for data on current treatment pathways from as many member states as possible are requested. Who will generate this data?	See response to comment 32.
157.	Eli Lily	Page 15,	It is not clear what document is being requested here. Is it the Clinical Study Report?	See response to comment 80.

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		section 2.3 and line 11: "Original Studies"		
158.	Eli Lily	Page 16, Table 1	General: this table needs to be more focused on sources of high quality evidence. – many of the websites listed do not seem to be appropriate sources for REA, (i.e. national health services websites, etc)	See response to comment 81.
159.	Eli Lily	Page 17, Line 10-11	Is there a requirement that the manufacturer provide updates over time to their HTA Core Model Submission – if so at what frequency and how should the updates be provided?	See response to comment 35.
160.	Eli Lily	Page 19, Line 18	It is not clear what is meant by "artificial" relevance – Please clarify	See response to comment 84.
161.	Eli Lily	Page 20, Line 1	Is there a suggested template or format for the manufacturers to use?	See response to comment 37.
162.	Eli Lily	Page 20, Line 7-12	Suggest that the sentence: "unsystematic gathering of information from ...the internet can be considered" – is either removed or the context is clarified* or as this approach will not make for the basis of a robust scientific review. <i>*perhaps this refers to the gathering of the "background" information such as burden of disease and epidemiology, but this needs to be clarified</i> Also this paragraph does not seem to be aligned with the rest of the document.= (i.e. it implies that a systematic review from the MA holder is not mandatory)	See response to comment 38.
163.	Eli Lily	Page 20, Line number 11-12	Does the entire regulatory submission to the EMEA need to be submitted?	See response to comment 39.
164.	Eli Lily	Page 20, line 30	General point for this section – perhaps worth including here the relevance of meta-analysis and where it lies within the levels of evidence.	See response to comment 40.
165.	Eli Lily	Page 20, Line number 52	What does full assessment mean here?	See response to comment 41.
166.	Eli Lily	Page 21, Line number 25-28	Of the three options listed for assessing bias in clinical effectiveness data – which is preferred?	See response to comment 43.
167.	Eli Lily	Page 23, Line numbers 38-40	Drug interactions in patient populations outside of the clinical trial are not likely to be known at the time of REA. Is there an expectation to provide updates on this information over time as it becomes available? This is another example of the clarity needed for a first launch vs. a follow-on launch after the product has been on the market elsewhere in the world.	See response to comment 97.

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168.	Eli Lily	Page 24, line numbers 6-11	The extent of medication errors are also not likely to be known at the time of a REA.	See response to comment 45.
169.	Eli Lily	Page 25, A0003	Is it expected that the manufacturer will do a literature search to identify and present prevalence of risk factors across geographic areas and subpopulations?	See response to comment 46.
170.	Eli Lily	Page 26, A0006	Based on the sources/methods listed – incidence/prevalence/mortality should not be identified via a literature review. If national statistics are to be used, aren't these country-specific? Does the manufacturer need to try to identify country-specific numbers via these national databases across all EU member states?	See response to comment 47.
171.	Eli Lily	Page 26, A0006	Guidance on whether EU or country specific data is preferred; if country specific, how many and which countries?	See response to comment 47.
172.	Eli Lily	Page 27, A0023	Does manufacturer need to identify and present the potential number of people in the target population for each of the EU member states?	See response to comment 49.
173.	Eli Lily	Page 27, A0023	"How many people belong to the target population?" The clarification notes that "this information is required e.g., for budget impact and other resource calculations," which are specifically called out of scope for the REA. I would think the guidance around this element should discuss the importance of this information for REA purposes, for example, increase in population exposed and greater potential for benefit/harm. It would also help to provide guidance around specific geographies to focus on (again, for REA rather than budget impact purposes).	See response to comment 50.
174.	Eli Lily	Page 33, B004 and B005	We could not determine who administers this and in what level of care it is administered and it will vary by country – Is it assumed this is consistent across the EU as a whole? This may not be a valid assumption.	See response to comment 52.
175.	Eli Lily	Page 34, B0011	"What kind of registry is needed to monitor the use of the technology and comparator?" This strikes us as fundamentally a regulatory concern. Is it proposed that both the EMA and a central HTA agency make this determination independently? Per earlier comments, this is not an appropriate issue for the HTA agency as it has at best the potential for redundancy and, at worst, the potential for conflict and confusion.	See response to comment 53.
176.	Eli Lily	Page 36, C002	The concept of dose relationship is introduced here. If this has been established in CTs, then it would have been taken into account in the approval process and the final recommended doses which would seek to optimise benefit risk...presumably doses which would tip the B/R into the marginal or negative would not be approved; similarly doses where the therapeutic index is so marginal .....if there were implications for training and organisation, then that would be covered in the conditions of approval with respect to the risk and covered in the RMP ...a publically	See response to comment 54.

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			available summary will be published	
177.	Eli Lily	Page 36, C004	It is difficult to see how this information will be available from controlled CTs...also it is in the purview of risk management and regulators and not HTA	See response to comment 55.
178.	Eli Lily	Page 36, C005	if these subgroups have been identified, then that it actually a positive point as it can help make appropriate mitigation	See response to comment 56.
179.	Eli Lily	Page 37, C008	This is a clinical judgement that may fit more with the regulators rather than the HTA agencies	See response to comment 57.
180.	Eli Lily	Page 39 General comment on section 3.4 Clinical effectiveness elements	General comment on the example clinical effectiveness elements: The sources listed for the Clinical effectiveness data are very broad especially if this needs to be applied to the selected comparators (observational data, registries are listed). Could the data sources listed be more focused and selective? Would the issue best be handled by a systematic review of RCT data and, if so, who should do it?	See response to comment 58.
181.	Eli Lily	Page 42, D0016, D0012, & D0013	We suggest that clarification is needed here. The guideline proposes to report the results in absolute terms and relative to the comparator. Please clarify whether this mean quantitatively relative to the comparator (i.e., an indirect meta-analysis)?	See response to comment 59..
182.	Eli Lily	Page 42, D0017	"Was the use of the technology worthwhile?" The clarification here calls for information on patients' perceptions of value and satisfaction. These are two very different issues, and we would propose that neither answers the question of whether a technology is worthwhile. We would suggest rephrasing this issue as "What is the effect of the technology on patient satisfaction?" and perhaps having another separate issue "What is the effect of the technology on patient perceptions of value?" to include data from contingent valuations, etc.	See response to comment 60.
183.	Eli Lily	Page 56, Template5	Assume that it would not be expected that this be completed for comparators and that we would report abbreviated data on comparators?	See response to comment 61.
184.	Eli Lily	Page 75, 76 Appendix 5	The specificity of these guidelines will be key to the implementation of this Core Model.	See response to comment 62.
185.	HIS	General	Use abbreviations consistently throughout the document e.g. once REA has been defined do not revert back to Rapid Effectiveness Assessment.	Thank you the abbreviation REA was added in all relevant places except in titles and in the names of the documents.
186.	HIS	General	The core model for REA ought not to assume prior working knowledge of the HTA core model.	The first paragraph of the introduction describes Core Model briefly and provides a link for further information. We agree that this may be insufficient for persons not

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				familiar with the EUnetHTA HTA Core Model. The extent of introduction can be considered again in the update of the REA model.
187.	HIS	General	The Guidelines on methodological issues (Appendix 5) should have been included in the consultation version as it is impossible to comment on any of the model content related to those guidelines (a substantial amount of the model content).	This is an unfortunate drawback of the timelines of Joint Action 1 as the guidelines were under consultation at the same time.
188.	HIS	Page 7 line 7 & 49	A clear statement of the 'who' involved in preparing REAs would be helpful early in the Introduction. 'Co-production of HTA reports (by multiple HTA agencies)' hints at it but the reader has to wait until the bullet point line 49 for clarification of what it actually means. Bring this information together.	The bullet point in line 49 has been moved upwards in the paragraph and is slightly reworded to improve clarity:
189.	HIS	Page 9 line 6-28	This should clarify that it's the health problem, current use of the technology and current management patterns <i>across member states</i> (not doing so raises the question of ...where? In the mind of this reader). This should be done in all parts of the document that refer to current practice – this includes the comparators.	This could indeed be a good amendment to systematically remind the users of the Model to provide information on the issues across Member States (if possible). This initiative will be taken to the REA model team to be considered for the update.
190.	HIS	Page 10 line 17	Does 'The HTA assessors' refer to the authors of the REA? If so, use consistent terminology throughout the document.	Thank you, all the 'assessors' replaced by 'authors'
191.	HIS	Page 13 line 49	I suggest moving the last sentence 'Preferably the comparator should be chosen based on input on the current treatment pathway from as much member states as possible.' to the beginning of the paragraph.	The sentence was moved.
192.	HIS	Page 13 line 39	Thorough familiarity with the dose-response relationships of the compared treatment is a prerequisite for interpreting the results of the comparisons' is an unrealistic expectation of authors of any 'rapid' assessment that is to include comparators used across all member states. Is it not familiarity with the recommended therapeutic doses of each comparator that is prerequisite?	The sentence is modified to be: <i>"Familiarity with the recommended therapeutic doses of each comparator and knowledge of their dose-response relationships are a prerequisite for interpreting the results of the comparisons."</i>
193.	HIS	Page 15 line 19	How feasible in the timeframe for REA stated on page 7 line 26 is 'a detailed search' of the type described?	The following sentence has been added: 'Doing a systematic search will lengthen the timelines within which a rapid assessment is feasible'
194.	HIS	Page 15 line 19	Does 'the HTA organisation' refer to the HTA agency preparing the REA?	HTA organisation has been replaced by 'the authors of the rapid assessment'
195.	HIS	Page 16 line 2	Be consistent in use of capitals (e.g. Medline or MEDLINE). It's PsycINFO not Psychinfo (no 'h')	Medline and PsycINFO have been corrected throughout the document.

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196.	HIS	Page 20 line 19	'scope of HTA assessors' is unclear (and, does 'HTA assessors' refer to the authors of the REA?)	The section has been reworded. The specific sentence referred to has been deleted.
197.	HIS	Page 20 line 35	'...where an RCT is not feasible (for example, if the therapist and/or patient have a strong preference for a specific therapy alternative)' that isn't really a reason why an RCT would not be feasible. A very rare condition might, for example, make an RCT practically infeasible; or an 'end of life' treatment may make an RCT ethically infeasible.	The brackets with content removed
198.	HIS	Page 21 line 20	'The risk of bias concept should be used to assess the internal validity of RCTs...' What about non-RCTs?	RCTs has been replaced by 'clinical studies'
199.	HIS	Page 22 line 33	I suggest that you consider separating Reporting from Interpreting (i.e. separate sections)	As suggested, they have been separated into 2 sections
200.	HIS	Page 22 line 34	'... is crucial when reporting a Core HTA' could this say REA, because that is what this document is about.	The suggested change has been made
201.	HIS	Page 22 line 45	Does 'HTA report' refer to REA report?	The suggested change has been made
202.	HIS	Page 23 line 26	Suggest <i>comparing</i> instead of 'calibrating'.	The suggested change has been made
203.	HIS	Page 23 line 29	Can you say REAs instead of 'HTAs' because that is what this document is about (the document doesn't need to allude to wider principles of HTA, and doing so detracts from the clarity of the guidance on REA).	The suggested change has been made
204.	HIS	Page 23 line 33 to page 24 line 17	This and page 20 line 14 to 27 should be more coherent (possibly they were written by different people?). Also, be precise in the use of the terms adverse events and adverse effects, don't use them interchangeably as they are not the same thing.	These text pieces are merged and harmonised as suggested
205.	HIS	Page 23 line 36	'will be assessed' is unclear; who will assess it (does it mean should be assessed by the authors of the REA)?	The sentence is modified to be: <i>"The authors of REA should check the evidence base of label warnings and the pharmaceutical precautions against published studies"</i> .
206.	HIS	Page 49 line 8	It's unclear why some guideline producers are listed and not others, the list ought to be either comprehensive (or have some rationale for which producers are listed) or should focus on guidelines collections.	It is the intention to have a list as comprehensive as possible. Suggestions making the list more complete are very welcome.
207.	HIS	Page 64 line 1	Appendix 3 contains references that aren't listed.	References added.
208.	HIS	Page 64 line 21	Is it a 'chapter'?	Has been reworded into 'appendix'. In addition, this section should be updated in the next version of the Model for Rapid REA.
209.	HIS	Page 64 line 13	The author may want to refer to the CRD guidance updated in 2009 as Khan 2001 is a very out of date document. Several other references to sources cited are also out of date (have	The reference has been changed. In addition, this section should be updated in the next version of the

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			subsequently been updated), and PRISMA is the updated version of QOROM.	Model for Rapid REA.
210.	HIS	Page 64 line 21	It's no longer the NHS CRD, it's just CRD.	The suggested change has been made. In addition, this section should be updated in the next version of the Model for Rapid REA.
211.	HIS	Page 64 line 46	'If the report is judged to be transferable to one's own health care system and the local setting, then this report could be the basis for the core assessment.' Does this contradict the REA core model, which seems to imply—although does not explicitly state—that a REA would address the use of a technology across member states. Perhaps 'who' authors REAs is obvious to users of the HTA core model, but the core model for REA ought not to assume prior working knowledge of the HTA core model.	The sentence has been removed. In addition, this section should be updated in the next version of the Model for Rapid REA.
212.	HIS	Page 64 line 52	'one might need to execute a full systematic review of clinical efficacy / effectiveness' How feasible is that in the timeframe for REA stated on page 7 line 26?	The following sentence has been added: 'Doing a systematic search will lengthen the timelines within which a rapid assessment is feasible'
213.	HIS	Page 64 line 52	'The following paragraphs provide a more detailed guidance for this task.' Firstly, I would question the need for this content in the model as there is already abundant (and better) guidance on how to conduct a systematic review of effectiveness. A concise summary of systematic review methodology with well-chosen references to current <b>key</b> resources would serve this purpose better. However, if this section is to be retained in its current format, the content needs to be much better integrated with the rest of the document (including appendix 5 when that is added) i.e. it should clearly relate the purpose of the systematic review being done to the context of the REA for which it is being done. It looks like the author of this section has not read the rest of the document.	Preferably, a submission file from the manufacturer should provide a search and results. However, it may be possible that in some case a submission file is not available or the provided search is of poor quality. In such a case we would like to provide the authors with some guidance on how to perform a search. We realise that the current section is outdated and does not fully fit it's purpose. Therefore, this section should be updated in the next version of the Model for Rapid REA.
214.	HIS	Page 69 lines 5 & 7	'...' is something missing?	... is replaced with e.g.
215.	HIS	Page 70 Appendix 4	How much of the repetition of the final [draft] model content is really necessary in this appendix? A good edit would make it much more effective in conveying key aspects in the model's development.	This appendix was considered necessary only for this version of this Model. In the subsequent updates there is probably less need to explain the background and processes of the project so carefully.
216.	HIS	Page 73 line 1	'(refs)'?	References added.