EUnetHTA WP5
Relative Effectiveness Assessment (REA) of Pharmaceuticals

Comments provided during public consultation of
Draft Background Review on
Relative Effectiveness Assessment of Pharmaceuticals

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1.	ISPOR	General	Authors suggested the following classification of [HTA] assessments – Rapid and Full. In the context of a particular document, 'Rapid' may not be the best word. Kudos to authors for including definitions and explanations for 'Rapid assessment' throughout the document. However, it seems that the word 'rapid' is perceived as confusing (even to the authors). E.g., authors often say "(single) rapid assessment' as a reference to a single therapeutic option (a drug or an intervention). Would you be able to change "Rapid" → "**Partial**"? In this case, a classification may look as follows: **Partial assessments** and **Full assessments**.	We understand the possible confusion regarding terminology as in general, terminology is often based on regional preferences instead of world-wide agreed terms. The authors believe that partial may be confusing as well. In general, a rapid review or rapid assessment is a common term in Europe. Therefore we choose to use this term. Further, "(single) rapid assessment' refers to an assessment of a (often new) pharmaceuticals relative to it's comparators. Hence, the 'single' represents the reason for initiating the assessment (a specific pharmaceutical) whereas there may be multiple comparators.
2.	ISPOR	General	This document represents a tremendous amount of work for a very useful purpose! I am not pleased with re-defining the terms "efficacy" and "effectiveness" as attempted. The new definitions include a "net" effect, whereas the standard definitions are absolute and based just on control of the particular condition. There is no operational quantification of either efficacy or effectiveness at the net, at the present time. Thus, even using these terms conceptually will still cause confusion. I recommend sticking to the traditional definitions but noting that they are viewed for HTA and less formal drug usage policy decision-making IN CONTEXT of safety.	Thank you for the complement. We agree that the definitions of the HLPF are not ideal. However, they are a consensus between many stakeholders and should therefore be basis of the work on relative effectiveness assessment within EUnetHTA.
3.	ISPOR	General	Throughout the document, there is a sense that all the countries involved are making relative effectiveness decisions to support reimbursement. In the UK that is not the case, at least in a direct way. Pharmaceuticals which have a product license are automatically reimbursed unless placed on a restricted list (where the NHS will not pay for any prescriptions). The advice from NICE and SMC is about use in clinical practice – if a product	A clarification is added to section 2.1.

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			receives a negative NICE review it is still technically reimbursed but it is not advised. Perhaps throughout it would be better to word as "support reimbursement and clinical management decisions" or at very least clear up the issue with NICE and SMC at the beginning of the document.	
4.	ISPOR	General	An assessment for additional commas could be done; many appear to be missing	Thank you for pointing this out.
5.	ISPOR	General	Congratulations on this mammoth effort. The information collated and presented in the report is of significant value to health outcomes researchers worldwide. The report is well written and the Appendix information is clearly structured and overall presents a clear picture of the current status.	Thank you for the complement.
6.	ISPOR	General	Did you consider the increasing use by EMA and FDA of imposing requirements for post-authorisation studies as a trend that may become more frequently used as a means to ensure that data to determine effectiveness in real world use becomes available within a given timeframe?	We agree that post marketing studies may be useful for relative effectiveness assessment in the real world. Currently however it is not quite clear how these data can be used because often only data on the new pharmaceutical are collected while information on the comparative treatment is not collected.
7.	ISPOR	General	I enjoyed reading this important and well-written background review. This EUnetHTA JA WP5: Relative Effectiveness Assessment (REA) of Pharmaceuticals reviews the scope, the process, and the scientific methods used for relative effectiveness assessment of pharmaceuticals through literature review and supplemental survey of 30 countries. In general, this review is thorough with a lot of information. However, I would like to see paragraphs or sentences categorizing these countries into different subgroups based on the similarities of their process or structure of reimbursement evaluation or performing REA. Also providing a little bit more historic reason for the current practice of REA in each country may help pave the way for future integration of REA across these countries (each REA model may have been designed unique to its health system). In addition, discussing main lessons learned from the different REAs	Thank you for the complement. We think this is a useful suggestion however as we have not the historic reason for the current practice of REA in various jurisdictions we cannot provide this information.

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			across these countries will be very helpful for policy makers in allocating budget for health services research.	
8.	ISPOR	General	All first word of footnote should be capitalized for consistency. Example to fix: page XIV footnote 82.. note this is not a complete list	Processed as suggested.
9.	ISPOR	General	Like to reiterate the importance of standards in terms of definitions (HTA, CER, EBM) and data	We agree with the comment as also suggested in the summary of most relevant challenges.
10.	ISPOR	General	There is no mention of observational or epidemiologic research methods as they apply to CER; there is extensive background on internal/external validity in design that would relate to this	These items will be discussed in the guidelines that are being developed within WP5.
11.	ISPOR	General	Good summary of the international groups involved in CER (relative effectiveness assessment)	Thank you for the complement.
12.	ISPOR	General	It may be useful to define who will use the tools and methods developed (page 9 line 21) for example industry, government, academia. Consider having a list of the size of population corresponding to each of the 30 countries for which information has been data extracted. In this way some variation in methods may later be explained by the magnitude of healthcare provision. Unfortunately there is no consideration of health economics – but as long as the working title is "effectiveness" – and not efficiency – this seems to be appropriate Several differentiations are addressed within the report: a) inpatient and outpatient, b) rapid and full assessment c), assessment and appraisal – it will be difficult to address all sub-items when designing a common tools to be used by all member	Thank you for your comments. Regarding the specific issues we would like to comment: These tools and methods will be developed in order to support reimbursement decisions. A list of the size of the populations is not included as it is not possible within the current timeframe to explore relationships between methods and size of population. The working title is indeed relative effectiveness and not efficiency. The authors feel that it is possible to design common tools for assessment (appraisal is not the remit of WP5). There will not be a specific tool for outpatient vs inpatient, however there will be different tools for rapid and full assessments.

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			states. I like the focus on relative effectiveness with three important elements (chapter 1.2.3) Unfortunately there is no focus on medical devices. For users it is more promising to use the appendix which presents details per country. Due to inhomogeneous health care systems a quantitative evaluation is of less importance The report is helpful for the identification of which item to consider. It does not really express what items are considered in the national health care settings.	 The focus of WP5 are pharmaceuticals, therefore other medical technologies will not be adressed. However within other workpackages in EUnetHTA other medical technologies will be covered. The authors feel that a quantative evaluation is relevant for WP5 as it shows if there is common ground for a shared assessment. The focus of WP5 is indeed to identify items to consider in a shared assessment and not focus on national health care settings.
13.	ISPOR	General	This is a very interesting and important aspect of effectiveness assessment relative to international perspective. The way you have structured the problem and the background is very comprehensive. This very nice review that worth the time and effort. See a few additional comments in the rows below.	Thank you for the complement.
14.	ISPOR	General	I would only comment, and not about content that does not seem questionable. I refer to the presentation of the tables, both in the main document as annexes. I would suggest that the presentation of tables and figures are more striking to the eyes with the use, for example, orange and yellow colours.	We appreciate the comment. The colours have been adapted.
15.	ISPOR	General	The mock 3-D graphs make it impossible to determine the value from end of the bar and the scale. For example, Figure 6 has four bars representing a value of 80% and the scale ends at 80% but the bars do not appear to be at the end of the scale. The best solution is to not use mock 3-D (it is visually confusing and misleading). Most of the figures use rectangular prisms for the bars, but	Processed

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			Figures 17 and 18 inconsistently use cylinders. The best solution would be not to use mock 3-D. The grey background in the figures is likely to lead to poor resolution if the document is copied/printed in black and white. A solution is to leave the background white. The use of solid (saturated) yellow and solid (saturated) red for most bars, while consistent with the colours in the EUnetHTA logo, may be difficult to distinguish if the document is copied/printed in black and white. Solutions are to use a less saturated colour for one of the bars (e.g.,, light yellow vs saturated red) or hatching (e.g., have red hatching on a light red background for the red bars). Whatever is decided for the graphs, they should be copied in black and white to check that they remain clear and legible when copied, since this is likely to have occurred for some readers of the document.	
16.	ISPOR	General	Congratulations on this mammoth effort. The information collated and presented in the report is of significant value to health outcomes researchers worldwide. The report is well written and the Appendix information is clearly structured and overall presents a clear picture of the current status.	Thank you for the complement.
17.	ISPOR	General	Thanks again for the opportunity to review this excellent report. Please include me again in any future review panel for this project.	Thank you for the complement and your interest in this project.
18.	ISPOR	General	(General) I really appreciate to have a chance to review the draft report, which is very important and informative to those in academics, government side and/or health insurance side. The authors did great job. They defined the terms and delivered information on the process and major criteria of relative effectiveness assessment.	Thank you for the complement.
19.	ISPOR	General	As for national activities outside of Europe, I wonder why they	The websites of CADTH and PHARMAC were searched as well

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			choose only AHRQ, ICER, PBAC, PCORI, DERP. Canada and New Zealand have nothing to do with REA?	(as mentioned in the introduction of chapter 3) however we did not find any activities to the production of specific guidelines.
20.	ISPOR	General	Still I am confused with the term "rapid assessment", it sounds like "priority review of FDA". If (single) rapid assessment is formal process to most countries, can it be called (more formally) standard assessment?	We understand the possible confusion regarding terminology as in general terminology is often based on regional preferences instead of world-wide agreed terms. (single) rapid assessment is a commonly used term in Europe referring to assessments that provide input for decision making and are conducted within a limited timeframe. Therefore the authors choose to stay with the term.
21.	ISPOR	General	All charts and graphs: 3D graphs are difficult to read, and inappropriate if no 3rd dimension is being presented	Processed
22.	ISPOR	General	The fact that all countries conduct REA does not mean that it can necessarily be shared between countries. One should further clarify how relative effectiveness is assessed in EU countries. At present, there are at least two different approaches: a continuous quantitative estimate in the context of cost-effectiveness modeling (e.g. NL, England) versus a categorical qualitative estimate of "added value" in some other countries (e.g. France, Belgium, Germany)	Your comments are worthwhile and are used in the current development of the guidelines within WP5. In this review we restrained ourselves to the REA, within our remit, and did not perform any detailed analysis of processes and methodology that relates to CEA.
23.	ISPOR	General	Efficacy and effectiveness are in fact on a continuous spectrum but that, from an operational standpoint, what matters is to clearly define the source of information from which relative efficacy and relative effectiveness estimates may be derived. Specifically: - Estimates of relative efficacy can be derived from (1) direct comparisons within randomised clinical trials, and (2) indirect comparison of information from separate clinical trials using meta-analytical methods. - Estimates of relative effectiveness can be derived from multiple sources that include e.g., (1) clinical studies that use a study population, comparator, or treatment scheme close to real world	Your comments are worthwhile and are used in the current development of the guidelines within WP5. We look forward to a discussion on the methodological guidelines in 2012.

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			practice, (2) observational studies (cohorts, case/control, exposed/non-exposed, registries, claims databases, etc.), and (3) models that bridge relative efficacy data with epidemiological information on the natural history of the disease and/or context-specific resource utilization data. We understand that these are currently looked at in the development of methodological guidelines and we would be pleased to be able to contribute to that on-going discussion.	
24.	ISPOR	Summary, Footnote on Page 5	"(Single) rapid assessment are assessments ..." should be either "(Single) rapid assessment is an assessment ..." or "Rapid assessments are those..."	Processed
25.	ISPOR	Summary, Page 6 Line 17	"technical characteristics if the technology" should be "technical characteristics of the technology"	Processed
26.	ISPOR	Summary, Table on Page 6	Suggest to use bullets for each cell of the right column	Processed
27.	ISPOR	Summary, Page 5 line 23	The paragraph starting at this line reads almost identically to section 4.2 – it may benefit from slight re-wording to emphasize key points rather than just repeat the discussion	Processed
28.	ISPOR	Summary, Page 6 line 11	This sentence suggests that "this comparative analysis" can be shared between countries but earlier it was pointed out that there could be different comparators etc. Should this be more clearly worded as "the methodology of comparative analysis"?	The authors feel that not only the methodology, but also the actual assessment may be shared in case of the same comparator. However, the decision based on the assessment is up to the individual member states. Therefore we have not changed the sentence.
29.	ISPOR	Summary, Page 6 line 8	As above, this paragraph is almost identical to section 4.3 so it doesn't draw your attention if you read the summary after the whole document. Perhaps some re-wording would make it stand out more.	Processed
30.	ISPOR	Summary, Page 6 line	In this table I would suggest some re-wording in the final row – perhaps what the guideline could focus on is "justification for the	The guideline includes general recommendations and good practice rules for the choice of the most appropriate comparator

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		Summary, 34	choice of comparator" rather than just the choice of comparator. Although different systems may end up with a different comparator, the steps taken to get there (i.e. to justify the choice) could be similar.	for relative effectiveness assessments which includes justification. We have rephrased the title of the guideline into: 'Criteria for the choice of the most appropriate comparator(s)'.
31.	ISPOR	Summary, Page 6 line 17	Should be "characteristics of"	Processed
32.	ISPOR	Summary, Page 6, line 18	----such as ethical, social - - -	Processed
33.	ISPOR	Summary, p5, line 14	'Unites' -> 'United'	Processed
34.	ISPOR	Summary, p5, line 31	'comparable' -> 'similar'; it is not that the outcomes being used are able to be compared [ie, that they can be validly analysed] that is the point here; rather, the point is that the same – or similar – outcomes are used in different countries	Processed
35.	ISPOR	Summary, p5, line 39	'differences,' -> 'differences' (i.e. comma is not required)	Processed
36.	ISPOR	Summary, 6:18	Insert 'as' between 'such' and 'ethical'	Processed
37.	ISPOR	Summary, 6:34	Consider adding to the table of challenges the issue that some countries may not recognise the value in adopting a common methodology especially where their economy is not able to support access to the newer technologies.	It is the scope of this background review to look at methodology for relative effectiveness assessment, the suggested challenge is out of the scope.
38.	ISPOR	Summary/Introduction	The purpose and intent of the overall effort is not made clear; it seems to be presenting an "academic" case for why this background is being provided, but not information as to what larger effort is being supported.	The authors feel that this is addressed in section 1.1.
39.	ISPOR	**Introduction,** Page 9, line 29-	Starting with 'an overview of the processes…' These sentences can be moved to the beginning of this paragraph before line 29	The authors feel that the current structure of this section is adequate.

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		35		
40.	ISPOR	**Introduction,** General-editorial (Appendix)	All first word of footnote should be capitalized for consistency. Example to fix: page XIV footnote 82.. note this is not a complete list	Processed
41.	ISPOR	**Introduction,** Page 12, line 39	Replace ';' with '.' Note this is not a complete list	Processed
42.	ISPOR	**Introduction,** Page 13 lines12-13	Suggest rephrasing title of 1.2.3.2. Perhaps introduce in acronyms: REA, HTA, EBA	The title has been rephrased into: Confusing terminology.
43.	ISPOR	**Introduction,** Page 13 **Introduction,** line 14-19	First sentence would read 'The terms evidence based medicine, comparative effectiveness research and health technology assessment are often used interchangeably.' The second sentence would read 'However, each of these entities is used to address health outcomes and policy questions from different perspectives motivated by different needs.'	This section has been rephrased.
44.	ISPOR	**Introduction,** Page 13 line 19-21	Modify phrasing of this sentence to 'It should be noted that in this graph, comparative effectiveness research is positioned as a *measure* that provides input	This section has been rephrased.
45.	ISPOR	**Introduction,** Page 13 line 19	Perhaps to add one sentence that describes that in HTA, the aspect of study design is to answer the following questions: Can it work? Will it work? Is it worth it at all? Having these headers first introduced in Figure 2 seems a little unclear	This section has been rephrased.
46.	ISPOR	**Introduction,** Page 15 line1	Change *clinic* to *clinical*	Processed
47.	ISPOR	**Introduction,** Page 15 line 7-9	This explanation seems unnecessary	The authors feel that the sentence is relevant as it emphasizes the fact that the meaning of these words are interpret differently by people which can cause confusion.

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48.	ISPOR	**Introduction,** Page 17 line 25	Change *usual* to *actual*	The definition provided is the official definition that was provided by the High Level Pharmaceutical Forum. Therefore the authors will not change the sentence.
49.	ISPOR	**Introduction,** Page 5, Line 32	"clinical relevant outcomes": change to "**clinically relevant outcomes**" or "**relevant clinical outcomes**"	Processed
50.	ISPOR	**Introduction,** Page 6, Line 15	Define EUnetHTA HTA Core Model. Authors provided a definition for all concepts as they appear in the text. This creates a flow of thoughts and is easy to read. EUnetHTA HTA Core Model is probably very familiar topic to authors. However, it would be great to include a brief definition for a lay person like me. I stumbled a few times and had to go to web to read about EUnetHTA HTA Core Model analytical framework.	Processed
51.	ISPOR	**Introduction,** Page 11, Line 4	Change "the Reinvestment Act" → "**Recovery** Act". Authors use "Recovery Act" on page 55 (table). US Government websites often cite American Recovery and Reinvestment Act as **Recovery Act**. This abbreviation also appears more often in various analytical reports.	Processed
52.	ISPOR	**Introduction,** Page 6, Lines 11-14	We conclude based on the results of our review that there is a common ground for the development of a shared methodology for this comparative analysis, the relative effectiveness assessment of pharmaceuticals. *→ this statement was earlier made (September 2010) in the Belgian background report in the frame of the Belgian EU presidency and accepted by the EU council recommendation end 2010. This should be acknowledged. See also chapter 4, Discussion.*	Your response is acknowledged. However we are not sure whether this report is publicly available. Therefore no reference to this report is added to our background review.
53.	ISPOR	**Introduction,** Page 6, line 22	Both Paid and full model are "except for cost and economic consideration" ? Unclear formulation.	Processed
54.	ISPOR	**Introduction,** P 14 L 19	The figure 2, from Drummond's paper in 2008, is kind of out-dated and not very accurate. Luce and Drummond have written a new paper to clarify the differences among EBM, HTA, and	Thank you for pointing this out. The section has been rephrased accordingly.

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			CER. The figure 2 should be updated with the newest version in his recent paper. Here is the reference: Luce, B. R., Drummond, M., JÖnsson, B., Neumann, P. J., Schwartz, J. S., Siebert, U. W. E., et al. (2010). EBM, HTA, and CER: Clearing the Confusion. Milbank Quarterly, 88(2), 256-276.	
55.	ISPOR	**Introduction,** P 17 L 29-35	Rapid assessment of relative effectiveness of pharmaceuticals and Full assessment of relative effectiveness of pharmaceuticals, if they are same as Rapid model and Full model, are not clear defined with detailed information. After reading the introduction part, the reader cannot clearly see the distinct difference between these two models. You might want to define them in the introductory part with more keywords, besides "rapid" and "full", even though I do see the description in Page 24.	The exact definitions used are still under debate. Therefore we did not make any changes to these definitions in our report.
56.	ISPOR	**Introduction,** Page 12 Line 1	"the following definition of IOM is adopted for..." should be "the following definition is adopted by IOM for..."	Processed
57.	ISPOR	**Introduction,** Page 16 Table1. (point 2)	"technical characteristics if the technology" should be "technical characteristics of the technology"	Processed
58.	ISPOR	**Introduction,** P13 line 8	In Figure 1 of the efficacy/effectiveness spectrum, Medical claims data is categorized in the absolute effectiveness end of the spectrum. I would suggest reconsidering this categorization, for medical claims data can be used to conduct case-control or cohort studies with or without comparators. In addition, if medical claims data is included in this spectrum, have you considered where EMR would be placed in the efficacy/effectiveness spectrum?	We agree with the commentator that the figure is a simplified presentation. However, as it is a figure from a specific source we do not choose to adapt the figure. We have added the following comment: 'as illustrated in Figure 1 which is a simplified presentation of the spectrum'.
59.	ISPOR	**Introduction,** Page 9 line 4	Not sure I agree with putting "(new innovative)" in this sentence. In the summary it is discussed that full evaluations may not take place when the product is new. Also, the adding the word 'innovative" at this stage raised many issues about what innovation is to different people – this issue has not been discussed in the document. My suggestions are to remove those words (new innovative) but perhaps also to think about adding a	The words 'new innovative' have been deleted. The authors agree that there is a overall need to clarify the word innovation. However, the authors have not added a discussion regarding how different agencies view 'innovation' as they feel this is not the focus of this background review.

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			discussion on how different agencies view innovation since it is a relevant topic in this discussion.	
60.	ISPOR	**Introduction,** Page 10 line 12	When I read this I was surprised that the statement included no wording about access to patients! In my mind the overarching idea is to get the right medicines to the right patients rather than just make money! .	In the preceding paragraph the overall aim of the HLPF is mentioned: 'to find relevant solutions to public health considerations regarding pharmaceuticals'.
61.	ISPOR	**Introduction,** Page 10 line 12	Here again the issue of innovation is raised but not really discussed	See answer to comments 59.
62.	ISPOR	**Introduction,** Page 12 line 1	Should read "definition from IDM"	Has been rephrased.
63.	ISPOR	**Introduction,** Page 12 line 10	This sentence states that the words "alternative methods" imply comparison in study populations typical of daily practice – those words do not mean that to me! Alternative methods to me meant just that there was a comparison. I felt uncomfortable reading this since it felt like it was taking a statement and making of it what was required rather than the spirit in which it was made.	The words 'typical of daily practice' have been deleted.
64.	ISPOR	**Introduction,** Page 12 line 32	I felt that this paragraph needed to finish with another sentence starting "However,.... The section ends with lots of issues about the definition rather than justifying why it is the one which will be used.	The following sentence was added Although the definition may not be without debate this definition will form the basis for WP5, as it is a consensus between many relevant stakeholders in Europe.
65.	ISPOR	**Introduction,** Page 12 line 41	This paragraph discusses issues of effectiveness yet it is sitting in a section entitled efficacy – that made it a little confusing to read	The title was changed to 'The efficacy/effectiveness spectrum'.
66.	ISPOR	**Introduction,** Page 15 line 28	This sentence states that comparisons are made with already existing interventions. While I accept that this is the case in many situations, I think it is too strong a statement for this place in the document. Earlier it is stated that full assessments can take place many years after license so you could in fact do a	We agree with the comment and have rephrased 'already existing interventions' in to alternative interventions.

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			relative effectiveness assessment with an established product compared with a new treatment coming to market.	
67.	ISPOR	**Introduction,** Page 12, 1.2.3 line 32	The concept is still the same; the ratio would be month: month in the comparison	It is not clear to us what is meant by this comment. No changes are made in the report.
68.	ISPOR	**Introduction,** Section 2.2.3	Should the concept of co-insurance be included—this is frequent in in-patient in the US (drugs are part of the total bill; this is a percentage of charge after deductible is met)	Co-insurance is also common in Europe, however this question focuses on the co-payment that is applicable to the basic benefit package. Co-insurance is complementary insurance in addition to the basic benefit package. As there is not basic benefit package in the USA the framework above is not applicable.
69.	ISPOR	**Introduction,** p13, line 4	'According to these Member States' – it is unclear as to whether this is the first or second set of Member States mentioned in the previous sentence. Perhaps omit this sentence and insert '(so as to obtain the best estimate of what happens in real life)' at the end of the previous sentence, if this is the intended meaning.	Rephrased to 'latter group'.
70.	ISPOR	**Introduction,** p15, line 15	In Australia, generics are rarely considered in a rapid assessment because, by definition, they have been registered as being interchangeable (on a population or patient basis) with the innovator drug. Whether to use a generic is then an issue of price, which is dealt with by the PBPA [Pharmaceutical Benefits Pricing Authority] rather than the PBAC. The PBAC assesses new formulations and strengths of a molecule, although the submission is usually a 'minor' submission (and may be only a couple of pages instead of many hundred or thousand pages). If a generic with a different formulation from the innovator (e.g., a controlled release instead of immediate release) wanted to be PBS-listed, it would need to be assessed before it could be listed.	This comment probably refers to figure 6 instead of p15, line 15. Australia as an example has been replaced by Scotland.

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			In addition, a generic requesting listing for a new indication has the same status as an innovator drug requesting listing for a new indication, and either would require a submission (typically a 'major' submission) to the PBAC. A new indication will necessarily require a new assessment of efficacy (for the new indication) and may even have a different comparator from the earlier indications. For example, an oncology drug with an original indication of last line use for a specific cancer site may have new indications requested for earlier line use for the same cancer site or for a different cancer site. Whether the oncology drug is the innovator or a generic is not relevant. Thalidomide for multiple myeloma comes to mind as an out-of-patent drug that had a totally different indication many years after it originally came to market. In a full assessment in Australia, there is no distinction made between the innovator and any generic versions of the same molecule (although characteristics of the formulation, eg controlled vs immediate release, may be considered). My view is that generics are not exempted from an evaluation in Australia, but if this is what the respondent for the PBAC said/wrote, then the text correctly reports this.	
71.	ISPOR	**Introduction,** p15, line 28	'compared to' -> 'compared with'	Processed
72.	ISPOR	**Introduction,** p16, line **Introduction,** 18, item 2	'if' -> 'of'	Processed

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Com-ment #	Provided by	Section	Comment	Response by authors
73.	ISPOR	**Introduction,** p16, line **Introduction,** 18, item 6	'Analysis' -> 'analysis'	Processed
74.	ISPOR	**Introduction,** p17, line 6	'Acknowledges' -> 'acknowledges' (provided this agrees with the original)	Processed
75.	ISPOR	**Introduction,** 10:20	Are you planning to survey recent literature to see if the common definitions are now broadly adopted?	This is a useful suggestion, however can not be realised within the timeframe of this report.
76.	ISPOR	**Introduction,** 12:12	While I cannot challenge the definitions of the HLPF I feel that reference to the target patient set is an important qualifier as many safety problems occur with off-label use.	This is a relevant issue however is not discussed in detail in this background review.
77.	ISPOR	**Introduction,** 15:1	'clinic' should be 'clinical'	Processed
78.	ISPOR	**Introduction,** 16:18	Table entry 2; 'if' should read 'of'	Processed
79.	ISPOR	**Introduction,** Section 1.2.3.2, page 13 to 15	Title of Section is confusing as the main part of this section is about comparative effectiveness, and only the last paragraph (lines 27 to 33, page 15) is about relative effectiveness assessment. It is also not 100% clear if comparative effectiveness as used in this section and in figure 2 is equivalent to the term defined in Section 1.2.2 (CE in the US).	The title and section have been rephrased.
80.	ISPOR	Introduction	Can a specific audience for this document be named?	The audience for this document is WP5 which is mentioned in 1.1.: An overview of the processes, the scope and the scientific methods currently used by Member States for relative

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				effectiveness assessment is necessary to set up common tools within WP5 that are based on and similar to what is already happening in daily practice in EU countries. Therefore this report focuses on a review of the current processes, methodologies and activities related to relative effectiveness assessment.
81.	ISPOR	**Introduction,** Page 9, line 29-35	Starting with 'an overview of the processes…' These sentences can be moved to the beginning of this paragraph before line 29	The authors feel that the current outline of this paragraph is adequate.
82.	ISPOR	**Introduction,** General-editorial (Appendix)	All first word of footnote should be capitalized for consistency. Example to fix: page XIV footnote 82.. note this is not a complete list	Processed
83.	ISPOR	Section 2, Page 19 line 20	Rephrase to 'Methods used for REA in 30 countries are included in this review…'	Also aspects of the scope and the process were included. Therefore the suggested change is not adopted.
84.	ISPOR	Section 2, Page 19 line 32	This line seems out of place	'countries' has been replaced by jurisdiction and consequently the sentence referred to could be erased.
85.	ISPOR	Section 2, Page 29 line 22	This line needs to be rephrased	The authors do not see the need to rephrase this sentence.
86.	ISPOR	Section 2, Page 36 line 8	Define 'internal'	This part of the sentence has been deleted. Internal referred to not being publicly available which is already mentioned in the first part of the sentence.
87.	ISPOR	Section 2, Page 38	The variable names listed on the Y axis are not matching the exact words on page 37 line 24	Processed

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Com-ment #	Provided by	Section	Comment	Response by authors
		Fig 13		
88.	ISPOR	Section 2, Page 40 line 25	Define 'justified cases'	This is decided on a case by case basis.
89.	ISPOR	Section 2, Page 40 line 34	Why are mortality/morbidity/QoL outcomes preferred?	These are considered final outcomes which relate to the final objective for the use of the technology, not just to clinical outputs, which is why they have great relevance for the patient and for overall prioritisation. An assessment of final outcomes makes it possible to compare different types of health technologies conditional on the final consequences being comparable.
90.	ISPOR	Section 2, Page 42 Fig 16	Change 'Are utilities used?' To 'Utilities used' to match with other variable names	Processed
91.	ISPOR	Section 2, Page 41 line 1	This line needs to be rephrased	Has been rephrased to: In all jurisdictions surrogate outcomes are accepted for the assessment. However many jurisdictions state that they are not preferred, they are considered less relevant for the final advice than clinical outcomes, and they are only included if they are considered clinically relevant and/or are validated.
92.	ISPOR	Section 2, Page 42 line 29	This line needs to be rephrased	Has been rephrased to: Although the relevance of this aspect in the overall assessment varies between jurisdictions and some only consider the contra-indications on a case by case basis.
93.	ISPOR	Section 2, Page 42 line 39	Why give surgical procedures as the sole example in this case?	This example was specifically mentioned by the interviewee.

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Com-ment #	Provided by	Section	Comment	Response by authors
94.	ISPOR	Section 2, Page 42 line 32	'Ease of use of the technology' is unclear in its meaning.	The authors are referring to properties of the technology that are patient friendly.
95.	ISPOR	Section 2, Page 42 line 13-16	These sentences need to be rephrased. Unclear in meaning.	This sentence has been deleted as a result of the validation of answers for New Zealand.
96.	ISPOR	Section 2, Page 28, figure	The difference between cost-effectiveness and value for money is not clear. In my opinion, there is not such a difference.	We agree that there might be overlap between these words.
97.	ISPOR	Section 2, P 37 line 24	In Switzerland, the law defines that " any comparable drug "if listed in the positive list (specialty list - SL) can be used for the cost comparison , does nowhere specify that it has to be used in the registration trials. An exception can be made to compare with non SL drugs, but needs to be justified.	It is formulated that ' Only three countries state that 'whatever was used in the registration trials' can be used as a choice option (Belgium, Spain and Switzerland).' This does not mean that the comparator **has to be used** in the registration trial. It is an option.
98.	ISPOR	Section 2, Pg40 L23	I believe 'logical regression' should be 'logistical regression'	Processed
99.	ISPOR	Section 2, P 40 L 12	It will be helpful if the mechanism of indirect comparison is described in the beginning of the section.	The following sentence was added: Indirect comparisons can be used to determine the relative effectiveness of two treatments in the absence of direct head-to-head evidence.
100.	ISPOR	Section 2, P 43 L 7	Listing he full name and reference of GRADE, SIGN and JADED will clear the reader's confusion on these concepts.	Sentence was rephrased: International classification systems mentioned to be used are for example Grading of Recommendations Assessment, Development and Evaluation (GRADE), Scottish Intercollegiate Guidelines Network (SIGN) and the JADAD scale.
101.	ISPOR	Section 2, Page 43, Line 7	Change 'JADED' by 'JADAD'	Processed
102.	ISPOR	Section 2,	suggest to use more tables and figures to become more readable	The authors feel that more tables and figures would not

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Com-ment #	Provided by	Section	Comment	Response by authors
		General for Chapter 2		contribute to improved reading as the purpose of the chapter is to provide an overview of aggregated results. For more details readers can consult the raw data in the appendix.
103.	ISPOR	Section 2, Minor: Section 2.2.4	For reimbursement, it may be worthwhile mentioning the new reimbursement mechanisms for pharmaceuticals, like coverage with evidence development, ceiling price, and risk-sharing schemes.	The focus off our report is the relative effectiveness assessment and not the reimbursement mechanisms. Therefore this was not discussed in detail in this report.
104.	ISPOR	Section 2, Minor: Section 2.3	It may be useful to include dissemination mechanisms for the REAs in different countries, a lay-friendly report will be provided?	We acknowledge that that dissemination mechanisms such as lay-friendly reports a relevant aspect, however as WP5 focuses on the methods for the assessment itself, this is not included in this backgrounds review.
105.	ISPOR	P20 line 17-20, 22	No interview was conducted for the USA and section C and D of the data abstraction were not conducted for the USA. Although there is no single organization that is involved in the national assessment of pharmaceuticals or reimbursement decisions of pharmaceuticals in the US, there are some major health plans. One suggestion is to potentially use data from Kaiser or United Healthcare (or another major health plan) in the USA. Although the results may not be generalizable to the rest of the country, it may still be important to obtain some data from the US. This is especially the case since many of the national activities on "relative effectiveness" outside of Europe (as described in section 3.3) are in the USA.	We agree with the commentator that data on relative effectiveness assessment in the USA would be useful information. However, we feel that this should then include information of different parties as there is single body to refer to. Unfortunately this is not realisable within the timeframe of WP5.
106.	ISPOR	Section 2, Page 19 line 22	Why is All Wales Medicines Strategy Group not included in this list? They have a similar remit to SMS in Scotland (although narrower and NICE is applicable in Wales too).	As NICE is applicable in Wales as well, this was the preferred choice.
107.	ISPOR	Section 2, Page 22 line 28	As mentioned previously, a negative decision from NICE or SMC in the UK does not mean that the product is not reimbursed. This is said or implied in a few places.	The sentence that is referred to is referring to the NHS blacklist (Part XVIIIA of the NHS Drug Tariff), which is not based on NICE/SMC recommendations. Whereas the comment is referring recommendations by NICE/SMC. This is explained in section

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Com-ment #	Provided by	Section	Comment	Response by authors
				2.2.4.3 Purpose, status and scope (just above table 4).
108.	ISPOR	Section 2, Page 24 line 20	This heading may be more accurate to say "Evaluations to support reimbursement decisions"?	Processed
109.	ISPOR	Section 2, Page 26 line 1	Same comment as page 24 line 20 - title of the Figure could be broader than "evaluation for reimbursement" since that is not actually the case in the UK (or add a footnote to explain, as has been done for France in respect of not including cost-effectiveness criteria)	Processed
110.	ISPOR	Section 2, Page 28 line 30	This statement is not strictly true in the UK – a manufacturer can approach NICE to ask for an appraisal	Sentence is deleted.
111.	ISPOR	Section 2, Page 30 line 12	In Scotland this is not a reimbursement decision	In results table 9 it is indicated that de reimbursement or funding decision is made by the Regional Health Authority. Therefore we feel that rephrasing is not required.
112.	ISPOR	Section 2, Page 32 line 40	In both cases in England / Wales the product is still reimbursed but you do not get this insight from the current text	To the authors knowledge only the positive decisions by NICE are mandatory (legislative): if NICE recommends the use of a product, it becomes mandatory for primary care trusts to provide and fund it (which we see as reimbursement). However, in case of a negative advice it is up to the primary care trusts to decide whether they want to fund (reimburse) the pharmaceutical.
113.	ISPOR	Section 2, Page 33 line 17	I would be interested to know more about the criteria you found which relate to publication or not – I think this would be very insightful.	We have not looked into the criteria for publication, only whether the documents are published or not. Therefore we can not provide this information.
114.	ISPOR	Section 2, Page 36 line 8	The context of the word "internal" is not clear – does this mean internal government use or internal manufacturer use or something else?	This part of the sentence has been deleted. Internal referred to not being publicly available which is already mentioned in the first part of the sentence.

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Com-ment #	Provided by	Section	Comment	Response by authors
115.	ISPOR	Section 2, Page 36 line 17	Add - were similar "to those for rapid assessments"	Processed
116.	ISPOR	Section 2, Page 40 line 23	Should this read "logistic regression" rather than "logical regression"?	Indeed should be logistic. Has been rephrased.
117.	ISPOR	Section 2, Page 42 line 6	Could use the abbreviation "HRQL" which was defined earlier	Processed
118.	ISPOR	Section 2, Page 42 line 35	In Scotland the submission document may not explicitly state ease of use but there is a section to discuss any additional non clinical factors which are important and ease of use would fit there if it were applicable	Thank you for providing this insight. This has been rephrased.
119.	ISPOR	Section 2, Page 27, lines 26-28	Sentence meaning is unclear.	Has been rephrased into: In order to be granted reimbursement in Norway, the marketing authorization holder has to demonstrate the seriousness of the disease/condition, that long-term treatment is necessary (more than 3 months) and the efficacy and cost-effectiveness.
120.	ISPOR	Section 2, Page 29, lines 22,23	Sentence meaning is unclear.	Has been rephrased into: We have identified the three steps in a reimbursement process that can include different organisations: 1) Assessment, 2) Advice, 3) Decision (Figure 8).
121.	ISPOR	Section 2, Page 31, lines 14-16	CADTH in Canada have also initiated patient input: details at http://www.cadth.ca/index.php/en/cdr/patient-group-input	The following sentence was added: The CADTH has developed a formal approach for incorporating patients' perspectives into its Common Drug Review (CDR) process by inviting patient organisations and individuals to submit information via a standardised form.
122.	ISPOR	Section 2, Page 36,	Sentence is unclear: Suggest: "The document is not publicly available in all countries, e.g. in Denmark, Malta and Spain the	Has been rephrased, see response to comment 214.

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Com-ment #	Provided by	Section	Comment	Response by authors
		lines 7-9	document is for internal use only."	
123.	ISPOR	Section 2, Page 42, lines 91-21	Sentence meaning is unclear.	Has been rephrased into: In order to be granted reimbursement in Norway, the marketing authorization holder has to demonstrate the seriousness of the disease/condition, that long-term treatment is necessary (more than 3 months) and the efficacy and cost-effectiveness.
124.	ISPOR	Section 2, Page 29, line 23	Change spelling to "advice"	Processed
125.	ISPOR	Section 2, Page 30, lines 13-14	In Poland...are the both really step 2?	Yes, but in collaboration with the National Health Fund.
126.	ISPOR	Section 2, Page 33, lines 7-8	Reword to something similar to "Not in all countries is the document publically available"	Processed
127.	ISPOR	Section 2, Page 40, line 23	Should that be" logistic" regression	Processed
128.	ISPOR	Section 2, Page 43, lines 5-6	Can the actual numbers for always, almost always and sometimes be used?	They have been added.
129.	ISPOR	Section 2, p27, line 15	'more than one criteria are' -> 'more than one criterion is'	Processed
130.	ISPOR	Section 2, p27, lines 15-16	The sentence about the categorisation of criteria is confusing since there are criteria for the categorisation as well as the 'criteria' that are being categorised. I suggest 'The criteria have	Processed

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Com-ment #	Provided by	Section	Comment	Response by authors
			been grouped into domains. However, the exact definitions of the domains differ …'. That is, perhaps replace 'criteria' with a synonym, 'domains'. Or: 'The criteria have been grouped and given commonly used names. However, the exact definitions of the names differ …'	
131.	ISPOR	Section 2, p27, line 18	'susceptible for' -> 'susceptible to'	Processed
132.	ISPOR	Section 2, p32, line 38	Yes, and this is why trastuzimab (Herceptin) has its own Australian government program separate from all other pharmaceuticals (the wife of the Prime Minister at the time had had breast cancer).	Thank you for providing this information.
133.	ISPOR	Section 2, p40, lines 11-30	I think there should be a brief introduction on indirect comparisons vs direct comparisons and why direct comparisons are usually preferred over indirect comparisons.	The following sentence has been added: Indirect comparisons can be used to determine the relative effectiveness of two treatments in the absence of direct head-to-head evidence.
134.	ISPOR	Section 2, p40, lines 12-13	'Most countries (96%) may …, except for Turkey' -> 'All countries except Turkey may …'	Processed
135.	ISPOR	Section 2, p40, line 23	'logical' -> 'logistic'	Processed
136.	ISPOR	Section 2, p40, lines 27-28	In a Full assessment of more than two products, it is inevitable that a single summary analysis combining data from studies of all products will include an element of indirect comparison (unless there is only one study or all studies include all products). The existing sentence reads poorly, and I suggest omitting it.	Processed
137.	ISPOR	Section 2,	omit 'very'	Processed

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Com-ment #	Provided by	Section	Comment	Response by authors
		p42, line 23		
138.	ISPOR	Section 2, 29:23	'advise' should read 'advice'	Processed
139.	ISPOR	Section 2, 39:13	'exemption' should read 'exception'	Processed
140.	ISPOR	Section 2, 25page/ Line 13-14	In the text **"Full assessments ..... (<20%)",** but in the figure 4. it shows 57%.	The percentage refers to figure 5.
141.	ISPOR	Section 2	Still I am confused with the term "rapid assessment", it sounds like "priority review of FDA". If (single) rapid assessment is formal process to most countries, can it be called (more formally) standard assessment ?	We understand the possible confusion regarding terminology as in general, terminology is often based on regional preferences instead of world-wide agreed terms. The authors believe that standard may be confusing as well. In general, a rapid review or rapid assessment is a common term in Europe. Therefore we choose to use this term.
142.	ISPOR	Section 2	(Just question) It told that "the majority of countries stated 'best standard care and/or other as the comparator. Will WP produce a guideline on choice of comparator, if so when? Is there any action plan for identified challenge? Thanks a lot.	The following guideline is under production: 'Criteria for the choice of the most appropriate comparator(s)'. The guideline includes general recommendations and good practice rules for the choice of the most appropriate comparator for relative effectiveness assessments. The guideline will be subject to public consultation in 2012.
143.	ISPOR	Section 2.2.4.2	Please provide explanation on why the organization of evaluations is key background information (e.g., do different types of organisations have implications for how or when relative effectiveness evaluations might be used)?	The authors feel that general background information on the organisation is useful for the context, however indeed this is not the main focus of the report.
144.	ISPOR	Section 2, p19, line 12	'to feed' is informal and possibly ambiguous; suggest 'required to inform', 'required to assist', 'as evidence to support' or 'to summarise evidence for'	Has been rephrased into: Hence, the assessments performed that provide input for reimbursement decisions regarding pharmaceuticals varies.

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Com-ment #	Provided by	Section	Comment	Response by authors
145.	ISPOR	Section 2, p19, line 16	'feed' is too informal	See response to comment 144
146.	ISPOR	Section 2, p19, line 17	'decision' -> 'decisions' ?	Processed
147.	ISPOR	Section 2, p19, line 23	'Consortium' -> 'Consortium [SMC]'; to be consistent with NICE mentioned earlier in this sentence	Processed
148.	ISPOR	Section 2, p22, lines 32-41 and p23, lines 1-3	These two paragraphs summarise analyses for outpatient use and for inpatient use, respectively. It would be clearer to begin each paragraph with: 'For outpatient use …' and 'For inpatient use'	Processed
149.	ISPOR	Section 2, p22, lines 32-33	The positioning of the material in brackets makes it unclear what the material applies to. Suggest re-wording of first sentence: 'For outpatient use, most countries work with national positive (83%, 25/30) or national negative (17%, 5/30) lists (see Figure 3).'	Processed
150.	ISPOR	Section 2, p22, lines 33-34	Slovakia also has both lists. Suggest 'Spain, Slovakia and Italy have both positive and negative lists.'	Processed
151.	ISPOR	Section 2, p22, lines 34-35	The meaning/intent of 'Actually' is unclear, and I don't follow why Italy needs the detailed comment. I suggest dropping this sentence unless the information is necessary/important.	Sentence has been rephrased: For Italy, these lists are combined in one list with the positive list being reimbursement category A (reimbursed) and the negative list being category C (not reimbursed).
152.	ISPOR	Section 2,	'included only' -> included,'	Processed

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Com-ment #	Provided by	Section	Comment	Response by authors
		p22, line 36		
153.	ISPOR	Section 2, p22, lines 36-37	'a national positive or negative lists' -> 'national positive or positive lists' or 'a national positive or a national negative list'	Processed
154.	ISPOR	Section 2, p23, line 14	'This' -> 'Malta' (I found it slightly unclear as to what 'this' was referring to)	Processed
155.	ISPOR	Section 2, p23, line 15	'all' could be 'any' or omitted	Processed
156.	ISPOR	Section 2, p23, line 24	'who' -> 'that' (who applies to persons not things)	Processed
157.	ISPOR	Section 2, p23, line 26	'is only applicable' -> 'applies'	Processed
158.	ISPOR	Section 2, p23, lines 26-27	'a limited number of' -> 'few'	Left as it was.
159.	ISPOR	Section 2, p24, lines 23-24	'in comparison to' -> 'compared with'	Processed
160.	ISPOR	Section 2, p24, lines 32-33	'almost all of the included countries. The USA is the only country where this is not applicable.' -> 'all included countries, except the USA.'	Processed
161.	ISPOR	Section 2,	omit '. Actually the Australian guidelines indicate a clear	Actually has been omitted.

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Com-ment #	Provided by	Section	Comment	Response by authors
		p45, lines 16-17	separation of three entities' – and definitely omit 'Actually'	
162.	ISPOR	Section 2, p47, line 11	'PCORI)' -> 'PCORI'	Processed
163.	ISPOR	**Section 3,** Page 47 line 66	Unclear of the definition of 'National' agencies	Sentence was rephrased into: The agencies listed above that are involved in reimbursement decisions of pharmaceuticals (CADTH, PBAC and PHARMAC) were screened for specific activities on the development of methodology for relative effectiveness assessment.
164.	ISPOR	**Section 3,** Page 53	In the text box, the bullets are in different format (squared and round)	Processed
165.	ISPOR	**Section 3,** Page 57	Change 'will' to .... or add an expected timeline...	Processed
166.	ISPOR	**Section 3,** Page 58	Change 'subjects' to 'areas of research'	Processed
167.	ISPOR	**Section 3,** P 46 L 11	References for "Examples of pre-modeling studies of transformation include transforming comparative treatment effects measured on surrogate outcomes to final outcomes and scenario-based studies to value health outcomes using utilities."	The text is based on guideline text of the PBAC. No references were provided in the guideline (page 91).
168.	ISPOR	**Section 3,** P 49 L 3; L14; P50 L 13	The tables for MEDEV, PPRI, PHIS could be better designed to present more organized information, and have the same style for all the tables in the Section 3.	The tables are not changed as the authors feel they present the necessary information.
169.	ISPOR	**Section 3,** Page 47, Line 5	Canadian Agency for Drugs and Technologies in Health (CADTH)	The name has already been used in the report in section 2. Therefore in section 3 only the abbreviation is provided.

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Com-ment #	Provided by	Section	Comment	Response by authors
170.	ISPOR	**Section 3,** General for Chapter 3.1	suggest to use a big table with most important information to compare EMA vs. MEDEV vs. PPRI vs. PHIS; too many details in current version (hard to follow)	We appreciate the suggestion however due to time restraints the presentation in this section is left as it was.
171.	ISPOR	**Section 3,** General for Chapter 3.3	suggest to use a big table with most distinguished characteristics to compare ICER vs. PBAC vs. PCORI vs. DERP	We appreciate the suggestion however due to time restraints the presentation in this section is left as it was.
172.	ISPOR	**Section 3,** Page 47 line 5	Did you also consider Centre for Reviews and Disseminations in York for methodology?	No, it was not included.
173.	ISPOR	**Section 3,** Page 57 line 6	Stated earlier that this would be referred to as "the Reinvestment Act" but then it is named in full here.	Processed
174.	ISPOR	Page 48, line 3 (EMA table)	Need to move "nervous system" and "Information on medical products" to their own lines	Processed
175.	ISPOR	**Section 3,** Page 54, about ½ down	Section starting "This guideline has set...—might change to "published with ongoing revision"	Processed
176.	ISPOR	**Section 3,** p51, lines 3-15	ISPOR has a journal, 'Value in Health' (list it for comparability with ISPE having a journal, 'Pharmacoepidemiology and Drug Safety').	Processed
177.	ISPOR	**Section 3,** p56, lines 6-16	Suggest moving Section 3.3.3 PBAC to the end of Section 3.3, so that an Australian entity is not imbedded among the US entities. If the entities are listed in order of importance, put it first	The section is ordered alphabetically.

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Com-ment #	Provided by	Section	Comment	Response by authors
			[Australian joke!]; or order the sections alphabetically.	
178.	ISPOR	**Section 3,** 47:5	For consistency show CADTH in full	See response to comment 169.
179.	ISPOR	**Section 3,** 47:11	Show PBAC in full	See response to comment 169.
180.	ISPOR	**Section 3,** 49:3	Suggest replace 'Rapid' with 'prompt'	Processed
181.	ISPOR	**Section 3,** 55:Table	Is it possible to publish a bibliography of the methodological papers published by AHRQ individuals?	The authors that this would be too detailed information for this background review.
182.	ISPOR	**Section 3,** 57:32	Is it planned to review and comment PCORIs planned activities when available?	This is not planned in the current WP5 however WP5 members will be interested in the ongoing developments.
183.	ISPOR	**Discussion,** Page 60 line 22	Spell out 11/30	Processed
184.	ISPOR	**Discussion,** Page 65 line 15-16	Define *products*	The Stakeholder Advisory Group (SAG) are asked to provide input in the relative effectiveness assessment models as well as the guidelines in production. In addition, a pilot assessment of a pharmaceutical will be conducted using the models and guidelines. The SAG will also be asked to comment on the assessment report. All of the products mentioned above will also undergo a public consultation similar to the consultation of this background review.
185.	ISPOR	**Discussion,** Page 64 line 15	Change 'does not differ a lot' to 'are similar in...'	Processed
186.	ISPOR	**Discussio**	delete "However there are no absolute boundaries"	The sentence has been rephrased into: However, boundaries are

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Com-ment #	Provided by	Section	Comment	Response by authors
		n, Page 59 Line 39		difficult to define as some social, organisational, legal and/or ethical aspects may be relevant input for the relative effectiveness as well.
187.	ISPOR	**Discussio n,** Page 60 Line 6-10	suggest to rewrite the last sentence -- lengthy and confusing	The sentence has been rephrased into: In order not to exclude evaluations of pharmaceuticals of jurisdictions based on the definition of the High Level Pharmaceutical Forum of relative effectiveness the following type of assessments were included: all 'comparative analysis' assessing the efficacy and/or effectiveness of pharmaceutical(s) in comparison to alternatives that provide input for national reimbursement decisions on pharmaceuticals have been included.
188.	ISPOR	**Discussio n,** General for **Discussio n,** Chapter 4	nice summary of the status quo; suggest to address "why" it is still important to develop models which can be applied across the Member States and emphasize "how" this task should be accomplished as planned	The final tools developed in WP5 will be freely accessible and although usage will not be mandatory, EUnetHTA will stimulate the use of the tools in the different participating European countries. In order to do so, EUnetHTA will develop a plan to support, where appropriate, the implementation of the use of the tools. An important step will be the planned Joint Action 2 in which, within WP5, joint assessments of pharmaceuticals will be produced.
189.	ISPOR	**Discussio n,** Page 60, Line 10	The end of the statement appears incomplete.	See response to comment 187.
190.	ISPOR	**Discussio n**	The report is helpful for the identification of which item to consider. It does not really express what items are considered in the national health care settings	It is not the purpose of the report to provide very detailed information for each national health care setting. It's purpose is to aggregate the information of the various health care settings.
191.	ISPOR	**Discussio n,** Pg64	I believe section on risk/benefit assessment as it relates to net therapeutic benefit needs to be expanded (on lines 45-47 need to be more explicit on weighting – intended/unintended effects)	The section has been extended.
192.	ISPOR	**Discussio**	Variance in usual care: needs to be further detailed as difference	Methods will be specified in detail in the guidelines that are

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		n, Pg65 L30	in standards of treatment, healthcare delivery system impact data and any consolidation of data – so methods for adjustments need to be explicit Comment on lack of effectiveness data – care needs to be used in the choice of wording 'extrapolating efficacy data'; effectiveness and efficacy are different	being produced as part of WP5.
193.	ISPOR	**Discussio n,** Page 59, Line 21	Change "questions pop-up" → "questions **arise**". A synonym would a better word for a formal document.	Processed
194.	ISPOR	**Discussio n,** P61 line 4	Was the term "cost-effectiveness" ever defined in the draft? Although this term was not predefined by the different countries, terms such as efficacy and effectiveness were previously defined on p17. It may be a good idea to add cost-effectiveness to the list of definitions on p17.	This section of the discussion is referring to results of the survey (section 2 of the background review). The definitions provided on p17 were not stated for this survey.
195.	ISPOR	**Discussio n,** Page 60 line 6	And footnote 39 – the decisions in the UK are not reimbursement decisions	The footnote has been rephrased: With the exception of England/Wales, Scotland and Canada. For England/Wales the assessments are performed NICE and they are used as input for regional reimbursement/funding decisions by regional health authorities. Similar for Scotland the assessments are performed by SMC and they are used as input for regional reimbursement/funding decisions by regional health authorities. In Canada the assessment is done nationally by the CADTH but the decision on reimbursement (based on the national assessment) is a regional responsibility.
196.	ISPOR	**Discussio n,** Page 60 line 18	Does the UK have a list of criteria for reimbursement? The HTA assessment is not reimbursement.	A footnote has been added to the appendix table for England/Wales and Scotland: The criteria presented are criteria for health technology assessment as reimbursement decisions are a regional responsibility.
197.	ISPOR	**Discussio n,** Page	Sentence meaning is unclear: Suggest: "The document is not publicly available in all countries and in general, the content of	Processed

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		61, lines 10-12	the guidelines (level of detail on methodology) is not very detailed."	
198.	ISPOR	**Discussion,** Page 64, lines 32-33	Sentence meaning is unclear.	Sentence has been rephrased: We feel that the confusion (or disagreement) seems to be caused mainly by the word, benefit/risk assessment, itself which is strongly associated with drug regulatory agencies as there seems to be agreement that in a net therapeutic benefit assessment (relative effectiveness assessment) that is used for a reimbursement decision the intended as well as the unintended effects are included with an emphasis on the nature of these effects relative to the comparator.
199.	ISPOR	**Discussion,** Page 59,line 27	Again, the concept is still the same; the ratio would be month: month in the comparison	It is not clear to us what is meant by this comment. No changes are made in the report.
200.	ISPOR	**Discussion,** Page 61, lines 2, 3 ,4	Change to "state" for all; change wording to "always look" in line 4	Processed
201.	ISPOR	**Discussion,** Page 64, line 14	Change does to do	Processed
202.	ISPOR	**Discussion,** Page 64, line 18	Remove "this" from the sentence	Processed
203.	ISPOR	**Discussion,** Page 64, line 19	Remove "also" from the sentence	Processed
204.	ISPOR	**Discussion,** Page 64, line 33	Change to itself	Processed

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205.	ISPOR	**Discussion,** p60, lines 6-10	This long sentence is very hard to read/understand. I think it is missing a final word 'considered', and a comma after 'effectiveness' [line 8] might help.	The sentence has been rephrased into: In order not to exclude evaluations of pharmaceuticals of jurisdictions based on the definition of the High Level Pharmaceutical Forum of relative effectiveness the following type of assessments were included: all 'comparative analysis' assessing the efficacy and/or effectiveness of pharmaceutical(s) in comparison to alternatives that provide input for national reimbursement decisions on pharmaceuticals have been included.
206.	ISPOR	**Discussion,** p61, lines 48-51	suggest replace with 'and the timing of the assessment (rapid is usually performed soon after market authorisation whereas full assessment is usually performed several years later when more clinical effectiveness data may be available)'	Processed
207.	ISPOR	**Discussion,** p62, line 14	'(based on' -> '(in', to avoid repetition of 'based on'	The paragraph has been reworded: Written input from WP5 (based on a letter by MEDEV) and two face-to-face meetings in 2010 have resulted in adaptation of the European Public Assessment Report template by EMA. The revised template was implemented from November 2010 onwards. Collaboration in 2011 will continue by means of an evaluation of the adapted European Public Assessment Reports.
208.	ISPOR	**Discussion,** p63, line 30	'doing actually' -> 'actually doing'	Processed
209.	ISPOR	**Discussion,** p64, line 5	'patients' -> 'patients)'	Processed
210.	ISPOR	**Discussion,** p64, lines 17-20	see comment for p61, lines 48-51	Processed

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211.	ISPOR	**Discussion,** p64, line 33	What does 'it self' [which should be spelled as 'itself'] refer to? Perhaps replace 'word it self' with 'label'	Sentence has been rephrased into: We feel that the confusion (or disagreement) seems to be caused mainly by the word, benefit/risk assessment, which is strongly associated with drug regulatory agencies as there seems to be agreement that in a net therapeutic benefit assessment (relative effectiveness assessment) that is used for a reimbursement decision the intended as well as the unintended effects are included with an emphasis on the nature of these effects relative to the comparator.
212.	ISPOR	**Discussion,** p64, lines 35-36	'relative nature of these effects to the comparator' -> 'nature of the effects relative to the comparator'	Processed
213.	ISPOR	**Discussion,** p65, lines 1-3	I agree with this strongly and expect that there will be (surprisingly) many instances where the comparator should differ between countries. A trivial example is where the comparator for one country is not available/used in another country. Manufacturers of drugs have similar problems when writing a 'global dossier' for a drug.	Thank you for comment.
214.	ISPOR	**Discussion,** p65, line 15	omit 'very'	Processed
215.	ISPOR	**Discussion,** p66, line 4	'must' -> 'will', unless 'must' is the intended meaning	Processed
216.	ISPOR	**Discussion,** Conclusion	I have reviewed the material and have provided comments. I paid particular attention to the material about the PBAC in Australia and can confirm that this material accurately reflects what happens in Australia (and from the detailed comments and their tone to the questionnaire I believe I know who they interviewed and, if I am correct, they will have had the best	Thank you for the comment.

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			possible advice and overview of the PBAC that they could have got).	
217.	ISPOR	**Discussion,** 59:35	Insert 'other' between 'to' and 'already'	The sentence has been rephrased into: The purpose of a relative effectiveness assessment is to inform health care professionals, patients and decision makers about the net therapeutic benefit of an intervention compared to alternative interventions.
218.	ISPOR	**Discussion,** 60:6	The sentence commencing 'In order not…' is incomprehensible	The sentence has been rephrased into: In order not to exclude evaluations of pharmaceuticals of jurisdictions based on the definition of the High Level Pharmaceutical Forum of relative effectiveness the following type of assessments were included: all 'comparative analysis' assessing the efficacy and/or effectiveness of pharmaceutical(s) in comparison to alternatives that provide input for national reimbursement decisions on pharmaceuticals have been included.
219.	ISPOR	**Discussion,** 61:2/3/4	In each line 'states' should be 'state'	Processed
220.	ISPOR	**Discussion,** 61:4	Replace 'to' with 'they'	Processed
221.	ISPOR	**Discussion,** 61:10	Replace 'Not in all' with 'In some' and insert 'not' between 'is' and 'publicly'	Processed
222.	ISPOR	**Discussion,** 61:29	Replace 'clinical' with 'clinically'	Processed
223.	ISPOR	**Discussion,** 61:50	Delete 'also' and 'data are available as'	Sentence is rephrased into: The main difference seem to be the number of comparators (more comparators for a full assessment) and the timing of the assessment (rapid is usually performed soon after market authorisation whereas full assessment is usually performed several years later when more clinical effectiveness data may be available).

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224.	ISPOR	**Discussion,** 61:51	Delete 'more' and 'years after market authorisation'	Sentence is rephrased into: The main difference seem to be the number of comparators (more comparators for a full assessment) and the timing of the assessment (rapid is usually performed soon after market authorisation whereas full assessment is usually performed several years later when more clinical effectiveness data may be available).
225.	ISPOR	**Discussion,** 62:30	Insert 'of' between 'domains' and 'ethical'	Processed
226.	ISPOR	**Discussion,** 62:47	Figure number?????	Processed
227.	ISPOR	**Discussion,** 63:30	Move 'actually' before 'doing'	Processed
228.	ISPOR	**Discussion,** 64:2	Are you considering the needs of different stakeholders (payers/providers/patients/etc. When developing the four guideline topics?	WP5 considers it relevant that stakeholders are involved in the production of the products (the models as well as the guidelines). Therefore, input on draft products is asked from the Stakeholder Advisory Group (which includes payers/providers/patients/etc). In addition, all products will be placed on the public EUnetHTA website for public consultation.
229.	ISPOR	**Discussion,** 64:14	Change 'does' to 'do'	Changed to: are similar.
230.	ISPOR	**Discussion,** 64:16	Figure number	Processed
231.	ISPOR	**Discussion,** 64:19/20	Delete 'also' and from 'as clinical effectiveness…….to 'market authorisation'	Sentence is rephrased into: and the timing of the assessment (rapid is usually performed soon after market authorisation whereas full assessment is usually performed several years later when more clinical effectiveness data may be available).

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232.	ISPOR	**Discussion,** 64:42	Insert comma after 'pharmaceutical'	Processed
233.	ISPOR	**Discussion,** 64:	I believe it would be helpful for assessment reports to justify the choice of comparator(s). If you agree, could you please incorporate this point in this section.	We have added the following sentence: Adequate justification of the reason for choice of comparator will be relevant for shared or adjusted assessments.
234.	ISPOR	**Discussion,** 65:20	Replace 'a' with 'some'	The authors feel that 'a' is more adequate and have therefore not processed the proposed change.
235.	ISPOR	**Discussion,** Figure 20	Not clear – what is the point – the cross-out sections – maybe there, but I missed it -	This is described in the paragraph before the figure: As presented in Figure 20 the scope of the Full model will be all domains of the HTA Core Model except for cost and economic considerations. The scope of the Rapid model will also be all domains of the HTA Core Model except for cost and economic considerations, however only a limited number of elements of the ethical analysis, the organisational analysis, the social aspects and the legal aspects will be included.
236.	ISPOR	**Discussion,** All charts and graphs	3D graphs are difficult to read, and inappropriate if no 3rd dimension is being presented.	Processed. Have been changed to 2D.
237.	ISPOR	Appendix, XIV	Switzerland has an annual copayment ceiling of max CHF 700 per annum (on addition to the min franchise of 300 per annum)	Processed
238.	ISPOR	Appendix, XXXIV	The role of the BAG (Federal Office of Health) is underrepresented here. The BAG is the main institution performing the rapid assessment. The Federal Medicines Commission is just advisory, not binding. In reality, all direct negotiations before and after the recommendation of the commission take place with the BAG staff and the commission's recommendation can be changed substantially.	The authors feel that this does not contradict the information provided in table 9. It states that the Federal Medicines Commission provides an advice, whereas the Federal Office of Health makes the decision.

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239.	ISPOR	Appendix, LX	29. Switzerland: there is a guideline describing how to do the relative effectiveness assessment, although not very detailed. This is the "Handbuch zur Spezialitätenliste" (SL Manual)	Thank you for providing the information. The comments has been processed.
240.	ISPOR	Appendix, LXXXII	29. Switzerland: The request to posterior submission of long-term data to support surrogate endpoints is nowhere stipulated in the law and not enforced.	Processed
241.	ISPOR	Appendix, LXXXIII	29. Switzerland: Benefit-risk assessment is been done. The basis is the term "Zweckmässigkeit" Art 30 KVV /Art. 65 KLV.	The following comment was added based on the interview: Benefit/risk assessment is the task of the approval authority Swissmedic, however the safety of the pharmaceutical is also considered for the discussions regarding reimbursement.
242.	ISPOR	Appendix, XCIII	29. Switzerland: Effectiveness can in fact be assessed via qualitative description or modelling extrapolation of efficacy. Also short term data can be extrapolated via modelling if no long term data exist.	This is not in line with the answer that was provided by the interviewee. This information was subsequently validated by the relevant organisation. So no changes in our report were made.
243.	ISPOR	Appendix, P V. table 2	The new US health care bill, by 2014, requires U.S. citizens and legal residents to have qualifying health coverage. Those without coverage pay a tax penalty of the greater of $695 per year up to a maximum of three times that amount ($2,085) per family or 2.5% of household income. So the category of "Are the following characteristics applicable to the insurance system" for the US should be Yes in the first item "Participation in health insurance is mandatory" rather than No.	The report is based on the current situation, however we have added the following comment: In 2014, everyone must purchase health insurance or face a $695 annual fine. There are some exceptions for low-income people.
244.	ISPOR	Appendix, Minor	I am wondering if the used questionnaire could be attached, although the questionnaire may have been integrated into the tables. It is unclear to me.	The questions of the questionnaire have been integrated in the tables of the appendix.
245.	ISPOR	Appendix, LXXX Page 41	I think that this review is very nice and useful for HTA researchers. In particular, the result table 18b is very interesting for me. I have one question. Which is right, figure 16 (46%) or table18b (57%) on that question "Are utilities used?"	Thank you for the compliment. Both state 46%.

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246.	ISPOR	Appendix, Page VIII, line 5	There is not national negative reimbursement list within the Slovak republic. Y should be changed to N	Reimbursement category N is regarded as a negative list. N: no reimbursement – not included in the List of pharmaceuticals, including over-the-counter (OTC) products, oral contraceptives and pharmaceuticals, where no proof of a therapeutic benefit could be found.
247.	ISPOR	Appendix, Page XIV, line 2	There is the annual-copayment ceiling for particular groups of patients (retired, disabled) in the Slovak republic. X should be inserted.	Processed
248.	ISPOR	Appendix, Page XXIV, lines 4,5	Severity of disease and cost-effectiveness are considered during the reimbursement decision making process. X should be inserted.	Processed
249.	ISPOR	Appendix, XXXVII, line 6	P and I should be included. Payers provide roles of initiator of assessment and provide data as well.	The role of initiator is discussed in table 8.
250.	ISPOR	Appendix, XLI, lines 2,3,4,5	There should be "A" for support reimbursement decision and support guidance and N for support pricing decision and other.	This is not in line with the answer that was provided by the interviewee. This information was subsequently validated by the relevant organisation. So no changes in our report were made.
251.	ISPOR	Appendix, XLVI, lines 2-9	There should be "A" for advice to decision making body and assessments made public and advice made public. For the rest of lines "N" should be included.	Processed
252.	ISPOR	Appendix, XLVIII, lines 3,4,5	NA should be included.	Processed
253.	ISPOR	Appendix, XLIX, lines 2-6	NA should be included.	Processed

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254.	ISPOR	Appendix, LI, line 26	Yes should be included. And the name of comparative evaluation is "pharmacoeconomic evaluation".	Yes is now included. The name of the comparative evaluation is referred to as 'medical opinion' as this was provided by the interviewee. (in this review we do not focus on the pharmacoeconomic analysis).
255.	ISPOR	Appendix, LIV, lines 2-7	There should be "A" for lines 2,3,4,5. For the lines 6 and 7 "Y" should be included.	Line: 2,3,4,5 the following answers were provided by the interviewee: A, S, S, A Line 6,7: the following answers were provided by the interviewee: Y, N (in this review we do not focus on the pharmacoeconomic analysis).
256.	ISPOR	Appendix, LXII, lines 2-10	There should be "A" for lines 2, 3, 4, 5, 6, 7. There should be "S" for the lines 8 and 9 and NA for the line 10	The following answers were provided by the interviewee: A, S, S, S, A,S, S, N.
257.	ISPOR	Appendix, LXIX, lines 2-6	There should be "A" for the line 4 and "N" for the line 6.	It is not clear to the authors to table this comment is referring to.
258.	ISPOR	Appendix, LXX, lines 2-7	There should be "A" for the line 2. There should be "S" for the lines 3,4,5. There should be "N" for the line 6. There should be "Y" for the line 7.	The following answers were provided by the interviewee: S for line 2,3,4 ,5 and 6. And N for line 7.
259.	ISPOR	Appendix, LXXIV, lines 2-10	NA should be included.	Processed
260.	ISPOR	Appendix, LXXV, lines 2-7	NA should be included.	Processed
261.	ISPOR	Appendix, LXXVIII, line 11	Presented my marketing authorisation holder and all clinical relevant endpoints should be included.	Processed

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262.	ISPOR	Appendix, LXXXI, line 6	There should be "Y" for the line 6.	Processed
263.	ISPOR	Appendix, LXXXII, lines 2-6	There should be "Y" for the lines 2,3,4,5 and 6.	Processed
264.	ISPOR	Appendix, LXXXIII, lines 2-5	There should be "N" for the line 2. There should be "Y" for the lines 3,4,5.	The following answers were provided by the interviewee: Y for all lines.
265.	ISPOR	Appendix, XCIII, lines 2-9	There should be "Y" for the lines 2,3,4, There should be "N" for the line 7. There should be "S" for the lines 5,6,8 and 9.	The following answers were provided by the interviewee: S, A, S, N, N, S, S, S.
266.	HTAi	General	Overview - This report and its appendix are clear and well-written and the HTAi Interest Sub-Group on Patient/Citizen Involvement in HTA welcomes the aim to harmonise methods for relative effectiveness. The Interest Sub-Group would like to ensure that the final version includes acknowledgement of the value of patient input in the process and outlines a number of situations below where this should be addressed.	Thank you.
267.	HTAi	General	This review does not recognise the value of patient input to full and rapid assessments. CADTH, NICE and SMC all take patient submissions for rapid assessments (this is not recorded accurately for SMC in the survey). Work by HEE has found that patients can provide important knowledge about the intended and unintended consequences of using a technology in a real-world setting. Work by EPPOSI has identified that these submissions are particularly helpful to 'translate' evidence of clinical efficacy into clinical effectiveness, by helping explain the meaning of treatment effect in terms of real-world patient experience and impact. Patient evidence is also important to	We acknowledge the importance of patient input. As indicated in the report this review mainly deals with the technical assessment; patient input is mostly included in the appraisal phase of the assessment. Your input will be taken into account in the development of these models in EUnetHTA.

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			contribute to discussions where the net benefit is marginal.	
268.	HTAi	General	It is noted that the purpose of relative effectiveness is to inform health-care professionals and patients of the most effective drugs, however the survey has not looked at dissemination and communication methods from relative effectiveness assessment to patients.	We recognise the relevance of dissemination and communication methods from relative effectiveness assessment to patients, however the authors feel that this is not the scope of WP5. The focus of this review is an assessment of the current methodology for performing relative effectiveness assessments of pharmaceuticals.
269.	HTAi	P31, l14-16.	The most important form of contributions of patients appear to be missed here – namely submissions of evidence from patients according to a standard format and published guidance (NICE, SMC, CADTH).	As indicated in comment 267 we do not believe that this is the focus of this current review but will be taken into account in the development of the methodology.
270.	HTAi	P33, l18-23	It would be helpful to know whether any agencies provide assessments/advice in a form that is designed to meet the information needs of patients.	We agree, however the authors feel that this is not the scope of WP5.
271.	HTAi	P36, l33	The forms of evidence that are submitted by patient groups could be referenced here – including membership surveys, qualitative research (particularly focus groups and interviews) and summaries of views generated through iterative social networking.	As indicated in comment 267 these forms of evidence are mostly not taken into account in the technical assessment phase of relative effectiveness but are part of the appraisal phase.
272.	HTAi	P42, l32	States that 'ease of use of technology' is considered in 80% of countries, but this does not tally with figure 7 which shows that this is only used as a reimbursement criteria <60% of the time.	There can be a difference between the reimbursement criteria and the evidence that is considered, depending for example on the relative weight of the type of evidence and formalisation of the type of evidence as criterion.
273.	HTAi	P22, l22-l30	It would be helpful to describe the SMC context where a drug is recommended as 'not for use due to non-submission'.	The following sentence is added in section 2.2.4.2 (organisation of the evaluations, initiation of the reimbursement evaluation): 'The SMC (Scotland) tracks all pharmaceuticals that receive marketing authorisation. Subsequently marketing authorisation holders are actively approached to submit application for a

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				product assessment. If the marketing authorisation holder refuses to submit an application the product will automatically receive a negative recommendation.'
274.	HTAi	P23, l14	Since April 2011, prescription charges have been abolished in Scotland and so there are no co-payments in Scotland or Malta.	Processed
275.	HTAi	P24, l21-29	It would be helpful to make reference to the HTA by ASERNIP-S that undertook a systematic comparison of rapid and full HTAs, which is summarised in the following paper: Watt A et al. Rapid versus full systematic reviews: validity in clinical practice? ANZ J Surg, 78:1037-1040 (2008).	Thank you for pointing out this useful article, however the authors do not feel that a reference in the suggested section to this article would be of added value.
276.	HTAi	P43, l28	The issue of sub-group analyses to identify optimal benefit of the technology is particularly important for REA and should be addressed.	The relevance of sub-group analysis for REA is obvious but was not taken into account in detail in this analysis. To get a very clear view on how subgroup analysis is used in countries a more detailed qualitative assessment of the procedures in the different countries would be necessary.
277.	HTAi	P48, table	There are a range of EMA guidance documents on methodology that would be helpful for consideration. In addition, EMA also makes use of the guidance from the International Conference on Harmonisation. E9 re statistical issues and E10 re non-inferiority trials are of particular relevance to relative effectiveness assessments.	The guidance documents of the EMA are important for the current guideline development within the current WP on REA. Because guidelines on specific issues are not addressed in detail in this review a comparison with EMA guidelines is not included in this review.
278.	HTAi	P48, l4	Reference should be made to the pharmacovigilance assessment work that is underway in EMA as collection of data post licensing could be expanded to cover elements relevant for HTA. In particular reference should be made to their Project on risk-benefit, which has reviewed a range of new methods for undertaking assessments of risk/benefit that are of major relevance for REA.	The following section is already included: The CHMP also plays an important role in this EU-wide 'pharmacovigilance' activity by closely monitoring reports of potential safety concerns and, when necessary, making recommendations to the European Commission regarding changes to a medicine's marketing authorisation, or its suspension/withdrawal from the market. A section on methodology for risk/benefit activities has been added.

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279.	MSD	General	Thank you for allowing the possibility to review the Background Review on Relative Effectiveness Assessment of Pharmaceuticals. We would like to compliment on the comprehensive analysis and we would like to let you know that we don't have any comments. We look forward to the next steps of WP5 in developing a shared methodology and models regarding this important subject.	Thank you
280.	EGA	General	**EGA RESPONSE TO PUBLIC CONSULTATION OF DRAFT BACKGROUND REVIEW ON RELATIVE EFFECTIVENESS ASSESSMENT OF PHARMACEUTICALS, 13 May 2011** Generic and biosimilar medicines are subject to HTA assessments in several EU member states and therefore the EGA welcomes EUnetHTA's initiative to organise a public consultation on the Draft Background Review on Relative Effectiveness Assessment of Pharmaceuticals. As is generally recognised, generic and biosimilar medicines offer equivalent medical treatments at lower costs for healthcare systems and patients, thus helping to ensure patient access to essential medicines and providing urgently needed budget headroom for the purchase of new and innovative treatments through rational use of medicines and relative effectiveness assessments. Health Technology Assessments have therefore a crucial role; both in recognising well established affordable medicines as first line treatments and in recognising incremental innovation to generic and biosimilar medicines, bringing added therapeutic value for patients. The five main EGA comments on the Draft Background Review on Relative Effectiveness Assessment of Pharmaceuticals are:	We thank the EGA for providing comments.
281.	EGA	General	1. **Timely patient access to generic and biosimilar medicines should not be hindered by additional levels of HTA assessment for generic and**	The aim of WP5 is to develop methodology for the assessment of relative effectiveness of pharmaceuticals. It is not in the scope of WP5 to determine which pharmaceuticals should be

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			biosimilar medicines: Where the rapid assessment is certainly key for innovative medicines, it is as crucial that high quality generic and biosimilar medicines are accessible for patients immediately after the loss of exclusivity of reference products. Therefore, HTA bodies should consider the relevance of additional assessments for these medicines, especially as these are well known substances with a proven positive risk-benefit profile. Therefore the EGA warns against adding additional assessments without any added value for generic and biosimilar medicines that could delay their access to patients.	assessed and which not.
282.	EGA	General	**2. Prescribing guidelines based on full relative effectiveness studies recommending generic and biosimilar medicines as first line treatments** Prescribing guidelines based on full assessment of relative effectiveness of substances are crucial for the use of generic and biosimilar medicines and their role for sustainable healthcare. Full HTA studies should be required for innovator medicines at the latest two to three years before the patent expires and should not be performed shortly before loss of exclusivity, when generic / biosimilar alternatives are launched. An alternative could be to have "regular rapid assessment" every five years, like for example in France. The criteria in terms of quantity and quality of data should be clearly defined.	This statement is not considered within the remit of this review.
283.	EGA	General	**3. Similarity of generic and biosimilar medicines should be valorised** As mentioned in the introduction, the main role of generic and biosimilar medicines is to offer equivalent medical treatments at lower costs for healthcare systems and patients, thus helping to ensure patient access to essential medicines and providing urgently needed budget headroom for the purchase of new and innovative treatments through rational use of medicines and	See response to comment 281 and 282.

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			relative effectiveness assessments. This is key to Europe's healthcare sustainability. As generic and bioismilar medicines are approved in line with the reference product in all of the following elements: clinical safety and efficacy, quality of life outcome, posology, administration with the exception of price, manufacturers should not be required to undertake a full HTA assessment but may choose to be assessed through an abbreviated process that focuses only on cost minimisation / budget impact. In addition any abbreviated process that demonstrated reduced costs / positive budget impact should result in automatic approval of the generic and biosimilar medicines. As an abbreviated approval process for generic and biosimilar medicines is a purely administrative process the timelines from submission to approval should be short (30 days maximum). Exceptions to the abbreviated approval process may arise if a generic or a biosimilar manufacturer has developed elements of non-clinical product differentiation that can be shown to improve the cost effectiveness of a product versus the reference and the manufacturer wants to use this to justify an increased price. In such cases a full HTA will be required for approval. In conclusion, criteria and assessment endpoints for HTA/relative effectiveness should be defined in such a way that similarity of generic and biosimilar products is valorised and recognised. The design of HTA models should not lead to the fact that similarity is considered as inferiority.	
284.	EGA	General	**4. Cost evaluation / cost-effectiveness** As different countries have different price and reimbursement policies and different healthcare budgets, cost evaluation (cost-effectiveness) should remain at national level. Therefore, HTA assessments should make a clear distinction between relative effectiveness and cost effectiveness phases.	This is in line with the recommendation of the High Level Pharmaceutical Forum that relative effectiveness and cost-effectiveness should be considered as two entities, that form the basis for the work of WP5 (see section 1.2.3.3. of the report).

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285.	EGA	General	**5. Conflict of interest** As an important part of relative effectiveness studies are performed by independent and academic experts, but as these experts' research is often sponsored by large pharmaceutical companies, possible conflicts of interest must be carefully addressed. Therefore, any financial sponsoring of related studies must be 100% transparent.	We agree in general with your statement, however these statements is consider outside the remit of our review.
286.	EGA	p.10, p. 11	**Transferability across countries** Transferability across countries of assessments must be approached in a very careful manner, because of different local products or local non-pharmaceutical alternatives (p. 10, p. 11).	This is a specific comment to statements of HLPF. This is not within the remit of this review.
287.	EGA	p. 11, point 6.3.	**Scientific advice meetings** "Scientific advice meetings" and especially joint scientific advice meeting with Regulators and HTA bodies, e.g. MHRA/NICE, AFSAPPS/HAS could be useful both for originators and biosimilars. It might be beneficial if there is some commitment to hold such meetings from the HTA organisation during product development to improve the generation of appropriate data as far as possible (p. 11, point 6.3).	Comments regarding scientific advice are not within the remit of this specific review.
288.	EGA	p.64, l 28-32	**Role of regulatory authorities and HTA authorities** The respective roles of regulatory authorities and HTA authorities should be clearly defined (p. 64 l28-32). If this point is not addressed, the result would be discrepancies between two assessments (as is the case in France where the HAS has decided that some pharmaceuticals with safety concerns should not be reimbursed anymore, e.g.: nimesulide).	Drug regulatory agencies have traditionally assessed the quality, safety and efficacy of drugs, and the current paradigm dictates that a new drug should be licensed when the benefits outweigh the risks. A relative effectiveness assessment focuses on the relative effect (unintended and intended effects) in comparison to available treatment(s).
289.	EFPIA	General	EFPIA welcomes the opportunity to comment on the background review as the first deliverable of WP5 and is committed to further contributing to ongoing reflections within EUnetHTA JA. As a member of the WP5 SAG, EFPIA already had the opportunity to provide comments on an earlier draft of the	We thank the EPFIA for providing comments and we look forward to a discussion regarding the content of the guidelines with the stakeholder advisory group next year. Also see response to comment 292.

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			background review. We would like to thank WP5 for this opportunity and for having taken many of the comments made by EFPIA on board. Since many of the sections of the review are descriptive in nature, we have limited our comments to those sections that we believe could be further clarified. Much of our comments refer to concepts and definitions, since we consider that a shared understanding of key concepts is a key prerequisite to any European discussion. Moving forward, EFPIA would favour being involved in the production of methodological guidelines, together with other stakeholders, as these are currently being developed in the framework of WP5. Such guidelines, based on sound and agreed definitions, have the potential to streamline procedures and to reduce unnecessary duplication of work. As regards to guideline development, EFPIA would favour a discussion on the use of multiple sources and types of data to inform assessments of relative effectiveness. As acknowledged by the background review, EFPIA agrees that efficacy and effectiveness are on a continuous spectrum. From an operational standpoint, what matters is to clearly define the source of information from which relative efficacy and relative effectiveness estimates may be derived, such as direct comparisons; indirect comparisons; clinical studies that use a study population, comparator, or treatment scheme close to real world practice; observational studies (cohorts, case/control, exposed/non-exposed, registries, claims databases, etc.), and models that bridge relative efficacy data with epidemiological information on the natural history of the disease and/or context-specific resource utilization data. Guidelines on approaches to different types of non-randomised data would be useful, and EFPIA would be pleased to contribute to such discussion.	

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			EFPIA further highlights the importance of taking into consideration the different approaches that exist in relative effectiveness assessment of pharmaceuticals across Europe today: a continuous quantitative estimate in the context of cost-effectiveness modeling (e.g. NL, England) versus a categorical qualitative estimate of "added value" in some other countries (e.g. France, Belgium, Germany). One should not overlook that the former model includes an inherent relative effectiveness assessment through modeling of relative efficacy data. Guidelines on acceptable sources of data would be very useful in that respect. Furthermore, EFPIA notes that the background review would have benefited from a discussion on the use by HTA bodies of the benefit/risk assessment conducted by regulatory authorities (including relative efficacy assessment and label). It would be interesting to understand in which circumstances HTA agencies reiterate these assessments and for which reason, in order to understand how to best avoid any duplication of work. A statement as well as inclusion in the forthcoming guidance document would be helpful in that respect.	
290.	EFPIA	Summary	Relative effectiveness assessment is equated with the terminology 'a comparative analysis of efficacy and/or effectiveness of pharmaceutical(s) in comparison to alternative(s)'. We would recommend to clarify the definition of relative effectiveness assessment at the beginning of the review, as defined by the HLPF, to avoid confusion.	A reference to the definition of HPLF is be added to the summary.
291.	EFPIA	p. 6, l. 8-10	We understand that the review of national reimbursement decisions was conducted since most reimbursement decisions take into account a comparative analysis of the efficacy and or effectiveness of pharmaceuticals. However we note that this comparative analysis might also impact on other dimensions	Processed

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			such as pricing, or other access decisions not in the form of pricing and reimbursement decisions. We would therefore suggest rephrasing into: "relative effectiveness assessments, amongst other criteria, are always considered by national decision-makers where making reimbursement decisions". This would also be more in line with the wording on p5, l16-17.	
292.	EFPIA	p. 6, l. 10-11	The fact that all countries conduct REA does not mean that it can necessarily be shared between countries. One should further clarify how relative effectiveness is assessed in EU countries. At present, there are at least two different approaches: a continuous quantitative estimate in the context of cost-effectiveness modeling (e.g. NL, England) versus a categorical qualitative estimate of "added value" in some other countries (e.g. France, Belgium, Germany). One should not overlook that the former model includes an inherent relative effectiveness assessment through modeling of relative efficacy data. Moving forward, EFPIA would favour being involved in the production of methodological guidelines, together with other stakeholders, as these are currently being developed in the framework of WP5. Key issues to be addressed in methodological guidelines include the way to conduct relative effectiveness assessments, sources of data and transferability of results between countries.	Your comments are worthwhile and are used in the current development of the guidelines within WP5. In this review we restrained ourselves to the REA, within our remit, and did not perform any detailed analysis of processes and methodology that relates to CEA.
293.	EFPIA	p. 6, l. 14-15	We note the introduction of a new terminology "net therapeutic benefit", but question whether this will really lead to a clarification of discussions.	The focus of WP5 is common methodology for relative effectiveness assessment. It is however up to the countries to determine the value of the relative effectiveness. The term net therapeutic benefit was chosen as it represent, in the view of the participants of WP5, most closely the purpose of a relative effectiveness assessment.
294.	EFPIA	p. 6, l. 15-19	We agree that the first four domains of the core model are the most transferable between countries. However we find it difficult to see how elements of ethical, social, legal and organizational aspects might be shared across countries, since these are by	We agree that in general elements from these domains may be more context specific. However, the items that were selected from these domains are very general in nature (e.g. does the pharmaceutical have a market authorization?). In addition, a

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			definition context-specific. These items may not be transferable between countries and we would welcome the opportunity to contribute to the discussion on whether and how to incorporate these elements.	pilot assessment of a pharmaceutical will be conducted in WP5 in 2011. This pilot should provide valuable information regarding the usefulness of the selected assessment elements for a Rapid assessment. Finally the model for relative effectiveness assessment of pharmaceuticals will be provided to the stakeholder advisory group of WP5 in 2012 for comments, followed by a public consultation.
295.	EFPIA	p. 6, l. 20-26	See comment above	See response comment 249.
296.	EFPIA	p. 6, table	We agree with the challenges outlined in the table. In addition, we consider that a common challenge faced by HTA processes across Europe is the lack of appropriate stakeholder involvement. Involving stakeholders such as patients, healthcare professionals and industry can support assessments by providing important evidence and further knowledge on methodologies. Not involving these stakeholders might lead to HTA which undervalue key societal aspects of technologies.	We realise that there are many aspects that can influence the value of a technology to patients and society as such. However within WP5 we should limit the scope to a relative effectiveness assessment based on available scientific evidence. The value of a technology to patients and society should be determined on a national level. Additionally, we believe that the involvement of stakeholders is organized in a very structural way in EUnetHTA, and WP5 in particular.
297.	EFPIA	p. 9, l. 38	The HLPF definition of relative effectiveness is based on a consensus between a wide range of stakeholders, including EU member states, health care professionals, patient groups and industry. We suggest adding a reference to the fact that WP5 endorses the definition of relative effectiveness and will encourage its wider use across all Work Packages, where applicable.	We believe that the statement as included in 1.2.3 is sufficient for this background review.
298.	EFPIA	p. 9, l. 41	We note the intention to focus on relative effectiveness assessment conducted by health technology assessment organizations for the purpose of supporting national reimbursement decisions. However HTA might also be conducted for other purposes (such as to support pricing and other access decisions). We would therefore suggest speaking about REA used as a tool to support access decisions.	We realise that, depending on the country, these assessment may or may not be used for other purposes. We have deliberately limited the country comparison to relative effectiveness assessments conducted by health technology assessment organisations for the specific purpose of supporting national reimbursement decisions as this is the one common element in the countries. In addition, the authors feel that

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				resulted subset of HTA organisations provide useful input for the WP5 tools under development. Therefore we feel it would not be adequate to make the suggested change.
299.	EFPIA	p. 11-12, section 1.2.2	EFPIA notes that the comparative effectiveness research project in the US is not limited to pharmaceuticals; it also includes medical devices and in vitro diagnostics. In addition to evaluating all technologies, the US health care reform law also requires the study of various health care services, as different modes of health care delivery can have a significant impact on the quality of care received. We also note that the PCORI governing board includes representatives from industry and the patient community – this important fact is not mentioned in section 3 of the EUnetHTA JA draft background review.	The reason why these are not mentioned is because we focus solely on activities/methods for relative effectiveness of pharmaceuticals.
300.	EFPIA	p. 12, section 1.2.3	See comment above on the definition of the HLPF.	See response to comment 297.
301.	EFPIA	p. 12, section 1.2.3.1 (l. 43-44)	We would like to note that efficacy and effectiveness are in fact on a continuous spectrum but that, from an operational standpoint, what matters is to clearly define the source of information from which relative efficacy and relative effectiveness estimates may be derived. Specifically: - Estimates of relative efficacy can be derived from (1) direct comparisons within randomised clinical trials, and (2) indirect comparison of information from separate clinical trials using meta-analytical methods. - Estimates of relative effectiveness can be derived from multiple sources that include e.g. : (1) clinical studies that use a study population, comparator, or treatment scheme close to real world practice, (2) observational studies (cohorts, case/control, exposed/non-exposed, registries, claims databases, etc.), and (3) models that bridge relative efficacy data with epidemiological information on the natural history of the disease and/or context-specific resource utilization data. We understand that these are	We look forward to a discussion on the methodological guidelines in 2012.

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			currently looked at in the development of methodological guidelines and we would be pleased to be able to contribute to that on-going discussion.	
302.	EFPIA	p. 13-15., section 1.2.3.2	We note that the concepts used within the section do not seem to match with the title. The section refers to comparative effectiveness research, whereas the title refers to relative effectiveness research. We suggest staying focused on the HLPF terminology of relative effectiveness assessment.	The title and the section has been rephrased.
303.	EFPIA	p. 15, l. 3 and l. 9	There seems to be two footnotes 11 that do not correspond to any reference.	They correspond to the following reference: nti L, Falco FJ, Boswell MV, Hirsch JA. Facts, fallacies, and politics of comparative effectiveness research: Part 2 - implications for interventional pain management. Pain Physician. 2010 Jan;13(1):E55-79. Review.
304.	EFPIA	p. 15, l. 21-25	We would recommend to include a reference to the three-fold definition of value of innovative medicines of the HLPF: therapeutic/clinical, quality of life and socio-economic (HLPF final report p. 100) after the sentence "In principle, health technology assessment explores all elements of value of a technology…".	Although we acknowledge this definition we feel that this is not within the scope of our review. For that reason this was not added in the text.
305.	EFPIA	p. 15, l. 28	We note the terminology "net therapeutic benefit" but question whether the introduction of a new concept will enhance clarity.	The focus of WP5 is common methodology for relative effectiveness assessment. It is however up to the countries to determine the value of the relative effectiveness. The term net therapeutic benefit was chosen as it represent, for the participants in WP5, most closely the purpose of a relative effectiveness assessment.
306.	EFPIA	p. 15, l. 30-33	We agree with this comment, which also confirms that relative effectiveness assessment does not discuss issues related to the economic and other context-specific aspects of a health technology, such as social, ethical, legal, organisational aspects. These items may not be transferable between countries and we would welcome the opportunity to contribute to the discussion	See response comment 294.

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			on whether and how to incorporate these elements.	
307.	EFPIA	p. 16, l. 3-4	The international use of HTA results is subject to transferability of elements, as is acknowledged by the HTA core model.	Thank you for your comment.
308.	EFPIA	p. 16, l. 6	We would like to understand how EUnetHTA JA intends to ensure that collaborative assessment results are used at both national and regional levels. If this is not ensured we see the risk of duplication of work.	It is too early to assess how the EUnetHTA collaborative work will be taken into the national and regional procedures. However it is the aim to facilitate the uptake of these collaborative assessments in national and regional procedures.
309.	EFPIA	p. 16, table 1 & l. 20 ff. and p. 17, l. 10	We note that it is difficult to comment on the core model without prior understanding of the status of work within EUnetHTA JA on various methodological guidelines. We would be pleased to be able to contribute to the development of such guidelines.	We look forward to a discussion on the methodological guidelines in 2012.
310.	EFPIA	p. 17, l. 5	We agree that the domain of cost-effectiveness should remain outside of the scope of WP5.	Comment noted.
311.	EFPIA	p. 19, footnote 17	This shows that HTA might impact other decisions than just reimbursement decisions. We would therefore recommend changing the wording throughout the document to refer to HTA as a tool to support healthcare decision-making, and in particular access decisions.	See response to comment 298.
312.	EFPIA	p. 19, section 2.1	We would like to get more clarity on EUnetHTA JA's data gathering, especially as regards to data collection. This would help to interpret the relevance of the information collected and whether any key environment/policy changes are ongoing or have occurred since the time of data collection.	A statement regarding the time of data gathering will be included in the final report.
313.	EFPIA	p. 20, l. 1-2	These are highly interesting pieces of information but they refer to the use of HTA to support healthcare decision-making. We would therefore suggest amending the wording used, as suggested above.	See response to comment 298.

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314.	EFPIA	p. 20, l. 12-13	We note that in most countries, reimbursement agencies differ from HTA agencies. HTA agencies also differ in terms of mandate and status (government body, independent body, ...). It would be interesting to understand how EUnetHTA JA will reconcile this.	In the current EUnetHTA JA both reimbursement and HTA agencies are involved in order to ensure their collaboration.
315.	EFPIA	p. 22, l. 26-27 and l. 29-30	We do not consider that 'reimbursement evaluations' is an appropriate term, nor that the process leading to reimbursement decisions can be equated to some form of health technology assessment. In our view, reimbursement decisions are taken based on a range of criteria, one of which is health technology assessment. We would therefore suggest referring to HTA as a tool to support healthcare decision-making, in particular access decisions.	The sentence has been reworded: It should be noted that for inclusion on a positive list the decision is often based on a reimbursement evaluation (*which in general includes* some form of health technology assessment).
316.	EFPIA	p. 24, l. 21-22	We think it might lead to some confusion to refer to the terminologies used in the framework of REA interchangeably with any criteria used in the framework of reimbursement decision. Again, to our understanding, HTA (and RE as part of HTA) is a tool to support healthcare decision-making, in particular access decisions. The US CER debate also acknowledged this by underlining that CER should support, but not directly feed into, individual coverage policies	The title of the section has been rephrased into: 2.2.4 Evaluations that provide input for reimbursement/funding decisions. The first sentence of the paragraph was rephrased into: In general, evaluations of pharmaceuticals that provide input for reimbursement decisions can be divided into (single) rapid assessment and full assessments of pharmaceuticals.
317.	EFPIA	p. 25, l. 14-21 and overall section 2.2.4	Over the years CJEU case-law has clarified the broad scope of the Directive, indicating that it encompasses all measures impacting pharmaceutical pricing and reimbursement, including HTA. Therefore we agree that the HTA impacting pricing and reimbursement decisions should follow the timelines of the Directive. However we would still consider that reimbursement decisions are not to be equated with HTA, which are a tool to support, but not replace, these decisions. Since the work of EUnetHTA aims at supporting collaboration on assessment, but no harmonization of decisions, we would welcome clarification of the link between the two.	The following sentence was added: It should be noted that pricing and reimbursement decisions are not to the same as a Rapid or Full assessment, which are a tool to support, but not replace, these decisions.

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318.	EFPIA	p. 29, figure 8	Is it fair to consider that the assessment concerns the HTA, that the advice is then a recommendation based on the results of an HTA, and that the decision takes into account a variety of other criteria by the decision-maker? This refers back to our earlier comment that HTA is a tool to support, but not replace, decision-making.	We agree with the comments. To clarify this the following sentence was added: It should be noted that the third step, the decision, is based on variety of criteria. The advice based on the assessment is only one these.
319.	EFPIA	p. 31, l.3	The results of the survey show room for improvement when it comes to stakeholder involvement in HTA across Europe. Given the importance of appropriate stakeholder involvement, also for the acceptance of WP5 deliverables, we suggest that there is the opportunity with the EUneHTA JA to set an example by agreeing on a broad stakeholder involvement for any assessment that would be conducted collaboratively by HTA agencies as pilot projects.	The pilot project to be undertaken by WP5 will be subject to consultation of the Stakeholder Advisory Group as well as a public consultation.
320.	EFPIA	p. 31, l. 31-36	Adequate and fair appeals processes are an important part of Good Governance in HTA. Information included in this section and in Table 11, highlight the fact that not all countries provide the opportunity to appeal and also that the appeals processes established look different across Europe. We believe that EUnetHTA JA could play a role in ensuring adequate and fair appeals processes across Europe. We would like to see in section 4 confirmation that the appeal process will be an integral part in the development of the rapid and full models. Even though we understand that this is not within the remit of WP5, we would suggest considering it within the broader scope of EUnetHTA JA. It would also be relevant to include such a mechanism when conducting pilot projects within WP5.	We recognise the relevance of appeal however this is not within the remit of this background review.
321.	EFPIA	p. 31, section 2.2.4.3	This confirms our previous comments on the broader scope of HTA as a tool to support healthcare decision-making, not only reimbursement decisions.	See response to comment 298.

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322.	EFPIA	p. 32, figure 10	In figure 10, 64% of respondents indicate that they use assessments to support pricing decisions. It would be interesting to understand the link with other pricing mechanisms such as international reference pricing, which are also widely used across Europe, but which fail to take into account the value of products.	We agree that this would be interesting however this is not within the remit of this background review.
323.	EFPIA	p. 36, section 2.3.1	We understand that the remit of WP5 is to work on methodologies for relative effectiveness assessments. We consider that common methodologies should lead to a convergence of data requirement for assessment to ensure increased efficiency in producing the evidence needed. EFPIA will be pleased to work jointly with WP5 to contribute to the development of methodologies for relative effectiveness assessment, in which the pharmaceutical industry has considerable experience over time and across countries.	Thank you for the comment.
324.	EFPIA	p. 40, Section 2.3.4	There is a need to recognize that HTA must be sufficiently flexible to handle uncertainty. Uncertainty should be dealt with in partnership with manufacturers and sensitivity analysis considered as a mechanism to address it.	Thank you for the comment.
325.	EFPIA	p. 48, l. 4	We are pleased that an ongoing collaboration with EMA is taking place, since that can lead to less duplication of work, and would be pleased to contribute to the evaluation of its effectiveness in the framework of the SAG.	Thank you for the comment.
326.	EFPIA	p. 59, l.6	We would like to point at the importance of ensuring that agreed methods and guidelines be adhered to in order to avoid unnecessary duplication and we would invite reflection on the best way to ensuring this.	The final tools developed in WP5 will be freely accessible and although usage will not be mandatory, EUnetHTA will stimulate the use of the tools in the different participating European countries. In order to so, EUnetHTA will develop a plan to support, where appropriate , the implementation of the use of the tools. An important step will be the planned Joint Action 2 in which, within WP5, European oganisation will produce joint assessment reports of pharmaceuticals.
327.	EFPIA	p. 59,	As mentioned above, we consider that, for the European context,	Thank you for the comment.

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		section 4.1	it is important to rely on the terminology relative effectiveness assessment as the one that was endorsed by a broad range of stakeholder in the High Level Pharmaceutical Forum.	
328.	EFPIA	p. 59, l. 31 and l. 35	We note the inclusion of yet another terminology with 'net clinical benefit' and 'net therapeutic benefit'. We question whether this will clarify the debate.	See response to comment 293.
329.	EFPIA	p. 60, l. 4-5	As mentioned above, we would refer to HTA as a tool to support healthcare decision-making, including access decisions, since in the background review it appears that those described HTA do not only support reimbursement decisions.	We agree on the comment that HTA is a tool to support healthcare decision-making, including access decisions. However, for the survey it was chosen to limit the analysis to assessments for the purpose of national reimbursement decisions. In addition, the authors feel that resulted subset of HTA organisations provide useful input for the WP5 tools under development.
330.	EFPIA	p. 60, l. 6-10	This paragraph is not very clear and we would suggest rephrasing it.	The section been rephrased into: In order not to exclude evaluations of pharmaceuticals of jurisdictions based on the definition of the High Level Pharmaceutical Forum of relative effectiveness the following type of assessments were included: all 'comparative analysis' assessing the efficacy and/or effectiveness of pharmaceutical(s) in comparison to alternatives that provide input for national reimbursement decisions on pharmaceuticals have been included.
331.	EFPIA	p. 60, l. 10	The end of the sentence seems to be missing.	See response to comment 330.
332.	EFPIA	p. 60, footnote 40	As previously mentioned, we would not consider that reimbursement decisions are based on a reimbursement evaluation which would be some sort of HTA. However we would consider that HTA is increasingly used to support access decisions, including reimbursement decisions, in European countries.	The footnote has been rephrased into: Inclusion on a positive list is often based on a reimbursement evaluation whereas negative lists (e.g. Germany and England/Wales) are often exclusions of specific types of pharmaceuticals such as non-prescription or life style pharmaceuticals which are not per definition subject to a reimbursement evaluation before being placed on the negative list.

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333.	EFPIA	p. 60, l. 12-23	It follows from the above that we would consider the three steps of assessment, advice and decision refer to the healthcare decision-making which is supported by HTA.	Thank you for this comment. We feel that this is sufficiently addressed in our report.
334.	EFPIA	p. 60-62, section 4.2	Since this section summarises the review, we refer to previous comments made throughout the document.	See responses to individual comments.
335.	EFPIA	p. 62, l. 24-27	The fact that all countries rely on relative effectiveness does not mean that this assessment can be shared between countries.	We acknowledge this. However, the fact that methodology is similar in countries, in our view, means that there is a common ground for potential future shared assessments.
336.	EFPIA	p. 62, l. 27-31	We agree that the four first domains of the core model are the most likely to be transferrable. We question how far ethical, organisational, social and legal aspects can be shared between countries, given that they are context-specific. These items may not be transferable between countries and we would welcome the opportunity to contribute to the discussion on whether and how to incorporate these elements.	See response comment 294.
337.	EFPIA	p. 62, l. 35	We agree with the statement that cost-effectiveness should be excluded from the scope of WP5.	Comment noted.
338.	EFPIA	p. 63, l. 1 and Figure 20	Again, we question how far ethical, organisational, social and legal aspects can be transferrable. Could you please specify which limited number of elements you are referring to? These items may not be transferable between countries and we would welcome the opportunity to contribute to the discussion on whether and how to incorporate these elements.	See response comment 294.
339.	EFPIA	p.63, section 4.3 figure 20	The HTA Core Model should include consideration of the patient impact and the innovation impact. The latter should reflect the importance of recognizing dynamic efficiency, or the impact on incentives to innovate versus static efficiency.	Thank you for the comment. Your considerations will be taken forward in the development of the model.
340.	EFPIA	p. 64, l. 2-	We would be pleased if we could contribute already at this stage	The guidelines are currently in an early stage of development.

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		8	to the development of methodological guidelines.	Involvement from stakeholders will be possible in 2012.
341.	EFPIA	p. 64, l. 33-34 and l. 42	We would prefer to refer to relative effectiveness assessment rather than introducing new terminology in the form of net therapeutic benefit assessment.	See response to comment 293.
342.	EFPIA	p. 65, l. 15-18	In addition to the very important contribution of stakeholders on guidelines, we consider that stakeholders should be involved in testing these guidelines in real life, i.e. in the pilots conducted by EUnetHTA JA, and in particular WP5, at an early stage of the process. Stakeholders bring expertise and experience of the products that will be assessed in pilots as well as extensive knowledge on HTA policy and methodology throughout countries and time.	We recognise the value of stakeholder input and look forward to collaboration in 2012.
343.	EFPIA	p. 65, table 8	As stated above, we agree with the challenges outlined in the table. In addition, we consider that a common challenge faced by HTA processes across Europe is the lack of appropriate stakeholder involvement and ensuring transparency. Involving stakeholders such as patients, healthcare professionals and industry can support assessments by providing important evidence and further knowledge on methodologies.	The remit of WP5 is to provide tools for relative effectiveness assessment of pharmaceuticals. In the development of these tools the mentioned stakeholder are and will be involved. Involvement of stakeholder in the general HTA process is not within the specific scope of WP5.
344.	EFPIA	p. 65, l. 20-22	We would like to stress the importance of agreeing on common definitions as a prerequisite to the development of methodological guidelines. Definitions should be in place before the rapid and full models respectively are finalised. Should this not happen, we see a risk of further duplication of work between the European and MS level.	We agree with the comment.
345.	CCCN	General	This Background paper is very comprehensive and identifies many of the issues that are relevant to patients and users of health care. It is put into perspective by including findings from a comprehensive survey of national approaches	Thank you.
346.	CCCN	General,	It is stated that for Rapid assessment, only a limited number of	Thank you for the comment

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		rapid assessment	elements of the ethical analysis, the organisational analysis, the social aspects and the legal aspects. This combined with the use of fewer comparators, surrogate and composite outcomes (due to assessment shortly after market approval) requires careful monitoring, especially if the ultimate aim is to use relative effectiveness assessment leading to the estimation of the net therapeutic benefit for a certain pharmaceutical a combination of the intended and unintended effects (which it should).	
347.	CCCN	General, intended and unintended effects	Integrating intended and unintended consequences of treatment is important I agree that the actual weighting of the intended and unintended effects, where there is a lack of clarity, is best being part of the remit of national decision makers (including patients) and will depend on the disease and its consequences, available options and other considerations including short and long-term costs. Considering variance in whether the weighting of the intended and unintended effects of an intervention is part of the assessment or if this is explicitly limited to the appraisal phase – I would argue that relative effectiveness assessment is a determination of clinical effectiveness and looks beyond strict randomized controlled controls. How an intervention is used and any consequences including harms are inherent to that assessment.	We take this comment into account and want to emphasise that a relative effectiveness assessment should look at the intended and unintended effects in comparison to available treatments.
348.	CCCN	General	Key stakeholders including patients are vital to both the assessment and the appraisal phase. The public do expect good, safe health care. I agree it is important to separate out cost and economic considerations in the assessment. The question here is clinical effectiveness	This is in line with the remit of WP5.
349.	CCCN	General, Comparators	Comparators is an issue As reported, the choice of comparator may differ between countries as usual care can differ between countries. Accepted and widely used treatments can vary. People can also look at important clinical trials differently,	Your comment is taken into account.

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			particularly when trying to assess the findings in terms of their health system/usual circumstances of care, country traditions and culture. - Different methodologies for direct and indirect comparison may be used to come to adjusted interpretations for countries with different forms of usual care is an interesting challenge.	
350.	CCCN	Summary table	The summary table is very helpful. It also raises important questions – about how well guidelines can successfully address some of the challenges; and what those guidelines will look like and how they can be used most effectively. For example for: terminology and definitions The ability to use standardized reporting, aggregate data on intended and unintended effects, and how these are looked at in different countries, is important information that can really help the users of health care. Transparency of that data is important. This is particularly so when there is a lack of effectiveness data; and when the efficacy data itself is limited; and when unexpected harms occur.	Transparency of data is a key element for sharing assessments.
351.	CCCN	General, to inform patients	To inform health-care professionals and patients on the most effective drugs – must still allow for special circumstances (and patient choice with informed consent) Responses to drugs are individual whereas the assessments are based on a population – and many other factors come into play. As well as differing in health system and the support they have (cultural, social, financial, legal and other differences), people have co-morbidites (and increasingly so, meaning they are on multiple treatments often for long periods of time or for the rest of their life even from an early age); health problems are not static (with global challenges eg H1N1 influenza); and innovation continues.	Your comment has been acknowledged.
352.	Porzsolt	general	The first step of an effective action is the harmonization of the used terms	Your comment has been acknowledged.
353.	Porzsolt	general	Neither single rapid nor full assessment will solve the problem. We need to develop new approaches of well controlled non-randomized trials. Our proposal is submitted to JAMA and will be	WP5 is focusing on how to do assessments of available data. Of course we agree that a well conducted assessment will not improve the underlying evidence. We look forward to the

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			available upon acceptance of the paper.	publication.
354.	Porzsolt	general	The methodology used is not transparent enough	It is not clear to the authors to which part of the used or proposed methodology the comment is referring to. Therefore we are not able to provide a response.
355.	Porzsolt	general	Any comparator is acceptable if it will solve the problem that has been defined BEFOREHAND by a shared patient-doctor decision. This means the definition of the exact problem is the critical point, not the method.	The authors consider both the definition of the research questions as well as the method are critical for conducting a useful assessment.
356.	Porzsolt	general	There are two clinically important outcomes, preventing disease-related death or disease-related impairment of Quality of Life (specify the aspect of QoL which is impaired). Surrogates are meaningless unless clearly related to one of the above outcomes.	Your comment has been acknowledged.
357.	Porzsolt	general	The present version of the REA does not include any new idea or concept that stimulates the discussion. It should be considered to include new ideas before proceeding to the next discussion round	The purpose of WP5 is not to invent new ideas but to efficiently make use of what is already available and be as close as possible to the national and international guidelines in order to come to standard for performing relative effectiveness assessments
358.	AESGP	General	The Background Review represents a positive step in the Work Package 5 process for the development of guidelines on important methodological issues concerning the Relative Effectiveness Assessment of pharmaceuticals. Through its participation at the Stakeholder Advisory Group, AESGP has had the opportunity to comment on specific issues concerning the Background Review. We would therefore like to use the occasion of the open consultation to provide two general remarks. - A choice for considering only context-non specific elements for the development of REA models is made	We thank the AESGP for providing these comments. Regarding the inclusion of some elements of the social, organisational, legal and ethical aspects the authors feel that a selection was made of those elements only that are non-context specific to a high degree. We realise that consultation periods for the stakeholder advisory group are short. This is due to the tight timelines of WP5 and the work that has to be done between 2010-2012. We are thankful for the cooperation of the stakeholder advisory group.

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			by the Work Package. This, however, does not only concern economic aspects (which are excluded from both rapid and full models), but also - to a varying extent - social, organisational, legal and ethical aspects. Extending or exceeding the scope of REA by including certain elements of these aspects in the full model, as intended, subjects the process to unnecessary risks – primarily concerning the transferability potential of guidelines developed based on the full model. - Although not entirely within the scope of this consultation, it should be noted here that stakeholder contribution to the process could, and should, be more effectively and efficiently used. Two main barriers are the fact that work progresses significantly by the time stakeholder consultation is requested and the lack of any communication between consultation periods. In the framework of this scientific process and in the light of the far more demanding work ahead, we strongly believe that a closer collaboration could go a long way. As a stakeholder involved in the EUnetHTA Joint Action, we remain at the disposal of the Work Package and look forward to contributing to the future steps of the process.	
359.	Flynn	Page 51, ISPOR 'box', 4th line from the bottom	Given large European and Australasian literature on the use of choice experiments in health care, the line "Conjoint Analysis in Health Good Research Practices" should ideally have a footnote applied to it stating "It should be noted that such methods are typically called 'Discrete Choice Experiments' in most of the world outside of North America." Some key references by world experts in the field are: Louviere JJ, Flynn TN, Carson RT. Discrete choice experiments are not conjoint analysis. Journal of Choice Modelling. 2010;3(3):57-72.	Processed

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			Louviere JJ, Hensher DA, Swait J. Stated choice methods: analysis and application. Cambridge: Cambridge University Press; 2000. Hensher DA, Rose JM, Greene WH. Applied choice analysis: a primer. Cambridge: Cambridge University Press; 2005.	
360.	Flynn	Page 52, same ISPOR 'box' continuing from P51, 4th line from the bottom	Same footnote to one above.	Processed
361.	EUCOPE	general	The first step of an effective action is the harmonisation of the used terms.	Your comment has been acknowledged.
362.	EUCOPE	general	First central assessment, a core Health Technology Assessment, will be useful	It is not up to WP5 to decide for the members states whether they are willing to do a central assessment. The final tools developed in WP5 will be freely accessible and although usage will not be mandatory, EUnetHTA will stimulate the use of the tools in the different participating European countries. In order to so, EUnetHTA will develop a plan to support, where appropriate , the implementation of the use of the tools. An important step will be the planned Joint Action 2 in which, within WP5, production of joint assessment of pharmaceuticals is foreseen.
363.	EUCOPE	general	Health Technology Assessment is becoming increasingly important in many Member States of the EU, as well as worldwide. The situation for the Pharmaceutical Industry is currently characterized by different requirements on data, trials, methods as well as different interpretations of terms and methods in the EU Member States. So as for many other processes before like clinical trials, regulatory approvement or	See response to comment 362.

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			pharmacovigilance, we urgently need a harmonisation and centralisation. EUCOPE sees the need for further cooperation between Member States and if possible and suitable harmonisation. As reimbursement decisions will remain national competences, we agree that a first central assessment, a core Health Technology Assessment, could be useful.	
364.	EUCOPE	general	All tools and methods for relative effectiveness assessment should be coordinated, where suitable harmonised, with the tools for early benefit assessment as in many countries, drugs are already assessed during clinical development (Horizon Scanning) or at time of first approval. Also relative efficacy of an intervention compared to one or more alternative interventions needs to follow coordinated and/or harmonised procedures and methods. The described rapid assessment of Relative Effectiveness of pharmaceuticals, defined as rapid assessment of a new technology at the time of introduction to the market and comparing the new technology to standard care, should only integrate efficacy data, focusing on clinical and patient reported outcomes collected alongside clinical trials.	Thank you for your comment.
365.	EUCOPE	general	Neither single rapid nor full assessment will solve the problem. We need to develop new approaches of well controlled non-randomized trials. Our proposal is submitted to JAMA and will be available upon acceptance of the paper.	We look forward to the paper.
366.	EUCOPE	general	The methodology used is not transparent enough.	Due to the general nature of the comment the authors are not able to provide a response.
367.	EUCOPE	general	Any comparator is acceptable if it will solve the problem that has been defined BEFOREHAND by a shared patient-doctor decision. This means the definition of the exact problem is the critical point, not the method.	Due to the general nature of the comment the authors are not able to provide a response.
368.	EUCOPE	general	There are two clinically important outcomes, preventing disease-	Your comment is taken into account.

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			related death or disease-related impairment of Quality of Life (specify the aspect of QoL which is impaired). Surrogates are meaningless unless clearly related to one of the above outcomes.	
369.	EUCOPE	general	The present version of the REA does not include any new idea or concept that stimulates the discussion. It should be considered to include new ideas before proceeding to the next discussion round.	The purpose of the background review is to provide an overview of what is currently happening.
370.	EUCOPE	general	A very interesting document. Good review concerning the current methods of valuation. Even the act for the restructuring of the drug market (AMNOG) is mentioned.	Thank you for the compliment.
371.	EUCOPE	p. 28, Initiation of the reimburse ment evaluation:	We would also like to point to the fact that in Germany an early benefit assessment under § 35a SGB V can also be conducted on the basis of an application of the market authorisation holder.	Processed