EUnetHTA WP5
Relative Effectiveness Assessment (REA) of Pharmaceuticals

Comments provided during public consultation of WP5 pilot assessment report: pazopanib for the treatment of advanced renal cell carcinoma

Com-ment #	Provided by	Page and line	Comment	Response by authors
1.	LBI-HTA	Page 15, Line 12ff	Exclusion of orphan drugs for draft – ok, but are there any planned instructions how to deal with assessment of these drugs? Difficult to assess new technologies when RCTs are missing; Same holds true for technologies other than drugs (e.g. surgical or more complex interventions) since the most common evidence for these technologies are case-series – much more difficult to then assess efficacy and safety of new interventions	We agree that for orphan drugs and other technologies the level of evidence is likely to differ. How to deal with this is out of scope of WP5 Joint Action. In WP5 Joint Action 2 it is intended to also do some pilots on orphan drugs. This will show the suitability of the model for these type of pharmaceuticals. In addition, we hope that how to deal with non- randomised evidence will be a relevant topic for WP7 in Joint Action 2.
2.	LBI-HTA	Page 22, Line 2	Choice of comparators: sometimes drugs are licensing based on RCT in comparison to another experimental drug?? (e.g. ipililumab 2nd line vs glycoprotein100). Would this comparator have been identified in the research question?	The WP5 guideline 'Criteria for the choice of the most appropriate comparator(s)"recommends: If required by national procedural rules, the comparator should have an EU or national marketing authorisation for the appropriate indication and line of treatment.
3.	LBI-HTA	Page 24f; Line 50ff	Mode of administration of alternative treatment options is missing, facilitates judgment on convenience for patients	The information is included in table 14 in the appendix (p118). The mode of administration has now been included in the summary of results section in the DTC domain in the main report (page 28).
4.	LBI-HTA	Page 29ff; General	displaying safety results only narratively = not very easy to get an overview (any of the tables of the appendix should be added)	We agree that for future assessment report this would be preferable. For this pilot report it is challenging because of the many comparators and the various sources (direct comparison and qualitative and quantitative indirect comparisons). The information is included in the summary table at the beginning of the report as schematic as possible.
5.	LBI-HTA	Page 35; Line 13	explain which factors led to downgrading according to GRADE, state number of studies results are based on as well as patients enrolled – however: does it make sense to apply GRADE if only one, pivotal study is available??	These details are included in the assessment elements (table 68 and table 74) Because of the indirect comparison we think the use of GRADE is justified.
6.	LBI-HTA	Page 35; Line 13	tables on efficacy are not sufficient to get an overview on underlying evidence	Illustrative efficacy tables are truly a matter of discussion and further development during JA2. In this pilot established models were used such as Cochrane and GRADE, but there is an apparent need to develop these into a more tailored set of presenting results.
7.	LBI-HTA	Page 48, Line 13	VERY GOOD: "a review of current practices […] or by means of a questionnaire to national HTA agencies, clinicians or hospital	This is indeed preferable but probably not always feasible in rapid assessment.

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			should be made"	
8.	LBI-HTA	General	Would be nice to have an open question section (which could feed into the EunetHTA database and vice-versa) & On-going developments and trials.	If this means that there should be an opportunity to add (or suggest) research questions in the REA Model, this is one of the feedback to Core Model developers that we have heard before too.
9.	LBI-HTA	General	How to reach overall conclusion – weighing risks and benefits? One of the most important and most difficult things to do? This point also connects with the stakeholder involvement	We did some preliminary work on methods used for balancing benefits and harms. It seems that these are quite few and novel and none of them is very well established. The solution presented in the Pazopanib pilot report is the first attempt, and it mainly aims at **presenting** the benefits and harms in a clear way, and not truly **weighing their significance** over each other. However, it should be noticed that the weighting is probably context-specific and therefore authors should be careful with interpretation when producing a joint assessment. The main aim of the assessment should be to present the evidence.
10.	LBI-HTA	General	Indirect comparisons if controlled studies are missing??	We are not sure what this refers to.
11.	LBI-HTA	General	Relevance of outcomes is not discussed, also confusing that e.g. ORR was extracted in the appendix but is not presented in the draft. CR/PR might be important, also for potentially estimating impact on QoL – high CR rates might improve symptoms from bulky disease – foremost in the absence of OS.	This is important notion. The inconsistencies probably rise from the fact that the outcome measures were not discussed in sufficient detail in the planning phases of this pilot. It is already planned that in future pilot assessments relevant outcome measures will be discussed more thoroughly in the scoping phase, which enables their coherent use throughout the document.
12.	Osteba	General	There is a wide variability between the different domains in the use of tools for assessing the quality of the studies. In my opinion this issue is the core of the EUnetHTA "CORE". I think they should make some effort to standardize this important aspect between groups. At least the transparency is guaranteed. Below I specify the pages of the document:	Thank you. Your comment about the need to standardize the use of quality assessment instruments across domains will be taken forward to guide the REA model development.
13.	Osteba	Page 24 Line: 1-4	Only refers to the use of AGREE Instrument. And, why not AGREE II?	AGREE II was launched in August 2010 and the search and evaluation was performed in March 2011. The researcher used the previous version of the instrument which they were used to, because they had not noticed that there was a new version available. AGREE is now replaced with AGREE II in the REA Model.
14.	Osteba	Page 27	Refers to JADAD, SPC and REPAR and a list of criteria (have been	Certainly most of the listed quality criteria are not validated.

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		Line: 15-32	validated?)	Rather, they reflect the everyday practices in HTA agencies. We agree that validated criteria should be preferred but due to the heterogeneity of the pre-clinical data various methods need to be used. However, we will list the quality assessment of pre-clinical data as one of the items where we would like to see more methodological guidance in the future.
15.	Osteba	Page 30 Line: 2-10	SIGN checklists, the National Cancer Institute scale for RCTs, and the STROBE checklist for observational studies..	We see your point you raised about the need to harmonize the methods used for quality assessment. This pilot clearly shows that the HTA agencies have their own preferences on the tools they use. In the future pilot rapid assessments in WP5 Joint Action 2, there will be only two authoring agencies (and no domain teams) will reduce this problem of diverging tools.
16.	Osteba	Page 33 Line: 5-13	There is no Quality appraisal section. But in Methods there is a reference to "Method card 2 in Appendix 1: "Risk of Bias".	We allowed this exceptional reporting for effectiveness domain team because they had made great effort in preparing clear method cards. This will not repeat in the future assessment projects as there will be no domain specific work division anymore.
17.	Osteba	General	It is an excellent document.	Thank you
18.	Eucomed	General	Eucomed as a SAG member already had an opportunity to comment on the document in the frame of SAG consultation however there are two main concerns that we would like to reiterate.	We thank Eucomed for their continuous input on this pilot report.
19.	Eucomed	49/46	250 working days were spent on the assessment, 150 days were used for coordination and plus the workload was assessed high. With the recommendation to use the MAH (Marketing Authorization Holder) submission file as basis we would advise to perform a comparative investigation of having the current process with core HTA model followed by National adaptation compared to National HTA using other member states HTA report assessing as outcome the overall time, working days, and quality of outcome for rapid assessments.	This kind of validation exercises have been considered, but as the Core Model and the whole process of using the Core Model is under substantial changes, this will not be relevant for the 1st version of the REA Model and the collaborative model used in this first pilot. Instead, the Model will be made lighter and the whole collaborative structure much simpler. This will likely reduce the time consumed substantially.
20.	Eucomed	46	Relevant beyond national context" it is unclear how this would be ensured. The content of domains HP and current use of clinical effectiveness are context specific and different standards apply for	In health problem and current use domain some elements are clearly transferable, such as definition of the disease, its risk factors and natural course. The transferability of other elements,

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			different countries. The selection of domain and countries contributing to the domain will have a significant influence on the ability to share. The description of process on how to reach out to other member states HTA agency did not have seen to be part of the process.	such as what is the prevalence of the disease? or how much is the technology used? depends on the manner the response is given. For certain diseases there are overall figure of Europe or statistics from most countries easily available. Sometimes the data from other countries may be helpful if there is no national data available. These are the reasons why we can still strive to providing answers that are at least partially useful to other countries. You mentioned the process of reaching out to other member states' HTA agencies: There are no plans to include this activity in the Core HTA process, because it has been too early for that. In the future when we have increasing amount of collaborative Core HTAs available in a database, there will probably be the need to start thinking how to promote the use of this information.
21.	Novartis	Comments on the objectives and main goal the of the pilot: General (continued from page 1)	Novartis welcomes this public consultation as well as the opportunity to provide comments. All comments provided in this document relate to the pilot assessment undertaken or to possible future pilot assessments undertaken by the EUnetHTA JA. Novartis does not commit to accepting or participating in the use of this pilot assessment in any form of systematic REA review. It is our understanding that this pilot was undertaken to test a form for assessment of Relative Effectiveness. However, we detect confusion and would see value in distinguishing between various components of drug review: • relative efficacy, • relative effectiveness, • differential therapeutic value. EUnetHTA has, in the past, acknowledged the High Level Pharmaceutical Forum definitions of relative efficacy and relative effectiveness respectively. Clearly distinguishing these terms seems necessary in the context of the pilot undertaken. Relative	Thank you, this comment of being more explicit with relative efficacy and effectiveness will be taken as one discussion item for the developers of the REA model.

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			efficacy can be fully assessed at launch. Relative effectiveness, on the other hand, can only be assessed once a health technology has been used in real life settings a certain period of time. At the time of launch, relative effectiveness can only be estimated from available efficacy data.	
22.	Novartis	Comments on the objectives and main goal the of the pilot: Page 14, Line 42-44	Clarification as to the intended use of an assessment report like the one produced would be of interest. For instance, will the final assessment report be submitted to every local agency? Will the report be available for use during national/ local HTA body review? What is the expected impact of the EUnetHTA JA REA on local assessment (national guideline review based on indirect comparison, reimbursement restriction according to REA conclusion)? Novartis believes that any conclusions drawn from this pilot cannot be extrapolated to other pharmaceuticals or other technical areas such as biosimilars, medical devices, diagnostics and vaccines.	The aim of the pilot was to test the feasibility of a new structured way of doing HTA (Core Model) and doing it jointly with several national HTA agencies. Therefore, we did not include yet plans for how to use this information. Now, after the pilot, several things will be changed in the Core Model and also in the way of collaboration. Therefore, it is very likely that also the format of the report will look very different after the next pilot. Additionally, when the online tool is taken into use, the card format will be more easily browsable. The expected impact would be reduced workload for national HTA agencies, as they can make use of the sharable pieces of information, and on top, add national data and national judgements. The aim is not to harmonize decisions, but rather to harmonize and improve the quality of the information that can be shared.
23.	Novartis	Comments on the objectives and main goal the of the pilot: Page 15, Line 2-29	Please share further insights on the drug selection process and criteria, for the undertaken pilot as well as for any future ones. How does EUnetHTA see its REA pilot(s) fitting into the existing regulatory/drug assessment framework? Also, going forward, are early joint dialogues with other stakeholders planned?	The topic selection process of the pilot is described in detail on page 15 as you indicated. Many of the principles will apply in the future WP5 Joints Action 2 pilot assessments too: the product has to be at least in the process of getting market authorisation, and preferably the manufacturer needs to volunteer sharing the submission file. For the future WP5 Joints Action 2 pilot assessments the preferable timing of the assessments would be to start the actual assessment as soon as the CHMP positive decision is available. The scoping phase should be finalised by then. Such a timing of the assessment would facilitate that the assessment would be available soon after market authorisation before the national processed have started in order to facilitate uptake in various countries.
24.	Novartis	Comments on the objectives and main goal	In our understanding, the undertaken assessment is more of a relative efficacy one. To conduct relative effectiveness studies	Thank you, this comment of being more explicit with relative efficacy and effectiveness will be taken as one discussion item for

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		the of the pilot: Page 39-40	requires real world evidence to assess real world effectiveness. Without a doubt, the ultimate effectiveness of a technology (pharmaceutical, vaccine, device, diagnostic) will be driven by patient adherence to treatment, as well as how the healthcare system is organized, and the implementation strategy that is adopted. How will future pilot assessments take into consideration these elements for the assessment of relative effectiveness?	the developers of the REA model.
25.	Novartis	Comments on the objectives and main goal the of the pilot: Page 40 Line 13-20	It is unclear what is meant in on page 40 (lines 13-20) by the discussion of price negotiations. Does the line 20-21 on this page suggest that EunetHTA pilot REA assessments would conduct value based pricing recommendations at the European or Member State level? Our understanding is that value assessments to inform price and price setting will be exclusively conducted at the member state level.	The sentences on lines 19-20 are changed to be: "In the future there is a need to collect evidence on safety, effectiveness and service provision in real clinical settings. This information could be used also in defining risk sharing schemes." The aim of EUnetHTA RE assessments is not to give any recommendations. The coverage and pricing decisions are a national competence.
26.	Novartis	Comments on the objectives and main goal the of the pilot: Page 52, Line 11	HTA should be separate from the regulatory review for the granting of marketing authorisation, as it currently is in Europe. However, to avoid duplication and maximize synergies, assessments of relative efficacy and effectiveness should build on work already undertaken by EMA. An HTA assessment, as a part of a pilot Joint Action, or in an established network should not challenge clinical judgments or the market access authorization of a regulatory body.	Point noted. There have been interactions between EUnetHTA JA and EMA on defining the best ways to collaborate and avoid duplicate efforts. This work will continue during the next period of EUnetHTA (JA2).
27.	Novartis	comments on how the pilot was carried out: General	Currently in Europe, the research-and development based pharmaceutical industry is faced with at least 27 different assessments of the therapeutic value of its products. Providing the information needed for these differing assessments represents a considerable challenge. Moreover, the differing outcomes contribute to the observed differences in patient access to medicines across Europe. European assessments of differential	The pazopanib pilot was based on submission file by MAH, EPAR and an additional literature search. The future (EUnetHTA JA2) REA assessments will have even more weight on submission file and EPAR. There will be a meeting arranged to discuss the scope and the submission file prior to the assessment. Your point about patient involvement is notified as an important issue, possibilities will be explored during JA2.

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			therapeutic value could reduce costs for development as well as increase predictability. European assessments of differential therapeutic value could also result in more equal and timely access to medicines. For these potential benefits to materialize however, it is imperative that the European statements of differential therapeutic value are recognized and accepted by all member states and stakeholders as the common basis for further evaluations. To ensure broad alignment, these European statements should: • be based on assessments performed according to standards agreed by all relevant parties, • originate from the Marketing Authorization Holder (MAH), • be developed in a process that closely involves therapeutic area specialists, patient representatives and the MAH, • build on the work undertaken by EMA during the approval process and the resulting EPAR. From what we understand, the involvement of stakeholders in undertaking the relative effectiveness assessment of pazopanib was very limited. We would like to see closer consultation with the MAH, EMA, therapeutic area clinical experts as well as patient representatives. The report suggests that the EUnetHTA JA is currently reviewing the process for undertaking future relative efficacy and relative effectiveness assessments. To reduce overall workload and redundancies in future pilots, we would suggest basing REA assessments on the MAH submission and the EMA EPAR. To facilitate this, we would like to propose a discussion between a wider industry consultation, EMA and the EUnetHTA to jointly	We agree with your point that a uniform structure for assessments could be a key to reduce the workload due to the 27 different assessments required, on conditions you mentioned (standards agreed by all, inclusive processes etc) however the determination of the therapeutic value is seen by most countries as their national competence.

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			agree on a reasonable submission format which would allow for more extensive use of the information provided by the MAH.	
28.	Novartis	comments on how the pilot was carried out: Page 05, Line 39-56	As presented, the information in the pilot assessment document does not allow for a comprehensive understanding of the evidence behind pazopanib such that a fair judgment on its adaptability for national purposes can be made. The content of the information within the document should go beyond summaries and discussions for each domain.	More detailed information and data are presented in the result cards (referred as codes such as D0001 in the summary), presented in the Appendix. The result cards will be electronically linked to the summary in the future versions of the RE assessments, so that the reader has easy access to the details when needed.
29.	Novartis	comments on how the pilot was carried out: Page 15, Line 34	Assigning each "Domain" to a different assessment group seems inefficient due to duplication of literature reviews. A possibility would be to use specialized external/independent academic bodies to do the assessment (similar as the way NICE in the UK operates).	This was one of the outcomes of this pilot: it was indeed not efficient to separate the domains in teams. In the upcoming RE-assessments by EUnetHTA WP5 a simplified collaborative model will be used, and its efficiency piloted.
30.	Novartis	comments on how the pilot was carried out: Page 18-21 Page 19-20, Line 37-43	Transparency in future pilots could be improved especially by including MAHs and having an open consultation in the scoping phase. We would also like to see involvement of patient and clinical representatives.	MAH will be included in the scoping of the future RE assessments of EUnetHTA JA2 WP5. Feasibility of other stakeholder involvement (e.g patients, clinicians) involvement within the strict timelines of the rapid assessments will be explored.
31.	Novartis	comments on how the pilot was carried out: Page 18-21	As previously stated, the involvement of stakeholders in the relative effectiveness assessment undertaken was very limited. We would like to see closer consultation with the MAH, therapeutic area clinical experts as well as patient representatives.	MAH will be included in the scoping of the future RE assessments of EUnetHTA JA2 WP5. Feasibility of other stakeholder involvement (e.g patients, clinicians) involvement within the strict timelines of the rapid assessments will be explored.
32.	Novartis	comments on how the pilot was carried	MAHs undertake extensive searches when preparing submission files. As we do not have access to the MAH's submission, we cannot evaluate the extent to which the searches already	In the upcoming RE assessments of EUnetHTA JA WP5 the assessment is based on the submission file (thus the search performed by MAH). Reporting explicit criteria for including and

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		out: Page 19, Line 5-14 and 20-27	undertaken by the MAH were considered, and how it is reflected in the reference list. It would be useful to see the MAH's literature review to verify if there is need for duplication of efforts by EUnetHTA. We would suggest building on the search already undertaken by the MAH. Thus to streamline the overall REA process, avoid duplication, and promote synergies. Also, in the interest of process reproducibility and to avoid subjectivity, we believe the study selection process applied merits further discussion.	excluding studies would indeed be the key for HTA assessors to be able to evaluate the search and inclusions by MAH.
33.	Novartis	comments on how the pilot was carried out: Page 20, Line 45 - Page 21, comments on how the pilot was carried out: Line 15	The amount of research questions and results cards used merits reflection as impacts assessment length.	The amount (and content) of research questions is likely going to change somewhat as we gain more experience from the collaborative RE assessments: some questions may be pooled, others split and new added. However, the experience from pazopanib pilot showed that the questions from the four last domains (ethical, organisational, social and legal) will need to be reduced. They will be removed from the Model and replaced by a check list which helps the assessors to quickly identify if there are relevant issues in these areas to be included in the rapid RE assessment.
34.	Novartis	comments on how the pilot was carried out: Page 20, Line 47	We would like to see deeper involvement of MAH, KOL and PAGs in the assessment & validation process.	Assessment will remain in the hands of HTA agencies. The consultation phase will include MAH consultation for the draft report. In addition other stakeholder involvement (e.g patient organisation, physician organisations) within the strict timelines of the consultation (as well as the scoping phase) will be explored.
35.	Novartis	comments on how the pilot was carried out: Page 23, line 4 - 7	The list of research questions is good; however, the summary provided does not provide full answers. There seem to be much more information available than what is presented.	More detailed information and data are presented in the result cards (referred as codes such as D0001 in the summary), presented in the Appendix. The result cards will be electronically linked to the summary in the future versions of the RE assessments, so that the reader has easy access to the details when needed.

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36.	Novartis	comments on how the pilot was carried out: Page 33-36	Critical for the pilot assessment is the engagement of disease area experts that can tackle the issues such as how to weight an endpoint of progression free survival. It is unclear to what extent clinical experts were involved, would you please clarify?	This was up to the HTA assessors and there was no explicit policy to guide clinical expert involvement. The authors were, however, encouraged to state in the methods section of their domain report, or the methods fields of respective result cards, if they consulted experts on this issue.
37.	Novartis	comments on how the pilot was carried out: Page 36, Line 34-40	It would be interesting to have more insights as to the expertise of the reviewers of each domain. Also of interest is whether the experts consulted a broader selection of stakeholders while conducting the domain reviews, e.g. clinicians reviewing clinical effectiveness, health economists economic data etc.?	The reviewers were assigned by expressed interest. No formal expertise requirements were used and the qualities were not recorded.
38.	Novartis	comments on how the pilot was carried out: Page 52, Line 16-18	We would suggest limiting the number of domains assessed (to the first four). For the domains that are to be analyzed, it is critical that data is compiled and reviewed according to the methodology criteria established for relative efficacy and relative effectiveness. It will also be important to ensure that persons with technical expertise in relative effectiveness assessments (clinicians and biostatisticians) be involved in future joint actions.	The domains will be limited to the first four in the upcoming RE-assessments of EUnetHTA JA2 WP5. Ensuring expertise in any assessment is of course important. This is particularly important in collaborative assessments where some HTA agencies are supposed to use the information provided by other HTA agencies.
39.	Novartis	Comments on the methods used in the pilot: General	Relative effectiveness is about clinical outcomes under usual circumstances. We would therefore like to stress the importance of not limiting the evidence considered to that generated in randomised, controlled, clinical trials. Evidence generated from other sources (e.g. registries and pragmatic trials) should also be considered. Also with the intention to reduce workload and optimize value, we would like to suggest for future pilots/European REAs to focus on the four domains most central to assessments of relative effectiveness, i.e. "Health problem and current use of the technology", "Description and technical characteristics of technology", "Safety" and "Clinical effectiveness".	There are differing views in different countries of evidence requirements for effectiveness. It would indeed be beneficial if we could gradually come closer to each other in that perspective. That is the aim of the methodological guidelines line of activity that has been on-going within EUnetHTA, and which will be strongly on-going in the next phase of EUnetHTA (JA2). As you suggested, the domains will be limited to the first four in the upcoming RE-assessments of EUnetHTA JA2 WP5.
40.	Novartis	Comments on	The REA does not factor into the methodology the need for and/or	The domain specific methods sections report only the methods

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		the methods used in the pilot: Page 29-36	the importance of meta-analyses as well as their associated limitations. Please take into consideration the importance of meta-analyses and evolving work on establishing best practices (ie; CIOMS,etc.)	planned and used in this assessment. The discussions of potentials and limitation of meta-analysis, and particularly the new methodologies, should be (and to some extent already are) captured in the Methods Guidelines.
41.	Novartis	Comments on the methods used in the pilot: Page 04, Line 10 – Page 5, Line 36 Page 14, Line 2-25 Page 364-365	From what we understand, the methodology does not include an agreed upon definition of "relative effectiveness". It is critical to achieve alignment on this up-front. It is unclear whether different aspects of efficacy and/or safety may have received a different degree of emphasis.	EUnetHTA WP5 uses the definition for "relative effectiveness" as it was formulated by Pharmaceutical Forum recommendations 2008. The definition is presented in the REA model that was used by the authors of the pazopanib pilot. The definition has been inserted in section 2.1 of the report.
42.	Novartis	Comments on the methods used in the pilot: Page 06, Line 34-39	In our view, current reimbursement status is not an aspect relevant for the assessment of relative effectiveness/differential therapeutic value. We would therefore suggest excluding this type of information.	As the rapid REAs should guide the national decision makers in their reimbursement decisions, this information is considered useful.
43.	Novartis	Comments on the methods used in the pilot: Page 07, Line 1, Table 1 Page 15, Line 2-29 Page 19, Line	Including a weighting of different "types" of trials/data to assess relative effectiveness might help provide clarity. For example, how are "real-world" observational trials weighted versus pivotal trials, how is HRQOL factored in.	This suggestion is taken to the Methods Guidelines producers

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		38-Page 20, Line 22		
44.	Novartis	Comments on the methods used in the pilot: Page 15, Line 19-22	It is important to ensure that all up-to-date evidence is considered when undertaking a relative effectiveness assessment. Depending on timing, the body of evidence may have increased significantly since regulatory approval; therefore steps should be taken to ensure product data analyzed is the most current, and perhaps more current than the regulatory submission data.	Important indeed. The updated process of performing rapid REAs will solve this to a great extent as it will target the products which have just received the positive opinion by EMA. It was chosen to not update the included literature in this report as the primary aim of this pilot is to test the model and guidelines and not an up to date REA. A clear disclaimer is included in the report that mentions emphasised that the results of this assessment are not suitable for drawing conclusions for decision making.
45.	Novartis	Comments on the methods used in the pilot: Page 15, Line 34 - 47	Although the objective was to test the Rapid Model for relative effectiveness assessments, what the report reflects is closer to a Full Model evaluation as ethical, organisational, social and legal aspects are covered. Going forward, we suggest concentrating on the four domains of the Rapid Model most relevant to the assessment of differential therapeutic value.	We agree. This will happen in the upcoming rapid REA projects.
46.	Novartis	Comments on the methods used in the pilot: Page 18-19, Line 14-36	As we do not have access to the Marketing Authorisation Holder's (MAH's) submission, we cannot evaluate the extent to which the content and conclusions from the MAH's file contributed to the present report. We would like to suggest however to base assessments primarily on a dossier provided by the MAH and on the assessments previously undertaken by EMA. Thus to streamline the overall REA process, avoid duplication, and promote synergy between the work of the MAH, EMA and the HTA agencies respectively.	This will be promoted in the upcoming rapid REA projects.
47.	Novartis	Comments on the methods used in the pilot: Page 24, line 13-57 and Page 25,	Relevance of the information for the European setting is missing and needs to be clarified. For instance, epidemiologic data from Gupta et al (2008) contains European-specific information; however, it is presented in the broader global context without mentioning: 1.) Regional figures for Europe; 2.) Comparison of Region EU data with Global data, and 3.) A relative assessment.	The incidence and mortality in different European countries are presented in result cards A0023 (Ljungberg 2011, Karim-Kos 2008). The card A0023 also states: "RCC shows a considerable geographical variation, reporting highest incidence rates for Europe, North America and Australia (Ferlay 2010)."

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		line 1-26		
48.	Novartis	Comments on the methods used in the pilot: Page 24, line 6-10	The paragraph implies that a less than comprehensive evidence-based review for the assessment was conducted. The reasons provided are not good enough and, for pilots, a thorough, comprehensive systematic literature review should be always conducted so that it facilitates interpretation, adaptability of information for study purposes and understanding the feasibility of a joint action. .	This is partly a matter of defining systematic review in the context of Core Model approach. The Core Model splits the HTA into a set of questions to be answered. Each of these questions actually would deserve an own systematic search. This means that one HTA (one systematic review) turns into N questions (N systematic reviews). This would mean in this case that the authors of the first domain (Health problem and current use) should have made 15 systematic reviews. As this is not feasible in a rapid review the authors were encouraged to be rational but report clearly when is there a systematic approach behind the answer, and when did they use a pragmatic qualitative approach to find the answer. For instance, some questions, such as "What is the natural course of the disease?", rarely require a systematic review to become properly answered.
49.	Novartis	Comments on the methods used in the pilot: Page 28, line 37-39	The summary section for this 'Domain' (3.3.2.) does not provide information to substantiate the statement of this sentence.	The sentence "'It is currently unclear how to choose an appropriate therapy clinically, considering the current information available about the efficacy and safety or pazopanib and other agents" is removed as it does not directly reflect description of the product .
50.	Novartis	Comments on the methods used in the pilot: Page 29-36	We would suggest more discussion of the strengths and weakness of various study methodologies and how the type of methods used would impact the consideration of data provided.	As there are differing views across countries about the appropriateness of different study methodologies we wanted to express certain methodological issues neutrally and allow readers to judge them. When there is greater agreement about methodological issues across countries (after development and use of the common methodological guidelines within EUnetHTA) there will be more space to discussions of strengths and weaknesses of various study methodologies in the rapid REAs too.
51.	Novartis	Comments on the methods used in the pilot: Page 30	Presentation of overall safety as per SPC and label (EMA/FDA) would be needed.	These documents were included as source documents, but the reporting structure (presentation of results) in this report is different than in those documents.

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52.	Novartis	Comments on the methods used in the pilot: Page 30	The pilot product, Pazopanib, has been on the market for some time by the time the pilot assessment was carried out. What added value would the REA pilot bring if it was run for a recently launched product? In that case, regulatory data/label is the main source of information and only relative efficacy comparisons can be made.	Bringing together the core evidence of relative efficacy of a new product, in a structured form, with uniform (and agreeable) methods, and transparently reported, could reduce the efforts needed to make (27 times) national assessments. In WP5 JA2 the pilots will focus on recently launched products as this should maximise the value of the REA for national agencies as they have the opportunity to use the REA in their national process.
53.	Novartis	Comments on the methods used in the pilot: Page 31, 34, 36,	A paragraph on overall safety as per SPC and label (EMA/FDA) would be needed.	These documents were included as source documents, but the reporting structure (presentation of results) in this report is different than in those documents.
54.	Novartis	Comments on the methods used in the pilot: Page 33-36	What would the considerations be if the primary endpoint was met in a robust fashion with one product but none of the secondary endpoints achieved significance and for the comparator the primary endpoint was met in a less robust fashion but multiple secondary endpoints were also significant?	It is true that although REA is looking mainly at the relative effectiveness, the absolute effectiveness of the comparator, per outcome, is essential. The authors should be carefully guided on these through the Methodological Guidelines.
55.	Novartis	Comments on the methods used in the pilot: Page 33-38	Please provide justification for the choice of comparators, patient population and outcomes.	Most prevalent treatment comparators, patient population and outcomes were looked at the basic documents (submission file, EPAR and pivotal articles) and discussed and formulated at an e-meeting. These were further discussed as the project proceeded as we noticed some differences in how these were weighed or formulated in different domains. One of the outcomes of pazopanib pilot was that the scoping phase needs to be more thorough and PICO definition more explicit including a justification of the choice.
56.	Novartis	Comments on the methods used in the pilot: Page 35 - 36	Indirect comparisons are a powerful tool to derive effectiveness estimates from efficacy data. The fact that indirect comparisons are considered (very) low quality evidence is therefore worrying. We would be happy to engage with EUnetHTA in a discussion on how indirect comparisons could be used.	We are aware of this discussion but wanted to use some established scheme for handling this (the GRADE rules). The Methodological Guideline by WP5 on direct and indirect comparisons will be developed to a document that guides the HTA doers sufficiently on this.

Comments provided during public consultation of WP5 pilot assessment report: pazopanib for the treatment of advanced renal cell carcinoma

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57.	Novartis	Comments on the methods used in the pilot: Page 41-42	It is unclear what was included in the social domain: does "social" mean "societal" perspective? Could you clarify the heading and content of this section?	Social is here not societal; it is rather patient perspective, including all areas of life, and the perspective of carers. We are aware of the different meanings and uses of the word "social". This needs a concept definition (or a change of name) in the future reports. In general, the social domain will not be included future pilot REAs.
58.	Novartis	Comments on the methods used in the pilot: Page 46, Line 33-37	The four first domains (HPCU, DTC, Safety, Clinical effectiveness) are relevant for a rapid assessment but some redundancy is observed in the questions.	Some redundancies and deficiencies have been identified by the pilot authors too. The set of questions and their formulation is a constant matter of improvement in the REA Model.
59.	Novartis	Comments on the methods used in the pilot: Page 48, Line 33-34	Assessments of relative effectiveness should look beyond RCTs. Authors seem to be primarily focused on RCTs and would seemingly prefer a placebo-controlled RCT rather than a comparative study using other methods, such as an observational study or indirect comparisons.	The methodological requirements for effectiveness and relative effectiveness vary across national HTA agencies. The Methodological Guidelines by WP5 on internal validity, applicability and direct and indirect comparisons are the tools with which we can hopefully in the future, gradually approach common standards for evidence of effectiveness, which most countries could accept. For now, due to limited time available in JA1, these guidelines mainly focus on RCTs however it is the intention to include other sources as well.
60.	Novartis	Comments on the methods used in the pilot: Page 52, Line 16-18	When it comes to joint assessments of relative efficacy or relative effectiveness, we see limited value of the last four domains being assessed at the European level (Ethical, Organizational, Social, and Legal). These assessments should remain at the Member State level.	Based on the experience from pazopanib pilot, the four last domains will be excluded from the Model for rapid REA, and replaced by a check list to help authors to screen possibly relevant eth&soc&org&legal issues quickly.
61.	EFPIA	General	EFPIA is the representative organisation of the pharmaceutical industry operating in Europe. As an umbrella organisation, it discusses health policy and methodological issues related to pharmaceuticals but does not comment on any product-specific matters. Therefore the EFPIA comments on this draft assessment are focused on methodologies and structure of the report. We understand that this remit is in line with the purpose of the undertaken pilot which was to test usability of the draft EUnetHTA	Thank you for this information and comments. Indeed the work on further developing the methodological guidelines will continue during JA2. The procedure for developing guidelines will be revised, including revision of stakeholder involvement. In addition, a workshop will be organised with stakeholders in January 2013 to discuss the endpoint guidelines produced in WP5 JA1, before finalising the guidelines.

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			model for rapid relative effectiveness assessments (REA) and the draft EUnetHTA methodological guidelines, and not to produce a REA report for decision making. We note that in some instances, it is difficult to provide comments on this report without the draft core model for REA and guidelines having been finalised, since the first batch of methodological guidelines was published for public consultation on 29 June. Moving forward, we welcome further discussion between industry and EUnetHTA partners on the development of methodologies, which we understand from various discussions is foreseen in the framework of Joint Action 2. We also note that extensive information is available in the annex document. However, in light of the timelines for response to this consultation and the concurrent consultations on various EUnetHTA documents, we would like to underline that we did not have the time to consult and comment on the annex. Overall, we welcome that this first pilot assessment was conducted on the basis of a submission file produced by the manufacturer of the product in question. We also welcome the fact that evidence available in the EPAR seems to have been used in the assessment. In some instances, we consider that further alignment would be needed and that direct discussions with regulatory authorities would be beneficial in order to limit unnecessary duplication of efforts. As we did not have access to all the evidence considered in this assessment, we also caution that some comments are difficult to make. In general, we welcome an iterative dialogue with the manufacturer along the line of the assessment process. We understand that this REA report was based on an existing submission file and that further involvement of stakeholders was	As for stakeholder involvement in the rapid REAs: There will be a further step of MAH involvement in the upcoming rapid REAs by WP5, namely at the scoping phase. Furthermore, MAH will receive the draft report for comments, as occurred in pazopanib pilot too. In addition, involvement of clinical experts and patients in the rapid REAs of WP5 JA2 will be explored. Regarding the procedures under development for WP5 JA2 Strand A, these are being developed in dialogue with manufacturers. Based on the experience from pazopanib pilot, the four last domains will be excluded from the Model for rapid REA, and replaced by a check list to help authors to screen possibly relevant eth&soc&org&legal issues quickly. Striving towards more efficiency is an important aim of the Joint Actions. Dialogue with regulatory agencies is ongoing to further reduce duplication of efforts. Also WP7 JA2 will focus on developing a manufacturer's submission template, which will be tested in WP5 JA2 pilots. This should facilitate optimisation of the submission file as a source for rapid REAs. Being transparent with the differing views of HTA agencies regarding preferred or accepted methods is interesting. Our aim is to produce something which can be accepted by most agencies. But, in deed in cases where there are clear discrepancies, transparent reporting of these discrepancies will be essential. The process of developing the model for rapid REA is indeed iterative: the model will be improved based on the feedback of the next ten rapid REAs performed by WP5 of EUnetHTA JA2.

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			limited. Going forward, and in the next REA pilots undertaken, we would like to see closer consultation with the MAH, therapeutic area clinical experts as well as patient representatives, especially – but not exclusively – when developing the research questions and for the discussion of results. To reduce overall workload and redundancies we would suggest, as is also concluded in the report, to focus on the four domains most central to assessments of relative effectiveness, i.e. "Health problem and current use of the technology", "Description and technical characteristics of technology", "Safety" and "Clinical effectiveness". Whilst we recognise that collaborative REA could identify some questions to be addressed at national level in the other domains (organisational, ethical, social, legal), these cannot realistically be assessed at a European level as they are very context specific. We would also suggest streamlining across some domains, as it seems that some domains, as well as some research questions, could be combined. Furthermore, we would suggest basing the REA report on the MAH submission to a larger extent in future pilots. To facilitate this, we would like to propose a discussion between a wider industry constitution and the EUnetHTA to jointly agree on a reasonable submission format which would allow for more extensive use of the information provided by the MAH. We understand that collaborative relative effectiveness assessments conducted by the European collaboration on HTA will constitute a core dossier that will be relied on in national decision-making. In order to ensure that there is no unnecessary duplication across levels, we would suggest to explicitly and transparently refer to all information and viewpoints that might differ between HTA agencies participating in a given assessment on e.g. issues such as type of endpoints, acceptance of certain types of methodologies and analytical techniques, views on the	

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			strength of the evidence base, views on indirect comparisons, views on the use of (statistical) modelling methods to project longer term outcomes (including survival and life-years gained) etc,. Moving forward, industry calls on the iterative process to collaborative assessments to remain pragmatic and to progressively explore what type of information included in a collaborative REA will add value to national decision-making.	
62.	EFPIA	Report structure	There is duplication across domains which could be avoided. For example, elements in the sections "Health problem and current use of the technology", "Description and technical characteristics of technology" appear very similar. The structure of the main document is complex, because it mixes the reporting of the work undertaken (in terms of piloting collaborative assessment), and the reporting of the product assessment results. In this large document, there are two levels of summarisation of the product REA: an overall summary (pages 4-10), and summaries in each of the sub-sections under section "Results" (pages 22-45). These summaries are themselves a distillation of the findings in the results cards. The main document could be streamlined to avoid redundancy. For example, the detailed summary table of relative effectiveness of Pazopanib (pages 7-10) overlaps with Table 3 page 35, while table 3 is more detailed (informative footnotes) than the summary table. The consistency of the document could be also improved. For example, there is no tabulated presentation of the safety results (pages 29-32) while there is one table (table 3) in the clinical effectiveness section. Likewise, there are three levels of discussion in the report: in the	Similarities, relations and even possible overlaps have been identified earlier too. REA model developers will address these in subsequent versions. However not all similarities are true overlaps and we need to be careful not to unnecessarily remove issues. The complex reporting is indeed partly due to the fact that this exercise was also about testing the feasibility of working together across agencies in many countries. A section (Background information on the pilot) has been added at the beginning of the summary of the report to explain the structure (page 4). The structure and readability of the document will likely improve in the next rapid REAs as there will be less domains and less authoring organisations. This will make it more likely that the reporting is more uniform across domain-chapters. Additionally, the electronic publishing platform will make the levels of the document clearer, as you can go by clicking into more details (instead of the confusing ID codes).

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			overall summary, in the results sub-sections, and in the results cards. There is an opportunity to streamline the information, and suggest keeping the discussions at the level of each "dimension" (safety, clinical effectiveness, etc.) Readability could be improved. References to the results card and codes are sometimes confusing, and require reading the entire report before understanding which elements are referred to.	
63.	EFPIA	p. 4-6 Summary of REA	It is unclear how the summary relates to the domains analysed in the results section, as there is no clear reference to the domains analysed.	The references are made as ID codes for the assessment elements (result cards) , e.g. A0001. The meaning of these codes in brackets is explained in the beginning of the Summary, on page 4.
64.	EFPIA	p. 5, l. 32-33 & 44-48	In light of their importance, it would be interesting to provide additional background on follow-up activities agreed with regulatory authorities, both in the framework of the risk management plan as well as in terms of ongoing comparative trials.	There is some more information on the risk management plan in result card C0007b as indicated in the text.
65.	EFPIA	p. 6, l. 34-39	Reimbursement status is not scientific evidence that can be included in a relative effectiveness assessment. Rather, relative effectiveness assessment can be used to support healthcare decision-making and therefore reimbursement decisions, which are very context-specific. We would therefore suggest not including this section in a scientific, evidence-based relative effectiveness assessment.	The aim of rapid REA is to provide core information useful for decision making for all (or most) countries. This includes issues other than scientific evidence. Reimbursement status in other countries is perceived as useful information.
66.	EFPIA	p. 7-10	The fact that most indirect comparisons are considered very low quality evidence is surprising. It is stressed that the randomised trial results applicability is context specific (e.g. different comparators). In that context, indirect comparisons are a powerful tool to derive effectiveness estimates from efficacy data. Because it aims at understanding the external validity of clinical efficacy data, HTA/REA necessarily takes a broader perspective than	We are aware of this discussion but as the views differ a lot in different national HTA units, we wanted to use some established scheme for handling this in this pilot (the GRADE rules). The Methodological Guideline by WP5 on direct and indirect comparisons will be developed to a document that guides the HTA doers sufficiently on this.

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			evidence-based grading of the strength of evidence narrowly based on internal validity. If there are diverging views between authors of the REA regarding strength of evidence given by indirect comparisons, this should be explicitly clarified.	
67.	EFPIA	p. 11, l. 22-23	It is unclear which opinions differ regarding the validity of progression free survival as a surrogate for overall survival in the treatment of renal cell carcinoma. If these divergence of views stem from the participating authors of the REA, this should be explicitly clarified. As outlined in the document, measurement of overall survival is constrained by insufficient duration of follow-up and crossover of patient to the treatment arm. The EMA also states that PFS is an acceptable primary endpoint for registration in its guideline on the evaluation of anticancer medicinal products in man. It would be interesting to trigger a discussion on a disease-specific guideline involving various stakeholders, including regulatory authorities, HTA agencies, industry and patients, to clarify which endpoints should be used in order to meet evidence requirements of various decision-makers.	The views on the relevance of progression free survival differ among participating HTA agencies. The sentence has been amended to include this information. We do not think that a REA report is a suitable place for presenting the discussion regarding different views. We choose to present the evidence in a manner that all agencies can use the information.
68.	EFPIA	p. 11, l. 26-278	The statement made here could be interpreted as an invalidation of all indirect comparisons. Indirect comparisons are highly valuable in assessments of relative effectiveness, especially when concerning new therapies where the evidence base is limited. If there are diverging views between authors of the REA regarding strength of evidence given by indirect comparisons, this should be explicitly clarified.	We agree that indirect comparisons can provide valuable information. However, the sentences referred ("The validity of the indirect comparison rests on the assumption of similarity. If the trials included in the evidence synthesis differ, however, and the differences are modifiers of relative treatment effect, the results of the indirect comparison are biased.") present neutrally common current perceptions. No changes made.
69.	EFPIA	p. 12, l. 6-7	It is unclear which opinions differ regarding the validity of progression free survival as a surrogate for overall survival in the treatment of renal cell carcinoma. If these divergence of views stem from the participating authors of the REA, this should be explicitly clarified. As outlined in the document, measurement of overall survival is constrained by insufficient duration of follow-up	We were explicit in the discussion section saying that there were differing views among authors. In the conclusion we find that the formulation "There are different opinions regarding the surrogacy of.." is clear and neutral expression and does not cause misinterpretation. No changes made. WP5 JA1 has focused on non-disease specific guidelines.

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			and crossover of patient to the treatment arm. The EMA also states that PFS is an acceptable primary endpoint for registration in its guideline on the evaluation of anticancer medicinal products in man. It would be interesting to trigger a discussion on a disease-specific guideline involving various stakeholders, including regulatory authorities, HTA agencies, industry and patients, to clarify which endpoints should be used in order to meet evidence requirements of various decision-makers.	However, it is the general perception that disease specific guidelines will be valuable as well. This will further explored in WP7 JA2.
70.	EFPIA	p. 12, l. 19-23	The fact that most indirect comparisons are considered very low quality evidence is surprising. It is stressed that the randomised trial results applicability is context specific (e.g. different comparators). In that context, indirect comparisons are a powerful tool to derive effectiveness estimates from efficacy data. Because it aims at understanding the external validity of clinical efficacy data, HTA/REA necessarily takes a broader perspective than evidence-based grading of the strength of evidence narrowly based on internal validity. If there are diverging views between authors of the REA regarding strength of evidence given by indirect comparisons, this should be explicitly clarified.	We agree that indirect comparisons can provide valuable information. However, the referred sentences ("Due to the lack of direct head-to-head trials all differences between pazopanib and its active comparators are based on indirect comparison. This, together with limited evidence on the comparators, makes confidence intervals wide. Randomised controlled trials directly comparing the agents would provide more evidence, potentially enabling more robust conclusions.") are neutrally phrased and do not carry a great risk of misinterpretation. No changes made.
71.	EFPIA	Introduction p. 14, l. 2-24	After the summary of the results it is confusion to receive an introduction which is more process-oriented and relates to the working process of the collaborative assessment pilot rather than about the technology in questions. The introduction clarifies that this pilot's objective was to test the Rapid Model. However this report is closer to a Full Model since ethical, organisational, social and legal aspects are covered. Likewise, there are several occurrences in the report related to the lack of real-world data that are to be expected in the Full rather than in the Rapid model. As outlined in the conclusion of the document, it would be more relevant for the purpose of a European assessment of REA, to concentrate on the 4 domains of	Pazopanib pilot is indeed an untypical report as it reports both the assessment and the new collaborative production model which was piloted. The future rapid REA reports of WP5 of EUnetHTA will not report the latter anymore (i.e. the collaborative method and its process outcomes). A section (Background information on the pilot) has been added at the beginning of the summary of the report to explain the structure of the report (page 4). Based on the experience from pazopanib pilot, the four last domains will be excluded from the Model for rapid REA, and replaced by a check list to help authors to screen possibly relevant eth&soc&org&legal issues quickly.

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			the Rapid Model.	
72.	EFPIA	Objectives p. 14, l. 27-28	It is difficult to assess whether the pilot appropriately used the draft methodology guidelines for WP5 since these are not yet publically available, and the first batch of guidelines was sent out for public consultation on 29 June.	This is unfortunately the case, due to the tight timelines of WP5 JA1 it was not possible to organise this in a different way. There will be more information on an article about the lessons learnt from this pilot, which will be published in 2013.
73.	EFPIA	Organisation of pilot p. 15, l. 34-47	There is value to looking for much simpler organisation schemes.	This was one of the outcomes of the pilot. The organisational model will be simplified in the future rapid REAs.
74.	EFPIA	p. 18, l. 15-18	It is difficult to assess whether the pilot appropriately used the draft methodology guidelines for WP5 since these are not yet publically available, and the first batch of guidelines was sent out for public consultation on 29 June.	This is unfortunately the case, due to the tight timelines of WP5 JA1 it was not possible to organise this in a different way. There will be more information on an article about the lessons learnt from this pilot, which will be published in 2013.
75.	EFPIA	p. 19, l. 15-19	It is welcomed that this first pilot assessment was conducted on the basis of a submission file produced by the manufacturer of the product in question, and that evidence available in the EPAR seems to have been used in the assessment. In some instances, further alignment would be needed and direct discussions with regulatory authorities would be beneficial in order to limit unnecessary duplication of efforts. An iterative dialogue with the manufacturer along the line of the assessment process would also be welcomed.	There will be a meeting arranged in the future rapid REAs with MAH to discuss the submission file and scoping of the rapid REA. Dialogue with regulatory agencies to further reduce duplication of efforts is ongoing. Regarding the procedures under development for WP5 JA2 Strand A, these are being developed in dialogue with manufacturers.
76.	EFPIA	Scoping p. 19, l. 37	In European REA assessments, scoping should be defined a priori, via technology and/or indication-specific recommendations to MAH. This could be done in guidelines as well as scoping meetings between the HTA and MAH.	There will be a meeting arranged in the future rapid REAs with MAH to discuss the submission file and scoping of the rapid REA.
77.	EFPIA	p. 20, l. 13	As experts have been consulted, the publication of the list of experts would make the process transparent.	This is a valid point which will be taken forward to the rapid REA coordinators for consideration in the next projects.
78.	EFPIA	p. 20, l. 10-22	The above comment (scoping) applies here. The research	There will be a meeting arranged in the future rapid REAs with

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			questions should be defined a priori, taking account of the technology and the disease/indication.	MAH to discuss the submission file and scoping of the rapid REA.
79.	EFPIA	Health problem and current use of the technology, p. 23ff	There is a link between this domain and the one called "description and technical characteristics of technology". There might be value in merging the two to avoid duplication and streamline resource use.	The two domains will not be merged in the Model but as the authoring organisations will be less in the future rapid REA projects, these will be coordinated better meaning that the risk of duplication is less likely.
80.	EFPIA	Research questions, P. 23, l. 6	Research questions are overlapping. Reducing their number in each of the 4 domains would make the REA simpler. In this section for example, there are "clusters" such as A0003-04-05, A0023-06-09, A0025-17-19.	This is an existing debate within Core Model development: what is the correct level of granularity? If we split the HTA into very small and narrow items we increase the explicitness but the Model becomes complex. On the other hand, if we increase the "grain size" and merge the issue into bigger clusters we loose the benefit of structuring information, and gradually end up into the "classical HTA reports" with "Background" and "Results". Merging and splitting the assessment element need to be considered for the whole Core Model. However, specific adjustments can be made to the Model for rapid REA which could guide the authors to take some questions in a cluster if that makes the assessment smoother. The number and content of the assessment elements will be further tested in the pilots in WP5 JA2.
81.	EFPIA	A0020 and A0021	Approval status in other regions of the world and reimbursement status across countries are not relevant scientific evidence for relative effectiveness assessment. See also comment to p. 6, l. 34-39.	The aim of rapid REA is to provide core information useful for decision making for all (or most) countries. This includes issues other than scientific evidence. Reimbursement status in other countries is perceived as useful information.
82.	EFPIA	A0011 and p. 23, l. 27	This is not surprising a rapid assessment is conducted close to marketing authorisation. Diffusion of the technology is likely to be still relatively low which is also the reason why evidence used will originate from pivotal trials used for the purpose of MA.	This is partly true: pazopanib had been in use for some time when the assessment started. No changes made.
83.	EFPIA	p. 24, l. 1-2	Why was the AGREE checklist chosen?	Agree is an instrument for assessing the reporting of guidelines. Some HTA agencies use it for assessing the quality of guidelines

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				too. By the time of the pilot there was an updated version of AGREE (AGREE 2) published but this was not used.
84.	EFPIA	p. 24, l. 6-10	It is unclear whether any additional sources from the manufacturer dossier were used here.	The used sources are listed in the result cards, which are in the Annex. The references are not categorized to show whether they derive from the submission file or from other source.
85.	EFPIA	Summary of main results, p. 24-25	Much of this information is likely to be available in the submission file.	It probably shows that the collaborative and structured way of preparing HTA does not distort the results.
86.	EFPIA	p. 25, l. 8-12 and 17-21 and l. 29-44 (discussion)	Information on market penetration, consumption and reimbursement status are not scientific evidence that will support relative effectiveness assessment. This information is therefore out of scope of this domain and exercise. See also comment to A0020, A0021 and p. 6, l. 34-39.	The aim of rapid REA is to provide core information useful for decision making for all (or most) countries. This includes issues other than scientific evidence. Market penetration, consumption and reimbursement status in other countries is perceived as useful information.
87.	EFPIA	Description and technical characteristics of technology, p. 26ff	As mentioned above, there is a clear link with the first domain. Both might benefit from being merged in order to avoid duplication and loss of time/resources. Furthermore, the majority of the information feeding into these domains is likely to come from the manufacturer file or the EPAR (as indicated on p. 27, l. 18-20). There is also some overlap with the domain clinical effectiveness. For example, the conclusion on the technology description reflects on the choice of the appropriate therapy given safety and efficacy information.	Merging or splitting of domains or issues (research questions) is a matter that needs to be decided for the whole Core Model. For pragmatic purposes, it is possible to streamline the work of rapid REA so that the issues from the two first domains are handled in a cluster by same individuals. This will also occur in the upcoming rapid REA projects by WP5 in EUnetHTA JA2. The new structured way of reporting and answer to a question shows how difficult it is to keep to the point. Authors tended to be broader than require in their responses, which resembles more to their regular way of producing text. This is why there are places where you can identify overlapping content. On the other hand, at least the result cards need to be understandable pieces of information even stand alone, without the reader needing to read all the other text, and therefore some repetition maybe necessary to facilitate understanding. The number and content of the assessment elements will be further tested in the pilots in WP5 JA2.
88.	EFPIA	p. 26, l. 6	Questions could be grouped. How were researchers, patients, and the MAH involved in setting the questions?	This would be a methodological question. This has been discussed during the Core Model development, and the current consensus is that we do not aim at producing "methods cards", we only

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				structure the content and report them in "result cards". For this pilot stakeholders were not involved in drafting the research questions. More involvement of stakeholder in the scoping phase will be explored in the pilots of WP5 JA2.
89.	EFPIA	p. 26, l. 6	There does not seem to be specific answers to B0011 / B0010.	Not in the summary, but there are the result cards in the appendix. The result cards B0010, page 123, presents the monitoring requirements as they are in EPAR. The result card B0011, page 124, contains a text about the general needs to monitor both safety and effectiveness.
90.	EFPIA	Summary of main results, p. 27-28	Much of this information is likely to be available in the submission file.	Indeed, but the idea was to make it more digestible by presenting it in a structured way.
91.	EFPIA	p. 28, 11-20	This information is already presented on p. 24-25 in a different format.	It is a valid point that describing the comparators belongs more logically to the current use domain. This feedback is taken to the REA model development: it could be highlighted in the guidance that the description of the comparators belongs to the first domain.
92.	EFPIA	Research questions, p. 29	How were MAH, therapeutic area/clinical specialists and patients involved in defining the research questions?	MAH and patients were not involved in defining the research questions in pazopanib pilot. The authors and reviewers from the 14 countries may have consulted clinical experts when preparing this task, but to what extent this occurred is not recorded. More involvement of stakeholder in the scoping phase will be explored in the pilots of WP5 JA2.
93.	EFPIA	Sources of information, p. 29	Much of this information is likely to be available in the submission file.	Much, but not necessarily all, and the main idea is that it is structured in a different way.
94.	EFPIA	Discussion, p. 31	Regarding safety evidence, we agree that post-launch large observational data play an important role in detecting and understanding adverse events.	Thank you for the comment
95.	EFPIA	Clinical effectiveness, research questions, p.	How were MAH, therapeutic area/clinical specialists and patients involved in defining the research questions?	MAH and patients were not involved in defining the research questions in pazopanib pilot. The authors and reviewers from the 14 countries may have consulted clinical experts when preparing this task, but to what extent this occurred is not recorded. More

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		33		involvement of stakeholder in the scoping phase will be explored in the pilots of WP5 JA2.
96.	EFPIA	p. 31, l. 20 compared to p. 34 l. 17-18	Questionnaires for measurement of quality of life are referred to in both safety and clinical effectiveness sections. It is unclear what type of questionnaires were used, and whether the same results are reported in these two domains.	Safety domain authors refer to the result card D0012 of the effectiveness domain which used the studies Motzer 2009, Escudier 2009 and VEG105192, which used the QoL tools (prseented in Table 88 of eff domain) • EQ-5D (VEG105192; Motzer 2009) • EQ-VAS (Motzer 2009) • EORTC-QLQ C-30 (VEG105192) • FACT-Kidney Symptom Index- Disease-related Symptom (FKSI-DRS Index) (Motzer 2009) • FACT-Kidney Symptom Index – 15 item scale (FKSI-15Index) (Motzer 2009; Escudier 2009) • Functional assessment of cancer therapy - general scale (FACT-G) (Motzer 2009)
97.	EFPIA	Domain framing p. 34, l. 20-24	Here the perspective of the decision-maker is highlighted. It would also be important to consider the perspective of the end-user, i.e. the patient.	As decision makers are the primary audience of the national HTA reports (in the future they will hopefully use the joint REA reports), we find highlighting the perspective of decision maker appropriate. No changes made.
98.	EFPIA	p. 36, l. 31-33	It is unclear which opinions differ regarding the validity of progression free survival as a surrogate for overall survival in the treatment of renal cell carcinoma. If these divergence of views stem from the participating authors of the REA, this should be explicitly clarified. As outlined in the document, measurement of overall survival is constrained by insufficient duration of follow-up and crossover of patient to the treatment arm. The EMA also states that PFS is an acceptable primary endpoint for registration in its guideline on the evaluation of anticancer medicinal products in man. It would be interesting to trigger a discussion on a disease-specific guideline involving various stakeholders, including regulatory authorities, HTA agencies, industry and patients, to clarify which endpoints should be used in order to meet evidence requirements of various decision-makers.	The sentence in the effectiveness domain discussion ("However, a robust comparison of survival and progression free survival is difficult, and there are different opinions regarding the surrogacy of progression free survival for overall survival in the treatment of RCC") is neutrally presented and does not cause misunderstanding. No changes. Instead, we reformulated the corresponding sentence in the Discussion section of the summary, on page 11, to indicate that there were differing views among authors of this pilot regarding this issue: However, a robust comparison of survival and progression free survival is difficult, and opinions differed among the authoring organisations of this pilot regarding the validity of progression free survival as a surrogate for overall survival in the treatment of renal cell carcinoma.

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				Finally, disease specific guidelines will further explored in WP7 JA2. In the development of these guidelines stakeholders will be involved too.
99.	EFPIA	p. 36, l. 34-40	Indirect comparisons are a powerful tool to derive effectiveness estimates from efficacy data. Because it aims at understanding the external validity of clinical efficacy data, HTA/REA necessarily takes a broader perspective than evidence-based grading of the strength of evidence narrowly based on internal validity. If there are diverging views between authors of the REA regarding strength of evidence given by indirect comparisons, this should be explicitly clarified.	As the value of indirect comparison has been dealt for instance in the quality assessment rules by GRADE, we do not see that differing perceptions would be specific to the authors of this pilot. Rather, it is a more general discrepancy which can be referred to. No changes made.
100.	EFPIA	p. 37ff	Ethical analyses do not belong to the Rapid Model.	As default no, but there may still be cases where ethical questions are critical even in rapid REAs which will be used in decision making. Ethical issues are not included to this extent in the future rapid REAs of WP5 EUnetHTA JA2. There will be a checklist to aid the authors to screen if there are relevant ethical issues for a particular rapid REA.
101.	EFPIA	p. 37ff	Patient-reported outcomes and health-related quality of life endpoints are important in REA. They should be included in the relative effectiveness section, rather than in the ethical domain which will be more relevant at the national level.	Patient-reported outcomes and health-related quality of life are included in the effectiveness domain. In ethical domain they are looked at from a different angle.
102.	EFPIA	p. 37, 4	How were MAH, therapeutic area/clinical specialists and patients involved in defining the research questions?	MAH and patients were not involved in defining the research questions in pazopanib pilot. The authors and reviewers from the 14 countries may have consulted clinical experts when preparing this task, but to what extent this occurred is not recorded. More involvement of stakeholder in the scoping phase will be explored in the pilots of WP5 JA2.
103.	EFPIA	F003	What is the rationale and background assumption behind including this question? Patient, caregivers and healthcare professionals would likely be able to provide valuable input on the research questions identified,	When defining the relevance of ethical questions, it is not always easy to say in beforehand, before examining the issue thoroughly, whether the answer to the question will be relevant. That is why the ethicists seem to be quite inclusive in their questions. Another

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			particularly regarding PRO/HRQoL endpoints.	reason is, that the ethical analysis does not provide results (i.e. morally correct practice rules) but rather presents the different standpoints and values, for information to the decision makers. The main aim is to remind of the expressed concerns (if there are such) of possible hidden or unintended consequences, without making any preferences of action.
104.	EFPIA	p. 38, 13-20	This section on pricing of pharmaceuticals seems out of scope of the ethical analysis. Relative effectiveness assessment can be used to support healthcare decision-making and therefore reimbursement or pricing decisions, which are regulated in most European countries.	It is indeed a very generic text, applicable to almost any novel pharmaceutical. As economic growth is part of business ethics, these kind of issues are not categorically excluded from ethical analysis. Economical aspects belong tightly to the ethics of societies too. Please note that in the next version of the Model for Rapid REA the ethics domain is not included any more.
105.	EFPIA	p. 38, l. 24-27	This seems out of scope of the ethical analysis.	Ethics of HTA include the ethics of research. Ethics of research includes a fundamental ethical question: "What should be studied?" Therefore we think that uncertainties in the body of current evidence is a critical ethical judgement for decision making in health care. Although reimbursement is regulated it does not override the ethical dilemma that sometimes the even legally correct action can be seen ethically questionable. We agree that rapid REAs should not go into these discussions: their forum is elsewhere. Please note that in the next version of the Model for Rapid REA the ethics domain is not included any more. It will be replaced by a checklist so that the authors can quickly identify whether there are relevant aspects even for rapid REA.
106.	EFPIA	p. 39ff	Organisational aspects do not belong to the Rapid Model.	In principle yes, but there may be some important exemptions. In future rapid REA projects of WP5 EUnetHTA JA2 the organisational questions will be replaced by a checklist so that the authors can quickly identify those organisational aspects that are relevant even for rapid REA.
107.	EFPIA	p. 40, 20-21	Again, this section on pricing of pharmaceuticals seems out of scope of the organisational section. Furthermore recommendations on risk-sharing schemes are very context-	As pricing decisions can be made also in hospitals, this information may be relevant for decisions related to introducing a product. However, in future rapid REAs by WP5 EUnetHTAJA2 this

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			specific and therefore best done at a national level, as they depend on the capabilities of a given system to administer such schemes.	kind of information has probably less significance.
108.	EFPIA	p. 41ff	The social domain is highly culture, country and context-specific and does not seem to belong to the Rapid Model.	The effect of an intervention on work ability or the role of carers is not necessarily very different in different countries: at least the information from other countries could well serve as an estimate. However, the role of the questions presented in the social domain of this pilot will be less in the upcoming rapid REAs of WP5 EUnetHTA JA2. They will be replaced by a checklist that aids the authors to quickly screen if there are relevant patient and carer related issues which need to be taken into account even in rapid REAs.
109.	EFPIA	p. 41, l. 18-27	How were patients, caregivers and clinical experts consulted when setting the only research question? Were the two patients' forums mentioned undertaken by EUnetHTA JA?	MAH and patients were not involved in defining the research questions in pazopanib pilot. The authors and reviewers from the 14 countries may have consulted clinical experts when preparing this task, but to what extent this occurred is not recorded. More involvement of stakeholder in the scoping phase will be explored in the pilots of WP5 JA2.
110.	EFPIA	p. 41, 43-46	These elements are from the safety domain, and seem duplicative in this instance.	There are some repetitions, as the domain specific text should also serve as stand-alone pieces of information, i.e. they should allow the reader to comprehend although he/she hasn't read all the report.
111.	EFPIA	p. 42, l. 1-2	In future pilots, there could be direct interaction with patients foreseen.	The short timeline reserved for future rapid REAs is probably a challenge to patient involvement. However, this issue is listed for discussion in the process development of rapid REAs and more involvement of stakeholder in the scoping and/or assessment phase will be explored in the pilots of WP5 JA2.
112.	EFPIA	p. 43, ff	Legal aspects do not seem to belong to the Rapid Model.	Legal domain (the last four domains) will be excluded in the future rapid REAs of WP5 EUnetHTA JA2. It will be replaced by a checklist which aids the authors to quickly screen if there are legal aspects which would be relevant even for rapid REA.
113.	EFPIA	p. 46, l. 33ff domains	We agree that the first four domains should build the REA. Furthermore, focussing on these domains would reduce the	This will occur in the upcoming rapid REAs of WP5 EUnetHTA JA2

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			amount of work and risk of duplication.	
114.	EFPIA	p. 47, l. 19 ff scoping	Endpoints: It is unclear which opinions differ regarding the validity of progression free survival as a surrogate for overall survival in the treatment of renal cell carcinoma. If these divergence of views stem from the participating authors of the REA, this should be explicitly clarified. It would be interesting to trigger a discussion on a disease-specific guideline involving various stakeholders, including regulatory authorities, HTA agencies, industry and patients, to clarify which endpoints should be used in order to meet evidence requirements of various decision-makers. Comparators: Technologies other than pharmaceuticals should whenever appropriate be considered as comparators for relative effectiveness assessments. In order to streamline the overall HTA process, it is important to identify the right comparator(s) that will ensure that there is no redundancy between the European and the National levels. This important question deserves further multipartite exchanges towards a mutually agreeable resolution.	The text in this discussion section clearly states that there were differing views among the authors of this pilot: *"However, it was noticed later during the project that a discussion and agreement about the significance of overall versus progression free survival would have helped the authors. The differing views of countries about using these outcomes in assessment resulted in modifications in the text of several domains so that both outcomes are presented in a neutral and balanced way, so that the results serve as many countries as possible."* No changes made. WP5 JA1 has focused on non-disease specific guidelines. However, it is the general perception that disease specific guidelines will be valuable as well. This will further explored in WP7 JA2. We agree that technologies others than pharmaceuticals can be comparators.
115.	EFPIA	p. 48, l. 30-36 keeping it comparative	It is important to ensure that any work conducted does not duplicate previous assessment. In particular, in the context of results from placebo-controlled studies, a lot of information is drawn from the marketing authorisation file, and does not need to be duplicated.	The point of this exercise was to create a structured presentation of the current evidence, available to HTA agencies, in order to facilitate the use of evidence in national HTAs and national decision making. Therefore same evidence and information appears in both documents.
116.	EFPIA	p. 49, l. 15-24 result cards	There is a need for an extended discussion of the Results Card approach, and of the number of cards per Domain. It is indeed important to ensure that all key questions are identified and addressed. It is equally important to keep them manageable within constrained review times and resources.	The manageable number of research questions is a valid point. It will be discussed in the close future by the REA Model developers and proper adjustments will be made in the subsequent versions of the Model. In addition, the WP5 JA2 pilots will further evaluate the proposed number of cards.
117.	EFPIA	p. 49, l. 25-31 guidelines	Whilst we understand the objective of the pilot is to test the usability of both the REA core model and the methodology	This is unfortunately the case, due to the tight timelines of WP5 JA1 it was not possible to organise this in a different way

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			guidelines, it is difficult to assess whether the pilot appropriately used the draft methodology guidelines for WP5 since these are not yet publically available, and the first batch of guidelines was sent out for public consultation on 29 June.	
118.	EFPIA	p. 49, l. 32ff duration and workload	We note the substantial amount of workdays that has gone into this project and the time it has taken to develop the pilot report. There are ways to reduce workload and time taken as well as duplication of work already undertaken by MAH and other institutions. For example, focussing on the first four domains, and streamlining some domains and questions could reduce the time taken. This would for additional time for increased consultation with MAH, healthcare professionals and patients.	Thank you for the valuable suggestions. The process of rapid REA production will change substantially based on the experiences from pazopanib pilot. We will continue monitoring and improving the efficiency of the process.
119.	EFPIA	p. 50, l. 25ff readers' perceptions	In addition to ensuring the buy-in of HTA doers, it is important to ensure that other key stakeholders in the process, in particular national decision-makers, are also made aware and support these developments, in order to avoid any unnecessary duplication at the national level.	As the EUnetHTA associate partners are nominated by their national government there is already a link to national decision making. We agree that all relevant parties should be kept well informed of the advances occurring in W5 of EUnetHTA JA2.