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EU REA – Learnings from the first three EUnetHTA Joint Action 3 assessments

Final Report

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Executive Summary

EFPIA asked Charles River Associates (CRA) to prepare an analysis of the first three EUnetHTA rapid effectiveness assessments (EU REAs) in Joint Action 3 (JA 3). In particular the objective was to:

- Provide a review of the three EU REA undertaken under JA 3 Work Package 4 (WP4) that have been conducted by EUnetHTA to date;
- Compare the findings from this study to the analysis[1] of the first five pilot EU REAs conducted in Joint Action 2 (JA 2) and assess the degree to which industry requests have been addressed and whether any new issues have arisen.

This report outlines the areas for improvement of the EUnetHTA production of EU REAs.

Background and approach

EUnetHTA was established in 2005 with the aim to facilitate HTA collaboration between European HTA organisations. A key part of EUnetHTA and its programmes has been the development, improvement and implementation of a HTA Core Model, which forms the basis of the joint assessment of a technology at a European level. The HTA Core Model was adapted for use in the EU REA process and was piloted in five assessments in JA 2 (2012 – 2015).[2] EFPIA commissioned from CRA an analysis these assessments, showing that EUnetHTA partners can collaborate on rapid REAs. But the process adopted in JA 2 could be improved as the EU REAs had not been published early enough to be used in the national HTA process.

In September 2016, EUnetHTA started rolling out JA 3 activities and started the process for the assessment of three pharmaceutical products in Q2 2017, all of them completed by January 2018 (Table 1).[3]

Table 1: The first three EU REAs conducted under JA 3

Molecule	Indication	Manufacturer	Publication date
Midostaurin	Midostaurin with standard chemotherapy in FLT3 positive Acute Myeloid Leukaemia (AML)	Novartis	09/11/2017
Regorafenib	Monotherapy for the treatment of adult patients with Hepatocellular Carcinoma (HCC) who have been previously treated with sorafenib	Bayer	25/10/2017
Alectinib	Monotherapy for the first line treatment of adult patients with ALK-positive advanced non-small cell lung cancer (NSCLC)	Roche	23/01/2018

1 CRA for EFPIA (2015), "An analysis of the EUnetHTA pilot assessments". Available at [last access 10 January 2018]: https://www.efpia.eu/media/25486/an-analysis-of-the-eunethta-pilot-assessments.pdf

2 A sixth, rapid REA of new pharmaceuticals for the treatment of Chronic Hepatitis C compared multiple technologies (while the first five pilots assesses a single technology).

3 EUnetHTA JA 3 WP4 is also undertaking the assessment of other technologies (e.g. medical devices) in addition to pharmaceuticals. The focus of this analysis is on pharmaceuticals only.

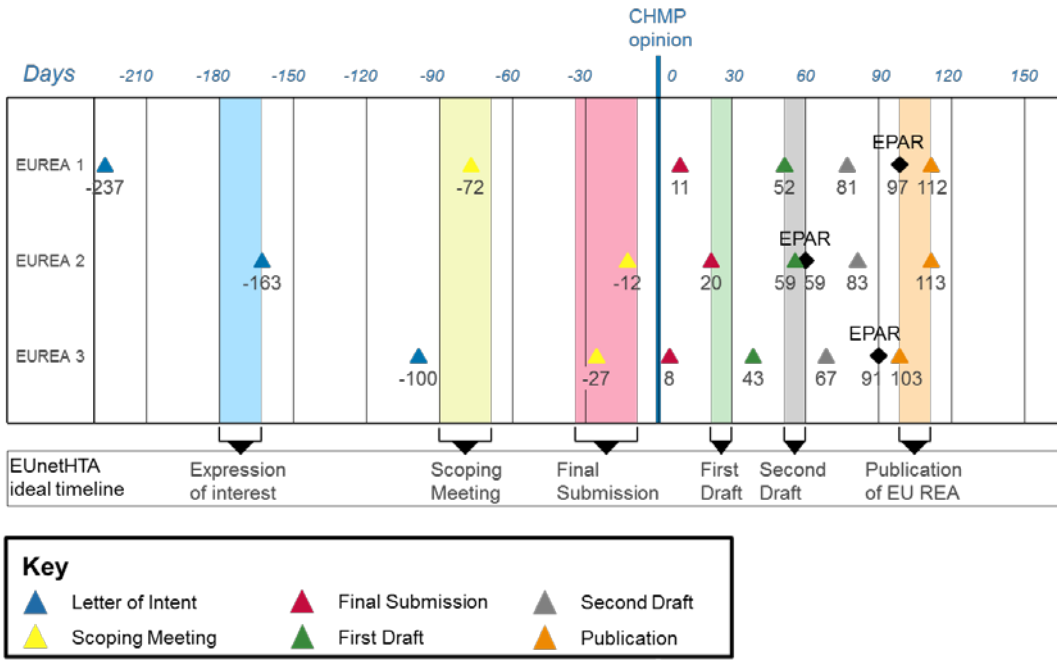
In order to gather the lessons from these three EU REAs, CRA has undertaken structured interviews with the manufacturers involved in the assessments; reviewed the documents published by EUnetHTA; discussed preliminary findings with the EFPIA steering group and undertook a workshop with the EFPIA HTA Working Group to discuss the lessons from the three assessments.

Lessons from the first three JA 3 EU REAs

Lessons can be derived for the timeline for the process, the different phases in the process and the use of the reports.

Timeline. One of the major issues observed in JA 2 assessments was that the final EUnetHTA reports were published too late in order for national HTA bodies to consider them without delaying the national HTA process. The EUnetHTA guidance sets out how the intention is for the publication of the EU REA report to follow closely after the publication of the market authorisation, or EPAR. To date, the timeline of the assessments undertaken under JA 3 are much closer to those intended. The initiation of the first two EU REAs was timely and they hit their target date for publication. The third EU REA also met its publication target despite a delayed initiation (Figure 1).

Figure 1: Timeline of the first three assessments in JA 3



Source: CRA analysis of EUnetHTA project plans and EU REA reports

Initiation process. In JA 3, most of the issues reported in JA 2 around the overall goal of the assessments and the selection of the authors and dedicated reviewers have mostly been addressed:

- The objectives, deliverables and milestones of the assessments are stated explicitly. The goal of individual assessments is clearly stated in the project plan, with indicators to measure it. However there is still some lack of clarity about the experimental nature of the JA 3, reflecting the EUnetHTA's potential need to improve the process and the methodology. It is unclear to what extent this is still

an experimental process and whether the process has changed adding flexibility or whether the secretariat is testing a change in the process in a particular assessment.

- The authors and the dedicated reviewers are appointed in a timely fashion. Although EUnetHTA retained the right to select and decide about authors, companies were able to provide suggestions regarding the author. However, there remains an issue regarding the role of dedicated reviewers, which is not communicated at the beginning of the process.

As for JA 2, in JA 3 participation remains voluntary with manufacturer being able to have a discussion with the EUnetHTA secretariat regarding the suitability and feasibility of a specific assessment. Manufacturers' expectation is that all JA 3 assessments will be initiated on a voluntary basis.

Scoping phase. In JA 2, there have been several issues affecting the scoping phase (i.e. the preparation and submission of the EU REA dossier), most of which have been addressed in the first three assessments in JA 3:

- EUnetHTA has been experimenting with provision of guidance prior to the scoping meeting. In the first three assessments, manufacturers obtained enough guidance prior to prepare their submission. In particular, prior to their draft submission and the scoping meeting, manufacturers have been able to discuss the methodology the authors were expecting to use for the analysis and their expectations. However, manufacturers were not able to discuss the PICO structure[4] prior to the draft submission and the scoping meeting: an early guidance on the PICO structure would be beneficial.
- Manufacturers were satisfied with the preparedness of the authors and the scoping meeting was constructive and informative of the final dossier submission. However, there is still room for improvement, as the scoping meeting would have benefitted from the involvement of clinical experts and patient organisations (which should be organised by EUnetHTA).

Assessment phase. In JA 2, there have been some issues during the assessment phase, which have partly been addressed in JA 3:

- Unlike to JA 2, EUnetHTA has been experimenting with using external experts in JA 3 assessments (in two out of the three EU REAs). However, the experts' involvement was not made clear to the manufacturers during the assessment process. Moreover, one of the issues limiting external experts' participation is the lack of a formal structure to involve them and of a protocol to avoid conflict of interest.
- Unlike to JA 2, individual patients have been involved in JA 3 assessments (in two out of the three EU REAs). However, it was not made clear to companies to what extent the patient's input has been considered (ideally, the opinion of patient representatives about the relevance of specific health outcomes should have informed the EUnetHTA assessment). Overall, to improve the quality of the input

4 The PICO is the framework to address the research question on Patient, Intervention, Comparator(s), Outcomes.

from patients, patient organisations should be engaged earlier in the process (e.g. a structure for patient involvement should be embedded into the process, allowing adequate representation throughout the whole process since the scoping phase).

As in JA 2, the authoring team managed to keep the timetable for the assessment. Moreover, there has also been some flexibility in the timelines, although this has not consistently reported across all the three assessments.

Methodology. In JA 3, some of concerns on the methodology expressed in JA 2 still persist but overall the methodology of the assessments is not perceived as problematic:

- Although manufacturers are generally satisfied with the assessment of clinical effectiveness, they still have concerns regarding the insufficient description of the methods used: authors should provide the rationale for the choice of comparator, the detailed description of how the analysis is performed and what the limitations of the analysis are. It was also noted that the methodology adopted was different depending on the assessment and the author (in particular, authors were including sections that were relevant for their national use of the report). This was seen as good from the perspective of increasing the potential use of the EU REA report but as a potential problem in terms of consistency. This lack of consistency is probably due to missing guidelines.[5] However, it was noted that the methodology guidance is currently being updated and this issue may be resolved (ideally, the guidance should also adopt a consistent taxonomy of terms). An increased level of consistency across different assessments would help companies, streamlining the participation and submission process. EUnetHTA's guidelines should be improved to increase the transparency (i.e. how results should be presented) and consistency.
- The role of the safety assessment is still unclear. For direct comparisons, the assessments appear to add little value compared to safety analysis in the EPAR (there is the possibility to include results from ongoing clinical studies that have not been included in the submission to EMA, however the safety analysis of direct comparisons in EU REA appears to duplicate the EPAR when new results are not considered). As for indirect comparisons, their inclusion in the safety analysis is not usually considered in the EPAR, but there are still some concerns about the methodological aspects of indirect safety comparison and how the safety experience from other indications should be integrated into the assessment.

Outcomes from the assessments. In JA 2, there have been some concerns on how the outcomes were presented, these have only partly been addressed in JA 3. In particular, in JA 3, one of the main concerns is the balance between assessment and appraisal. In one of the assessments there is considerable judgemental language that is seen as going beyond the JA 2 experience. In addition, there is a need to follow best practice guidelines on reporting of indirect comparisons and European clinical guidelines (rather than national ones) when referring to the standard of care (in some cases, the manufacturers needed to remember authors on best practices). Finally, there should be a process that permits the

5 For instance, in one assessment the manufacturer identified two missing guidelines regarding the reporting of indirect treatment comparisons and how to handle single-arm studies. In case EUnetHTA did not develop its own guidelines to cover both topics, it should adopt published "best practice" guidelines.

manufacturer to request a hearing with the authors to discuss the assessment rather than only providing written comments on specific sections.

Potential for use of EU REAs in national settings. Given the first three assessments in JA 3 has been completed only recently, it is premature to assess if use has improved and to what extent. However, there are some early signs indicating that there is improvement:

- In JA 3, authors have shown higher commitment to use the EU REA or to produce only one REA report that serves as national REA and EU REA at the same time, although this was not consistent across the three assessments.
- Use is prioritised in JA 3: it is clearly stated as an objective, both as an overall goal of the Joint Action and in individual project plans for the assessments.
- However, too little consideration is given to whether products will be assessed at the national HTA process and the implications for the selection of the authors. It would be preferable to only select authors from countries that are likely to use the EU REAs.

Conclusions

Overall, in terms of the process, the assessments undertaken in JA 3 have shown considerable improvement with respect to JA 2. This was made possible by the collaborative and constructive attitude of the EUnetHTA secretariat in particular, but also of the participating EUnetHTA members and the individual companies, who worked together to find flexible and pragmatic approaches to address issues.

However, a number of new issues have also emerged that need to be considered throughout JA 3:

- The extent of and goals of experimentation should be made more transparent. In the first three assessments, EUnetHTA has experimented with the process in order to test process improvements that may make it easier for companies to participate in future assessments and for Member States to use the resulting REA reports. This pragmatism is useful but should be made more transparent, allowing lessons to be learnt and built upon. Moreover, different authors have applied different approaches to the presentation of the results (in one case, the results were presented in a too judgemental way). There should be more objectivity and consistency across all the authoring institutions. It may be beneficial to revisit methodological guidance and to refine reporting standards for clinical benefit assessments (e.g. on indirect comparisons).
- EUnetHTA still needs to develop a more systematic process to involve external experts and patient organisations. There should be a formal structure to involve them since the beginning of the process and to consider their input throughout all the different phases of the assessment.
- The role (and the actual input) of the dedicated reviewers, the external experts and the patient organisations is not fully transparent to the manufacturers. This should be clarified prior to the beginning of the EU REA to reduce uncertainty from the manufacturers' side.

In addition, some of the issues observed in JA 2 remain unsolved:

- A template/procedure for agreeing data sharing confidentiality at the beginning of the process has not yet been established.
- Given in JA 3 the regulatory assessment and approval and the EUnetHTA assessments are concomitant, it is important that EUnetHTA is cautious about the publication of information that, although it is not confidential, could be misleading to stakeholders should it change during the later stages of the marketing authorization process (e.g. the description of the product indication).
- There is room for further improvement in the scoping phase: earlier guidance on the PICO structure (i.e. a discussion of the PICO before the manufacturer starts drafting the submission) would be beneficial. Moreover, to ensure that all the comments and questions from the authors and dedicated reviewers are understood fully, a more formalised and direct commenting structure involving follow up calls would be welcome.
- Authors should provide more justification and description of the methodology used.
- Compared to the EPAR, the safety analysis allows the inclusion of indirect comparisons. However, there are some concerns about the methodological aspects of indirect safety comparison and how the safety experience from other indications should be integrated into the assessment.

Finally, although it is still premature to judge how the use of the EU REA in the national setting has changed, it is important that use of the reports is proactively emphasised, and the efficiencies achieved and the national impact are monitored throughout the process.

1. Introduction

EFPIA asked Charles River Associates (CRA) to prepare an analysis of the first three EUnetHTA rapid effectiveness[6] assessments (EU REAs) in Joint Action 3 (JA 3). In particular the objective was to:

- Provide a review of the three EU REA undertaken under JA 3 Work Package 4 (WP4) that have been conducted by EUnetHTA to date;
- Compare the findings from this study to the analysis[7] of the first five pilot EU REAs conducted in Joint Action 2 (JA 2) and assess the degree to which industry requests have been addressed and whether any new issues have arisen.

The ultimate objective is to provide a report outlining the areas for improvement of the EUnetHTA production of EU REAs.

1.1. Background

The European network for Health Technology Assessment (EUnetHTA) was established in 2005 with the aim to facilitate HTA collaboration between European HTA organisations. A key part of EUnetHTA and its programmes has been the development, improvement and implementation of a HTA Core Model, which is a generic methodological HTA framework based on best practices that forms the basis of the joint assessment of a technology at a European level.

In JA 2, the HTA Core Model was adapted for use in the EU REA process and was piloted in five assessments.[8] EFPIA commissioned from CRA an analysis of these assessments,[9] showing that EUnetHTA partners can collaborate on rapid REAs. But the process adopted in JA 2 could be improved as the EU REAs had not been published timely enough to reduce duplication and improve efficiencies for all stakeholders. The study included 15 recommendations based on the experience of the five pilots (as set out in Appendix A).

These recommendations have been discussed by EFPIA in technical roundtables with EUnetHTA and have also informed the model for EU REA in JA 3. In particular, EUnetHTA started rolling out JA 3 activities in September 2016 and started the process for the

6 Although EUnetHTA uses the term “effectiveness”, the industry has noted that it would be more appropriate to refer to efficacy, as EUnetHTA assesses evidence from clinical trials (i.e. from an ideal world setting) and not evidence from usual, real-world practices (see, for instance, Eichler HG et al. (2010), “Relative efficacy of drugs: an emerging issue between regulatory agencies and third-party payers”, Nature Reviews Drug Discovery 9, 277-291).

7 CRA for EFPIA (2015), “An analysis of the EUnetHTA pilot assessments”. Available at [last access 10 January 2018]: https://www.efpia.eu/media/25486/an-analysis-of-the-eunethta-pilot-assessments.pdf

8 Joint Action 2 also included a sixth, rapid REA of new pharmaceuticals for the treatment of Chronic Hepatitis C. This assessment considered and compared multiple technologies (while the first five pilots assesses a single technology).

9 CRA for EFPIA (2015), “An analysis of the EUnetHTA pilot assessments”. Available at [last access 10 January 2018]: https://www.efpia.eu/media/25486/an-analysis-of-the-eunethta-pilot-assessments.pdf

assessment of three products in Q2 2017. As of January 2018, EUnetHTA completed three EU REAs (Table 2).

Table 2: The first three EU REAs conducted under JA 3 by EUnetHTA for pharmaceutical products

Molecule	Indication	Manufacturer	Publication date
Midostaurin	Midostaurin with standard chemotherapy in FLT3 positive Acute Myeloid Leukaemia (AML)	Novartis	09/11/2017
Regorafenib	Monotherapy for the treatment of adult patients with Hepatocellular Carcinoma (HCC) who have been previously treated with sorafenib	Bayer	25/10/2017
Alectinib	Monotherapy for the first line treatment of adult patients with ALK-positive advanced non-small cell lung cancer (NSCLC)	Roche	23/01/2018

Source: EUnetHTA[10]

By 2020 EUnetHTA is expected to complete 30 additional EU REAs.[11] Although three assessments represent a small share of the total to be produced in JA 3, their analysis can provide insightful information and guidance on how to conduct the remaining of JA 3 EU REAs.[12]

1.2. The approach

The approach involved a variety of different tasks:

- Structured interviews with each of the companies involved in the three EUnetHTA assessments, focusing on the process, the methodology, the outcomes and any evidence of the use of the reports
- A review of the documents published by EUnetHTA (the project plans of the three assessments, the assessment reports and the input from external experts and manufacturers on the second draft assessment)
- Discussions with the EFPIA steering committee

10 EUnetHTA website [last access 10 January 2018]: http://eunethta.eu/joint-assessments

11 EUnetHTA website [last access 10 January 2018]: http://eunethta.eu/activities/eunethta-joint-action-3-2016-20/work-package-4-joint-production

12 EUnetHTA JA 3 WP4 is also undertaking the assessment of other technologies (e.g. medical devices) in addition to pharmaceuticals. The focus of this analysis is on pharmaceuticals only.

- A workshop with the EFPIA HTA Working Group on 13th November 2017, which discussed the lessons that could be drawn across the three assessments.

The objective is to draw lessons across the three assessments and we are cautious about highlighting issues affecting only a single assessment or identifying particular products. It should be noted that the report is based on interviews and public documentation, we did not have the opportunity to interview the EUnetHTA WP4 coordination team, EU REA authors or reviewers during this project. The report therefore does not incorporate their perspective unless it is reported in public documents.

1.3. Structure of the report

The rest of the report is structured as follows:

- Chapter 2 reviews the lessons on the process for undertaking the EUnetHTA assessments, the methodology applied in the assessments and the outcomes. It also considers preliminary indications about potential use in national settings. In particular, the chapter compares the findings from the assessments in JA 3 with the learnings from JA 2
- Chapter 3 reviews the proposals made by the industry for a future sustainable model given the experience of the first three EU REAs and sets out the conclusions.

2. Lessons on the process, methodology and use of Joint Action 3 EU REAs

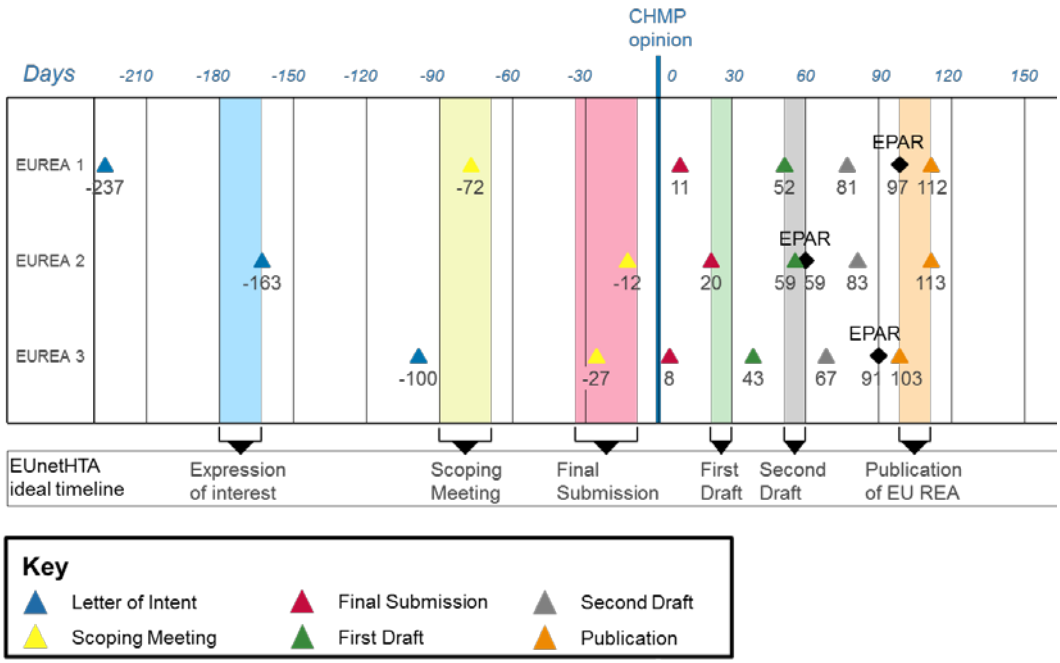
This chapter describes the lessons from first three assessments in JA 3 and compares the findings with those from JA 2. We first consider the timeline for the process, we then look at the different phases in the process and finally consider the use of the reports.

2.1. The timeline of the first three assessments in Joint Action 3

One of the major issues observed in JA 2 assessments was that the final EUnetHTA reports were published too late in order for national HTA bodies to consider them meaningfully and without delaying the national HTA process. From the EUnetHTA perspective, EU REAs should be published straight after the publication of the EPAR.[13] This is also compatible with the need to align the EPAR and the EU REA content and language and avoid inconsistency. The delays accumulated in the publication of JA 2 assessments were mostly attributable to a late initiation of the assessment (the actual target of completing the assessment within 100 days since the submission of manufacturer's dossier to the EUnetHTA authors was largely kept to).

To date, the experience with timelines in JA 3 has been successful. The initiation of the first two EU REAs was timely and they hit their target date for publication. The third EU REA also met its publication target despite a delayed initiation (Figure 2). This is a considerable achievement, which has been possible thanks to the flexibility of EUnetHTA and the commitment from participating companies to work with strict timelines.

Figure 2: Timeline of the first three assessments in JA 3



13 EUnetHTA WP5 Joint Action 2 (2015), "Procedure manual WP5 Strand A: Rapid Relative Effectiveness Assessment of Pharmaceuticals", V4 April 2015

Source: CRA analysis of EUnetHTA project plans

2.2. The initiation process

In addition to the late initiation of the process in JA 2, which caused the delays in the publication of the reports, there have been other issues in the initiation phase of JA 2 assessments. These issues have been mostly addressed in the first three JA 3 assessments (Figure 3).

Overall goal of the assessments. In JA 2, the overall goal of the pilots was stated explicitly: "[the goal is] to produce rapid assessment reports based on cross-border collaboration and to test the usability of the model for rapid REA including guidelines".[14] However, it was unclear if usability referred to using the model or using the results of the assessment (in reality, it appears the primary aim was to test the process rather than test its use).

In JA 3, the objectives, deliverables and milestones are stated explicitly.[15] The goal of individual assessments is clearly stated in the project plan, with indicators to measure it:[16]

- "To produce joint assessments on pharmaceuticals, that are fit for purpose, of high quality and of timely availability.
- To apply these collaboratively produced rapid assessments into local (e.g. regional or national) context."

Although the manufacturers generally welcome the opportunity to further improve the REA process, they perceive a lack of clarity about the experimental nature of the JA 3. It is unclear to what extent this is still an experimental process and where there is flexibility. In particular, clarity regarding if there is any flexibility in the process for particular products would be beneficial. According to the interviews, this would help improve participation and collaboration: the team from the manufacturer has to justify the use of scarce resources internally (often when the company is focused on launching an important new product). Even greater clarity on the goal of particular assessments would be beneficial.

Selection of the authors and dedicated reviewers. In JA2, the choice of the EUnetHTA authoring team (authors and dedicated reviewers) was often delayed (apparently due to lack of availability), with a knock on impact on the overall timeline. In addition, the selection of the authors caused concern for the manufacturers, in particular regarding the role of HTA agencies that were not commonly involved in national HTA processes. More transparency on the different roles of the authors would have helped manufacturers identifying those responsible for each section of the report and reduce their concerns regarding the less experienced HTA agency.

14 EUnetHTA WP5 Joint Action 2 (2015), "Procedure manual WP5 Strand A: Rapid Relative Effectiveness Assessment of Pharmaceuticals", V4 April 2015

15 EUnetHTA website [last access 10 January 2018]: http://eunethta.eu/activities/eunethta-joint-action-3-2016-20/work-package-4-joint-production

16 EUnetHTA website [last access 10 January 2018]: http://eunethta.eu/sites/default/files/Project%20Plan%20PTJA01%20Midostaurin%20for%20AML%20FINAL_1_0.pdf

In JA 3, the selection of the authoring team has improved: authors and dedicated reviewers were appointed in a timely fashion. Companies were able to provide suggestions regarding the authors, however these suggestions have not systematically been taken into account (in some cases, companies suggested a number of preferred authors and one of them had been selected, although it is not clear if the company's suggestion had any impact on the EUnetHTA choice). Although the criteria for the selection of the authoring team are not fully transparent, the role of the authors was not seen as problematic with manufacturers assuming that the most experienced author is in charge of the relevant sections of the EUnetHTA report (Table 3). In addition, the authors in two assessments were also EMA rapporteur or co-rapporteur.[17] This is seen as a favourable change and useful for future consideration.

Table 3: Authors, co-authors and dedicated reviewers in JA 3 assessments

EU REA	Authors	Co-author(s)	Dedicated reviewers
Midostaurin	FIMEA – Finland	NOMA – Norway	AEMPS – Spain ZIN – Netherlands* TLV – Sweden NICE – UK HAS – France IQWiG – Germany**
Regorafenib	HAS – France	INFARMED – Portugal	AAZ – Croatia AETSA – Spain FIMEA – Finland LBI – Austria OGYEI – Hungary SNHTA – Switzerland
Alectinib	TLV – Sweden	HVB – Austria AAZ – Croatia	NICE – United Kingdom Regione Veneto – Italy AETSA – Spain NIPN – Hungary

Notes

* Despite ZIN is indicated as a dedicated reviewer in the final EU REA report for midostaurin, the manufacturer indicates that ZIN was only acting as the coordinator of the assessment, as it was in the other two assessments.

17 For midostaurin, the EMA co-rapporteur was from the Norwegian Medicine Agency (NoMA); the EUnetHTA co-author was also from NoMA. For alecensa, the EMA rapporteur was from the Swedish Medical Products Agency (MPA) and the EUnetHTA author from the Swedish TLV.

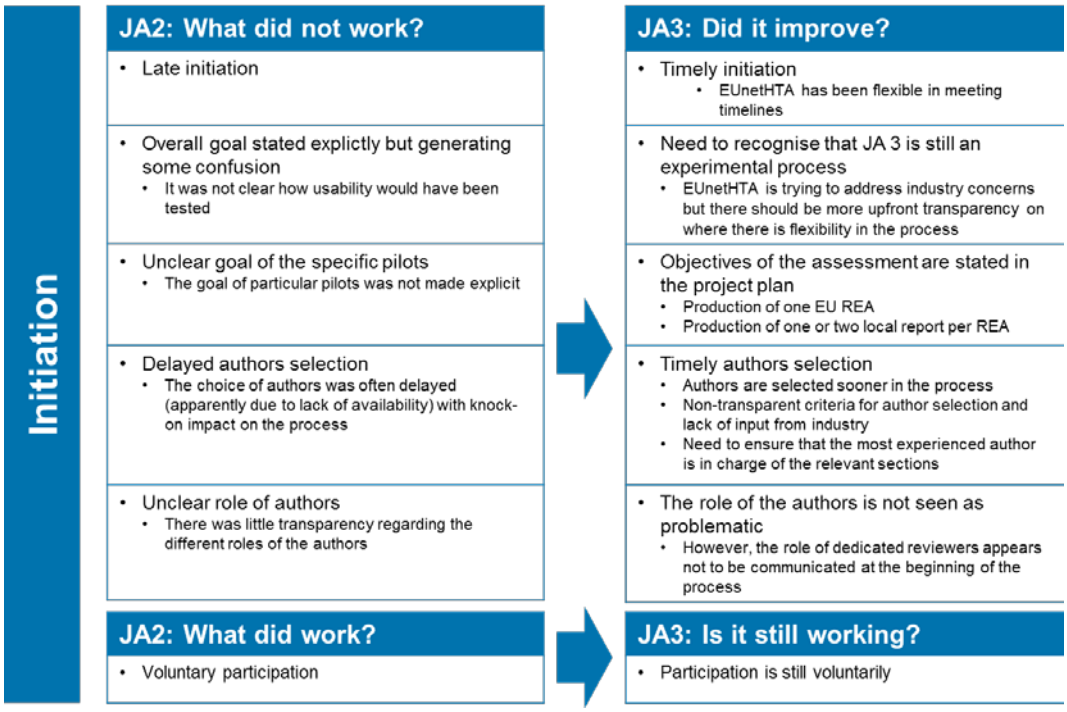
** Unlike for the other dedicated reviewers, the final EU REA notes that IQWiG participated for "information retrieval only". It is unclear how this role differentiates from the role of the other dedicated reviewers.

Source: CRA analysis of EUnetHTA project plans

There remains an issue regarding the role of dedicated reviewers, which was not communicated at the beginning of the process (i.e. it is unclear to what extent they are expected to contribute to the final EU REA report). This is still a concern for manufacturers. In addition, changes to the dedicated reviewers' team do not appear to be communicated to the manufacturers promptly. In one case, one national HTA body (Uniba, Slovakia) was originally set up to be a dedicated reviewer, but were unable to assist the assessment: the manufacturer was not made aware of this until the publication of the final EU REA.[18]

Voluntary participation. In JA 2, it was important for manufacturers that participation was "voluntary", with the manufacturer choosing to participate, by sending a letter of intent to the Secretariat, after some interaction with EUnetHTA. In the first three assessments in JA 3 participation was voluntary with manufacturer being able to have a discussion with the EUnetHTA secretariat, prior to sending the letter of intent, regarding the indications to be included in the assessment and the feasibility in general. Manufacturers' expectation is that all JA 3 assessments will be initiated on a voluntary basis.

Figure 3: Initiation process: changes since JA 2



Source: CRA analysis

18 EUnetHTA JA3 WP4 - Pharmaceuticals, PTJA03 Comments on the 2nd draft rapid assessment on alectinib as monotherapy for the first-line treatment of adult patients with alk-positive advanced non-small cell lung cancer

2.3. The scoping phase

In JA 2, there were several issues associated to the scoping phase (i.e. the preparation and submission of the EU REA dossier), most of which have been addressed in the first three assessments in JA 3 (Figure 4).

Lack of pre-submission discussion and insufficient time for the manufacturers to address the feedback. In JA 2, the manufacturers were submitting a full dossier prior to the scoping meeting, with limited or no prior guidance on the content and the details of the submission. The scoping meeting happened too late in the process, leaving only approximately four weeks to the manufacturer to make any substantial changes. In JA 3, this aspect has improved and manufacturers obtained enough guidance prior to prepare their submission. In particular, prior to their draft submission and the scoping meeting, manufacturers have been able to discuss the methodology the authors were expecting to use for the analysis and their expectations. However, manufacturers have not been able to discuss the PICO structure in the pre-submission phase:[19] early guidance also on the PICO structure would be beneficial. The discussions usually occurred offline with the intermediation of the EUnetHTA secretariat. This improves the submission experience by increasing efficiency (the manufacturers do not waste time and resources in the draft submission) and allowing more time to address the authors' feedback (benefitting both the whole process timeline and the quality of the submission).

Lack of authors' preparedness. In JA 2, the manufacturers felt that the authors were insufficiently prepared for scoping meetings and that, in certain instances, they had not formed opinions on the relevant and necessary comparators or the appropriate types of analyses (it has been recognised that the authors did not seem to have sufficient time for preparation). In JA 3, manufacturers were more satisfied with the preparedness of the authors and the scoping meeting was constructive and informative of the final dossier submission. However, there are still areas for improvement. In particular, the relevant experts from the authoring team should be involved earlier in the drafting process to inform on the technical aspects (e.g. on the network meta-analysis or on the systematic literature review). It would also be beneficial to understand which expert(s) provided comments so that manufacturers can give the appropriate weighting to different comments and that the key experts from the manufacturer's side are present at the scoping meeting. In JA 3, communication through the EUnetHTA secretariat prior to the scoping meeting also allowed authors to prepare for the meeting. However, to ensure that all the comments and questions from the authors and dedicated reviewers are understood fully, a more formalised and direct commenting structure involving follow up calls would be welcome. It is essential that queries are clearly stated prior to the second draft phase especially if further analysis is being requested (in particular, additional analysis should also be requested earlier in the REA process).

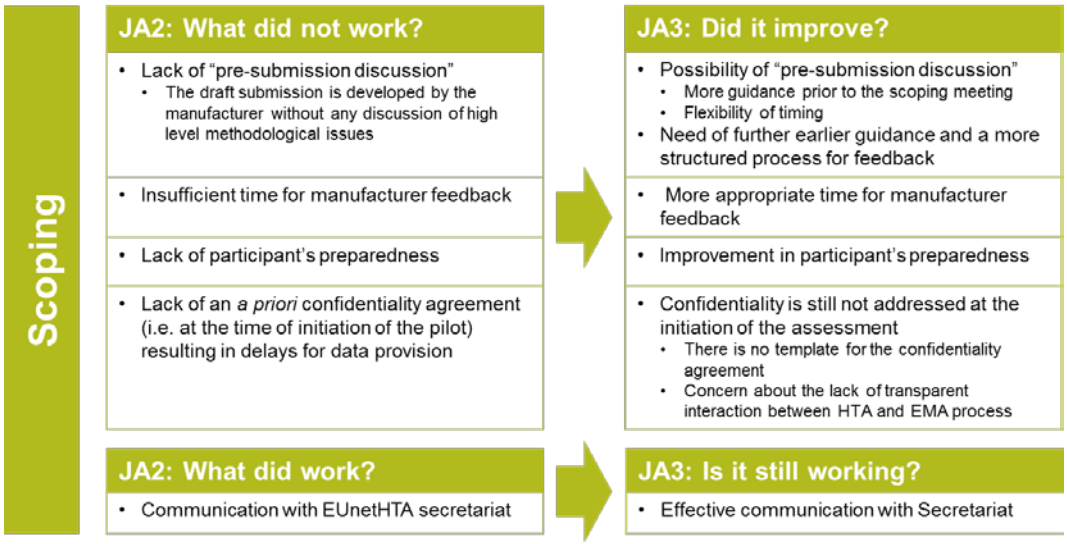
Lack of an a priori confidentiality agreement. In JA 2 the lack of *a priori* agreement on the publication of confidential data caused some delays during the scoping and assessment phases as it was necessary for EUnetHTA and the manufacturer to pause the process to agree which data would have been included in the final EU REA report. In JA 3, the absence of an established template for the confidentiality agreement, which could be signed off at

19 The PICO is the framework to address the research question on Patient, Intervention, Comparator(s), Outcomes.

the assessment initiation, remains a concern. This is an important issue as manufacturers are cautious to forward studies or data submitted in the EMA process prior to the publication of the EPAR. An agreement at the beginning of the process on what data from these studies can be published and what data should instead remain confidential would accelerate the provision of data later on.

Communication with the EUnetHTA secretariat. In JA 2, the communication between the manufacturers and the EUnetHTA secretariat was effective and helped the coordination between the manufacturers and the authors. In JA 3, the communication is still effective.

Figure 4: Scoping phase: changes since JA 2



Source: CRA analysis

In addition, in the first three JA 3 assessments emerged that there is no transparency on the information shared between the EMA rapporteur/co-rapporteur and the EUnetHTA authors. This lack of transparent interaction between HTA and EMA process gives rise to concern and speculation on the side of the manufacturer. This lack of transparency could be a barrier for companies participating in the REA pilots.

2.4. The assessment phase

In JA 2 there were a number of issues associated to the assessment phase, these have been partly addressed in JA 3 (Figure 5).

Lack of involvement of external experts. In JA 2, the involvement of external clinical experts was not explored. This was a limitation, as their perspectives would have provided useful insight for the assessment, adding value and quality to the final EU REA. In JA 3, there have been some improvements to this regard (Table 4). In one case, the manufacturer has been able to invite an external expert at the scoping meeting. However, there was no expert contribution in the assessment phase. As noted in the final EU REA, "according to EUnetHTA procedures and as stated in the project plan, clinical experts as well as payers should be included in the assessment. Unfortunately, neither of these groups

could be involved".[20] In the other two cases, the input from external experts has been considered in the final version of the EU REA, implying they have been consulted in the assessment phase (however, the experts involvement was not made clear to the manufacturers during the assessment process). One of the issues limiting external experts' participation is the lack of a formal structure to involve them, which instead should be in place before the EU REA is initiated. Importantly, it is necessary to establish a process and a protocol to avoid conflict of interest (this is particularly relevant for the assessment of orphan medicines, where there is a limited number of experts to be involved and most of them are likely to have collaborations with the industry).

Lack of involvement of patient organisations. In JA 2, patient organisations were not included in the assessment process. In JA 3, patient organisations have also been involved (Table 4), although there is a lack of systematic and timely approach and their impact on the final assessment is unclear. In the first assessment, after consultation with patient organisations, a patient was identified. An open interview was conducted with this patient to inform the outcomes taken into consideration for the assessment. The EU REA authors recognised that "the process for patient involvement in joint assessment REA is still under development".[21] In the second assessment, several patient organisations have been contacted to assist in identifying patients who may be interested in participating in the Joint Assessment. However, no response from patients has been received.[22] In the third assessment, the inclusion of a relevant patient organisation was planned in the project plan. However, "despite repeated efforts by the coordinator this was not possible in an early phase of the assessment". An individual patient agreed to participate in a telephone interview and provided her input. The authors recognised this input had some limitations as it was coming from only one patient and not a patient organisation.[23]

To improve the quality of the input from patients, patient organisations should be engaged earlier in the process (e.g. a structure for patient involvement should be embedded into the process, allowing adequate representation throughout the whole process since the scoping phase). Moreover, to improve the credibility of the evidence/grading, there should be clear guidance on the qualitative methods permitted (e.g. how to reference to different types of patient feedback).

20 Dental and Pharmaceutical Benefits Agency (TLV), Main Association of Austrian Social Security Institutions (HVB), Agency for Quality and Accreditation in Health Care and Social Welfare (AAZ). Rapid assessment on pharmaceutical technologies using the HTA Core Model for Rapid Relative Effectiveness Assessment. Alectinib as monotherapy for the first-line treatment of adult patients with ALK-positive advanced non-small cell lung cancer. EUnetHTA Project ID: PTJA03. 2017. ["Alectinib assessment"]

21 Finnish Medicines Agency, Norwegian Medicines Agency. Midostaurin with standard chemotherapy in FLT3-positive acute myeloid leukaemia. Rapid assessment of other health technologies using the HTA Core Model for Rapid Relative Effectiveness Assessment. EUnetHTA Project ID: PTJA01. 2017.

22 HAS; INFARMED et al. regorafenib indicated as monotherapy for the treatment of adult patients with hepatocellular carcinoma who have been previously treated with sorafenib. Rapid assessment on other health technologies using the HTA Core Model for Rapid Relative Effectiveness Assessment. EUnetHTA Project ID: PTJA02 2017.

23 Alectinib assessment.

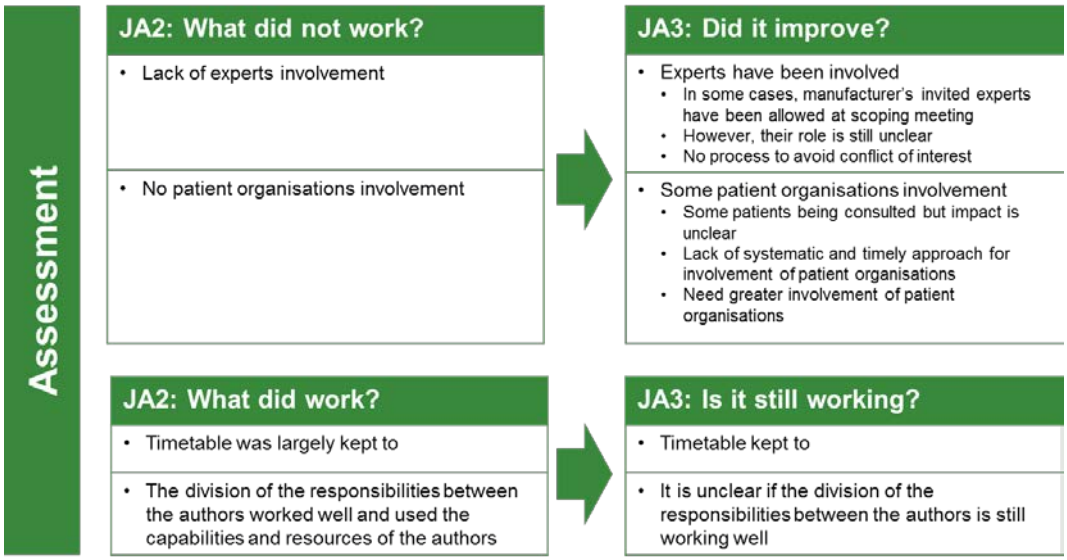
Table 4: External experts and patient organisations consulted in JA 3 assessments

EU REA	External experts	Patient(s) / Patient organisation(s)
Midostaurin	Chairman of the leukaemia group of European Organisation for Research and Treatment of Cancer Doctor from the University Medical Center Groningen	A Romanian patient with AML
Regorafenib	Ulm University Hospital	-
Alectinib	-	Individual patient with ALK-positive NSCLC

Source: CRA analysis of project plans and EU REAs

Timeline of the assessment. In JA 2, despite of the delays in starting the assessment with respect to the planned timeline, the authors were able to keep the timetable and deliver the final report within the scheduled target (about 100 days after the initiation of the assessment). In JA 3, the authoring team also managed to keep the timetable, contributing to the publication of the report straight after the EPAR was published. There has also been some flexibility in the timelines, although this has not consistently reported across all the three assessments. In particular, in one case, the manufacturer was able to request to the authors to obtain an additional week to provide feedback on the draft assessment.

Figure 5: Assessment phase: changes since JA 2



Source: CRA analysis

Finally, in JA 2, although it was difficult for the manufacturers to assess, it appeared that the division of the responsibilities between the authors worked well and used the capabilities and resources of the authors. In JA 3, it still proves difficult to assess whether

the division of responsibilities is still working well, however no manufacturers raised concerns about this.

2.5. The methodology of the assessments

In JA 2, there were some concerns regarding the methodology used in the assessment. In JA 3, some concerns still persist (Figure 6) but overall the methodology of the assessments is not perceived as problematic. There are more concerns regarding how results are presented and the wording in the EU REAs, which is discussed in the next section.

Assessment of the clinical effectiveness. In JA 2, manufacturers were generally satisfied with their experience regarding the assessment of clinical effectiveness: the selection of comparators was agreed between manufacturers and authors, manufacturers were also satisfied with the selection of endpoints and the acceptance of surrogate endpoints. However, there were still some concerns expressed regarding the how indirect comparison have been used in the assessment and how their results have been presented. As an area for improvement, it was suggested to provide greater clarity in the description and motivation of the methods used for the assessment. In JA 3, manufacturers still have concerns regarding the description of the methods used (which is still not detailed enough) but did not express particular concerns on the comparators and type of comparison adopted (Table 5). It was also noted that the methodology adopted was different depending on the assessment and the author (in particular, authors were including sections that were relevant for their national use of the report). This was seen as good from the perspective of increasing the potential for use e.g. in the author countries but as a potential problem in terms of consistency. However, it was noted that the methodology guidance is currently being updated and this issue may be resolved (ideally, the guidance should also adopt a consistent taxonomy of terms).[24]

Table 5: Comparators and type of comparison in JA 3 assessments

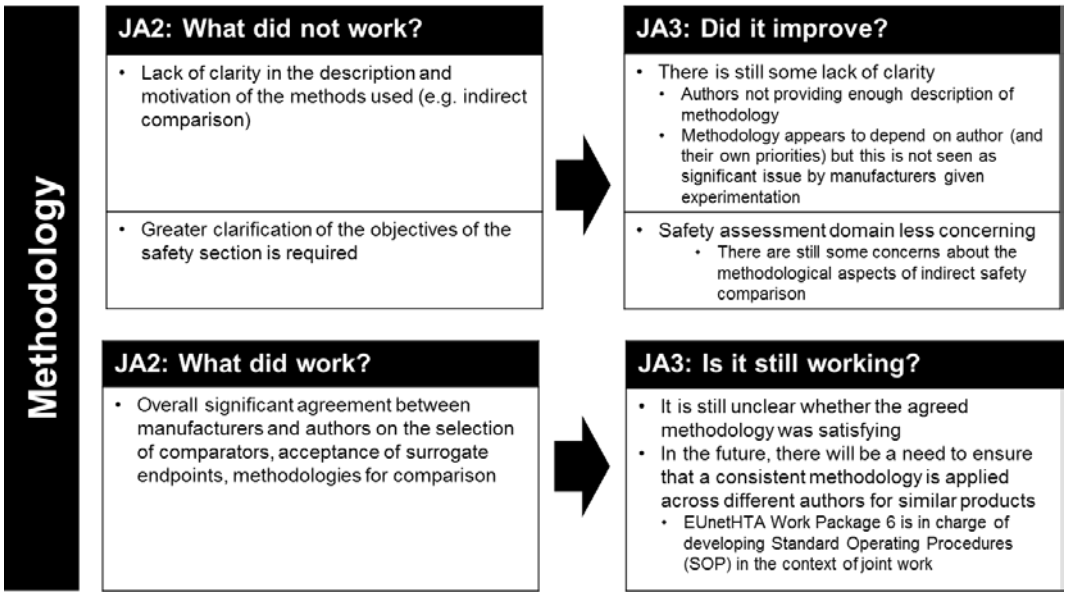
EU REA	Comparator(s)	Type of comparison
Midostaurin	Induction therapy with standard-of-care chemotherapy recommended by European guidelines or placebo/no chemotherapy	Direct comparison; Indirect comparison
Regorafenib	Placebo in combination with best supportive care (or palliative care)	Direct comparison
Alectinib	Active comparators (chosen on the basis of information from the manufacturer submission file, relevant EPARs and SmPCs, clinical guidelines and EUnetHTA guidelines	Direct comparison; Indirect comparison

Source: CRA analysis of project plans and EU REAs

24 For instance, in one assessment the manufacturer identified two missing guidelines regarding the reporting of indirect treatment comparisons and how to handle single-arm studies. In case EUnetHTA did not develop its own guidelines to cover both topics, it should adopt published “best practice” guidelines.

Assessment of safety. In JA 2, the assessment of safety has been problematic and there was some dissatisfaction from the manufacturers. In particular, there was a need for clarification of the objectives of the section as it appeared to be duplicating the EPAR. In JA 3, the value of the safety assessment is still unclear for direct comparisons as the assessment does not appear to be differentiated from the safety analysis in the EPAR (EUnetHTA direct comparisons appear to duplicate the EMA's assessment). However, the inclusion in of indirect comparisons in the safety analysis is not usually considered in the EPAR.[25] In general, there are still some concerns about the methodological aspects of indirect safety comparison and how the safety experience from other indications should be integrated into the assessment.

Figure 6: Methodology: changes since JA 2



Source: CRA analysis

In addition, it has been noted that the first products assessed are in the orphan space and have not many comparators. The methodological approach would be tested more severely with products launching in more crowded classes where there will be more issues with respect to the comparators and the methodology used.

2.6. The outcomes from the assessments

In JA 2, there were some concerns regarding the outcome from the assessment, i.e. how the results were presented and how the manufacturer's feedback on the process would have been accounted for in subsequent assessments. These concerns have partially been address in JA 3 (Figure 7).

Presentation of the results. In JA 2, manufacturers had mixed views on how the results from the assessments were presented. In some cases, it was considered that the authors used a balanced tone to present the findings. In other cases, manufacturers felt that authors did not provide explanations why some of the data submitted were not used or that the

25 For further details, see the comparison between the EPAR and the EU REA of the first two assessments provided in Appendix A.

presentation of safety and clinical effectiveness sections were not adequately balanced. In particular, there was concern that the safety section received undue attention in relation to the discussion given to the clinical effectiveness section. In JA 3, one of the main concerns arisen is the balance between assessment and appraisal. In particular, in one of the assessments, there is considerable use of judgemental language that is seen as going beyond the JA 2 experience. An example of this can noted by comparing the language of the EPAR with that of the EU REA. In the other assessments this was seen as a small issue (Table 6, see Appendix B for the extended comparison).

Table 6: Regorafenib: summary comparison between the language used in the EPAR and in the EU REA

Language used in the EPAR	Language used in the EU REA
"The observed 2.8 months gain in median OS, confirmed by the updated analysis (cut off 23 January 2017) and supported by consistent improvement in PFS and TTP, is considered of clinical benefit and able to outweigh the substantial treatment related toxicity." (p.89)	*"The addition of regorafenib to BSC induced a **modest** gain in terms of OS (+2.8 months in median) at the expense of a **worsened safety profile**, notably in terms of Grade ≥3 drug-related AEs, drug-related SAEs and dose reduction or discontinuation due to AEs." (p.52)* *"… insufficient evidence to determine the relative impact of regorafenib on HRQoL in comparison with placebo. As clinical management of end-stage patients must aim to improve or maintain quality of life, this is **particularly regrettable**." (p.52)*

Source: CRA analysis

Manufacturers and external experts[26] were able to provide a written feedback on the second draft of the EU REAs.[27,28,29] In addition to the concerns about the judgemental language, there are also other lessons on the presentation of the results that can be learnt by analysis this feedback and how the EUnetHTA authors have addressed it (Table 7):

- There is a need to follow best practice guidelines on reporting of indirect comparisons
- Authors should refer to European guidelines (rather than national ones) when referring to the standard of care
- Description of the target population needs to be accurate

26 The feedback from external experts has been provided by the University of Liège for the midostraurin's assessment and by the Ulm University Hospital for the regorafenib's assessment (no external experts provided a written feedback for the alectinib's assessment). Comments from the external experts are limited to typos and requests for clarification.

27 EUnetHTA JA3 WP4 - Pharmaceuticals, PTJA01 Comments on the 2nd draft rapid assessment on Midostaurin with standard chemotherapy in FLT3-positive acute myeloid leukaemia

28 EUnetHTA JA3 WP4 - Pharmaceuticals, PTJA02 Comments on the 2nd draft rapid assessment on Regorafenib as monotherapy for the treatment of adult patients with hepatocellular carcinoma who have been previously treated with sorafenib

29 EUnetHTA JA3 WP4 - Pharmaceuticals, PTJA03 Comments on the 2nd draft rapid assessment on alectinib as monotherapy for the first-line treatment of adult patients with alk-positive advanced non-small cell lung cancer

- Before its finalisation, the EU REA report should be updated to account for updated in the regulatory information, safety results, upcoming evidence and the reimbursement status in selected European countries.

Table 7: Learnings from the manufacturer's consultation process

	Manufacturers' comments	Assessment	Author's reply
Presentation of the results	There is an inconsistency between the conclusion of the EUnetHTA authors and available medical benchmarks	Regorafenib	Change not accepted: authors consider it is a divergence in terms of results interpretation
	More detailed description about the method for indirect comparison, the results and the methodological limitations	Midostaurin Alectinib	Suggested details added
	Requests for more accuracy: "standard" of care is defined according to the author's national guideline, not to the European guideline	Midostaurin	Revised as per manufacturer's request
Needs for updates	Need of more description of the target population	Alectinib	Change accepted
	Need to update regulatory information to reflect progress in the regulatory process	Midostaurin Alectinib	Update performed
	Need to update the safety results	Midostaurin	Update performed
	Need to indicate upcoming QoL data	Midostaurin	Suggestion accepted
	Need to update the reimbursement status in selected European countries	Alectinib	Update performed

Source: CRA analysis of input from manufacturers on the second draft assessments

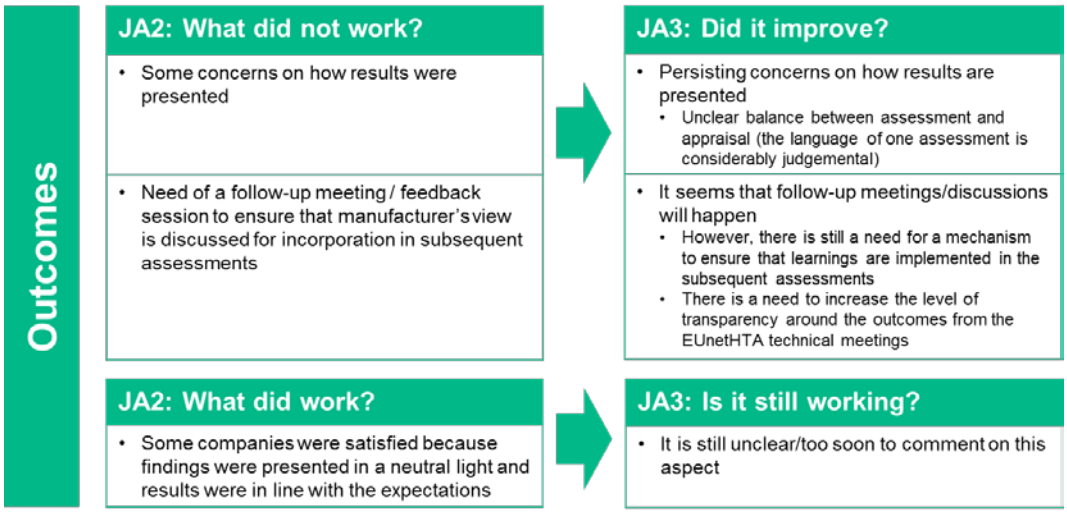
As there appears to be considerable heterogeneity in the presentation of the results and conclusions of the REA across different authors, it is important to achieve greater harmonisation in the approach going forward. The EU REA conclusions should not be judgemental but should be factual and rely on established methodology guidelines, evidence standards, and agreed principles of how to interpret and report the findings from REA.

Discussion of the results. Manufacturers' experience in providing written comments to the second draft of the assessments suggests that there should be a process permitting the manufacturer to request a hearing with the authors. The hearing would allow them to discuss the assessment rather than only providing written comments on specific sections, making the process similar to existing ones with national HTA bodies.

Feedback. In JA 2, it was noted that a post-publication feedback/debriefing could help to ensure that a manufacturer's view is discussed for incorporation in subsequent assessments. Given the authors change frequently gathering feedback and ensuring

lessons are leant in subsequent assessment was considered vital. In JA 3, it appears that follow-up discussions have happened, however there is still the need for a more structured mechanism to ensure that learnings are incorporated in the subsequent assessments. An increase in the transparency around the outcomes from the EUnetHTA technical meetings could also help clarifying if and how EUnetHTA's approach towards the assessments is evolving.

Figure 7: Outcomes: changes since JA 2



Source: CRA analysis

2.7. The potential for use of EU REAs in national setting

One of the main issues reported in JA 2 was the limited use of EU REAs in the national settings. Although a survey by EUnetHTA indicated a certain level of use, it could not be determined whether the rapid REA replaced any part of the national assessment or whether it has been used as a supplementary piece of information. In particular, the survey indicated a greater level of use than was apparent to the companies but did not allow to determine whether this resulted in improved efficiency. Clearly, the late publication of the EU REAs (with respect to the planned target at the EPAR publication) undermined the possibility for use in national HTA process. As noted in the companion CRA report for EFPIA about national barriers for use of EU REAs,[30] for many countries and national HTA agencies it is critical that EU REA are available at the time the is EPAR is published (or even earlier) in order to guarantee it can be used in a meaningful way in the national HTA process, although the EU REAs may still be relevant in the subsequent national or regional pricing and reimbursement processes.

As already noted, use of EU REAs was not a main objective of JA 2, but it is a key objective for JA 3: to determine whether EU REAs and EUnetHTA model are a successful way forward for European cooperation on HTA, it is crucial that JA 3 assessments are used in a meaningful way in national setting. Given the first three assessments in JA 3 have been completed only recently, it is premature to assess if use has changed and to what extent. However, early signs indicate that there is some improvement in the use of EU REA: as

30 CRA for EFPIA (2018), "EU REA – A discussion of barriers for adoption and possible action plans".

discussed below, use of EU REA in national settings has been prioritised in the project plans and some EUnetHTA authors have directly committed to their use. Nevertheless, more effort is required from all the stakeholders to ensure that use will be effective in JA 3. For instance, all the authors and dedicated reviewers of the assessment could commit to a meaningful use of the EU REA in their national HTA process. Moreover, the EUnetHTA secretariat could place even greater emphasis on the importance of national use of EU REA (Figure 8).

Prioritisation. In JA 2, one of the reasons for the limited use was that national adoption of EU REA was not a prioritised objective. In JA 3, use is now clearly stated as an objective, both as an overall goal of the Joint Action and in individual project plans for the assessments (Table 8).

Table 8: Use of EU REAs in national setting as an objective of JA 3

Overall goal of JA 3	Individual EU REA project plan[31]
An objective of Work Package 4 is "to develop a process that facilitates the implementation of the joint assessment in the national and regional practice."[32]	One of the project objectives is "to apply [the] collaboratively produced rapid assessments into local (e.g. regional or national) context. As indicator (and target) for this objective is the "production of ≥ 2 national/local reports based on the REA".

Source: CRA analysis of JA 3 project plans

Nevertheless, based on interviews with manufacturers this objective could be further emphasised to ensure that it is successfully achieved. Moreover, use would be more likely and meaningful if the authors are selected depending on their likelihood of using the EU REAs. To this regard, the EUnetHTA secretariat could support a more explicit discussion between authors and manufacturers about the plans for use. In addition, the dedicated reviewers should also be encouraged to adopt EU REAs.

Product selection. In JA 2, the products selected for the EU REA assessment did not qualify for a national assessment meaning that use was limited from the outset. In JA 3, greater emphasis should be given to identifying which products would be eligible for use of EU REA in the national HTA process (e.g. hospital products do not always go through national HTA).[33] This aspect is also relevant for the selection of the authors, as it would be preferable to appoint authors from countries that are likely to use the EU REAs.

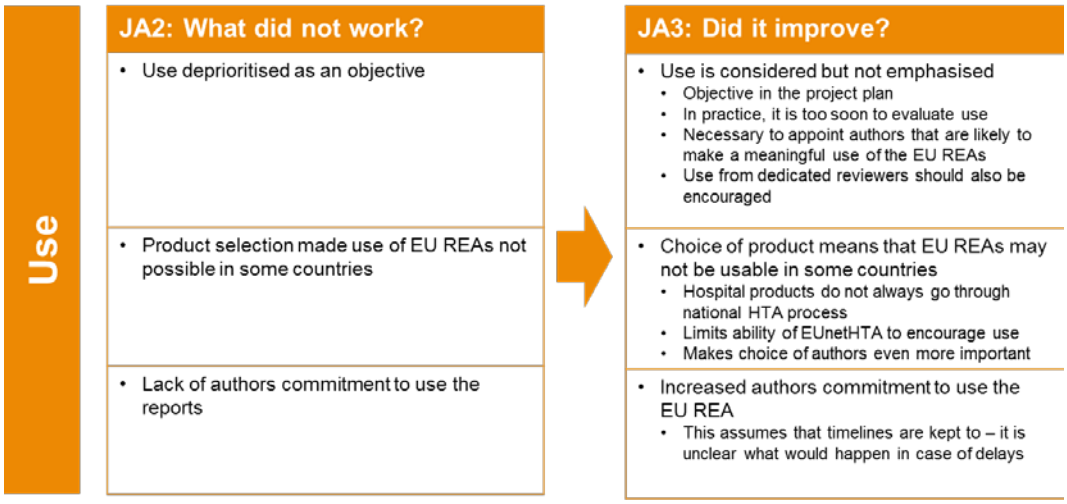
31 There was only one difference across the three project plans, otherwise the objectives were the same across the three. In one case, the project plan indicated that the target is "production of ≥ 1 national/local report based on the REA". Source: EUnetHTA website [last access 12 January 2018]: http://eunethta.eu/sites/default/files/Project%20Plan%20PTJA01%20Midostaurin%20for%20AML%20FINAL_1_0.pdf

32 EUnetHTA website [last access 12 January 2018]: http://eunethta.eu/activities/eunethta-joint-action-3-2016-20/work-package-4-joint-production

33 The companion report "CRA for EFPIA (2018), EU REA – A discussion of barriers for adoption and possible action plans" identifies which products are more suitable.

Commitment. In JA 2, there was limited or no commitment from the EUnetHTA authors to use EU REA in their national HTA process (this also happened because in some cases the national HTA process was completed before the EUnetHTA assessment). In JA 3, authors have shown a higher level of commitment to use the EU REAs (possibly because this is also a stated objective of each assessment). In particular, in two cases, during the initial meeting in the scoping phase, the authors committed to the use of the EUnetHTA report in the national HTA process. In one case, one EUnetHTA author committed to share the report with the colleagues in charge of the national assessment. In another case, one EUnetHTA author committed to the direct replacement of the national assessment. Although this commitment was seen as positive, it was not consistent across the three assessments. A crucial assumption for this commitment to happen is that timelines are kept to: any delay in the EU REA publication would also result in a delayed national HTA process to the detriment of all stakeholders.

Figure 8: Use of EU REAs in national setting: changes since JA 2



Source: CRA analysis

3. Conclusions

The experience with JA 2 assessments showed the process for the assessment largely worked out but did not show the use of the EU REA reports. In JA 2, there have been several issues regarding the initiation of the assessment, the scoping phase, the assessment phase, the methodology used, the presentation of the outcomes. However, the most significant issue was the timing of initiation and the knock-on impact this had on the timing of publication. The assessments undertaken in JA 3 have been published in accordance with the guidelines, which is a significant step forward. Some of the issues associated with JA 2 process have also improved:

- Scoping meeting. In JA 3, the communication prior to the scoping meeting was effective and provided greater guidance to the manufacturer and the authors to have a constructive discussion during the scoping meeting. Compared to the feedback from JA 2, the manufacturers involved in the first three assessments were significantly less concerned about the efficiency of the scoping process. However, there is room for further improvement: earlier guidance on the PICO structure (i.e. prior to the draft submission) would be beneficial. Moreover, to ensure that all the comments and questions from the authors and dedicated reviewers are understood fully, a more formalised and direct commenting structure involving follow up calls would be welcome.
- Involvement of external experts and patient organisations. While in JA 2, the involvement of external stakeholders was not tested, in JA 3 there has been only limited progress so far. The input of two external experts that had been invited by the companies to the scoping meeting has informed two EU REAs (although it is not clear how it has been considered). It is not clear if external experts had been consulted by the authors during the assessment or how the few clinical experts had been selected that provided feedback on the REA reports. There has been even less progress with the systematic involvement of patient organisations (with only input from individual patients provided during the assessment phase in two of the cases), which should begin earlier and involve patient organisations throughout the whole process.
- Commitment to use. Use of the EU REAs in national settings is a higher priority in JA 3. During the scoping phase, some of the authors committed to use the EUnetHTA reports in their national HTA processes. At least in one case, an author has replaced the national REA assessment step directly with the EUnetHTA REA assessment
- Opportunity to provide feedback. In JA 3, manufacturers could provide feedback on their experience with the EUnetHTA process (although there is still the need for a more structured mechanism to ensure that learnings are incorporated in the subsequent assessments).

Overall, in terms of the process, JA 3 showed considerable improvement with respect to JA 2. This was made possible by considerable effort of the EUnetHTA secretariat, the participating EUnetHTA members and the companies working together to develop flexible and pragmatic approaches to address procedural issues. Nevertheless, given that this analysis is only based on three JA 3 assessments, the potential progress needs to be

monitored in order to ensure these improvements are systematically incorporated in future EU REAs and the updated EUnetHTA guidance that is being developed.

However, a number of new issues have emerged that need to be considered throughout JA 3:

- Flexibility. EUnetHTA is still experimenting with changes in the process and there are significant differences between the three JA 3 assessments. These changes are often welcomed by the manufacturers involved in the particular assessment. This pragmatism is useful but should be made more transparent, allowing lessons to be learnt, systematically integrated in the EUnetHTA REA process description so that authors of future assessments and the manufacturers involved can benefit from these process improvements.
- Selection of authors likely to use the EU REAs. In order to further support the national adoption of EU REAs, it would be helpful if the authors appointed are those that are the most likely to use the EU REAs in the national context, ideally are willing to replace the corresponding national assessment step.
- Involvement of external groups and role of patients. EUnetHTA is still developing a process to systematically involve external experts and patient organisations in the REA process. Adequate resources should be (re-)allocated within EUnetHTA to facilitate this engagement.
- Transparency of the input from different stakeholders. The role (and the actual input) of the dedicated reviewers, the EMA and regulatory rapporteur(s), the external experts and the patient organisations is not fully transparent to the manufacturers.

In addition, some of the issues observed in JA 2 remain unsolved:

- Confidentiality agreement. A standard template/procedure that sets out data sharing confidentiality at the beginning of the process has not yet been established. Moreover, given in JA 3 the CHMP assessment for the regulatory approval and the EUnetHTA assessments are concomitant, it is important that EUnetHTA does not publish information (e.g. the product indication) that could change during the final stages of the regulatory process. This would avoid generating confusion between the different stakeholders (e.g. patients or national payers preparing for a product's indication different from that one finally approved).
- Clarity of the methodology used. Authors should provide more justification and description of the methodology used, which should follow EUnetHTA guidelines.
- Ambition of the safety analysis. Compared to the EPAR, the safety analysis allows the inclusion in of indirect comparisons (which are not usually considered in the EPAR). However, there are still some concerns about the methodological aspects of indirect safety comparison and how the safety experience from other indications should be integrated into the assessment.
- Objective presentation of the results of the analysis and a process to discuss the results of the analysis. Different authors have adopted different approaches to the presentation of the REA results and conclusions (in one case, the results include significant judgemental language, inappropriate for a "factual" REA assessment). There should be more objectivity and consistency across all the authoring

institutions. In addition, there should be a process that permits the manufacturer to request a hearing with the authors to discuss the assessment rather than only providing written comments on specific sections.

Finally, for some issues it is still premature to assess progress. This is particularly the case for the use of the EU REA in the national setting. Given the centrality of national use for the success of JA 3, it is important that national use of the reports is proactively emphasised, and the efficiencies achieved and the national impact are monitored throughout the process (Table 9).

Table 9: Emerging or unresolved issues in JA 3

	Some emerging or unresolved issues

Initiation	• Lack of *a priori* agreements on the publication of confidential data was an issue in JA 2
	  • In JA 3, there is still a need for a confidentiality agreement at the beginning of the process: this would accelerate the provision of data and avoid a delay as the issue of confidentiality is resolved for that particular assessment
	  • The framework agreement between EMA and EUnetHTA should be made public

	• Need to recognise that JA 3 is still an experimental process • EUnetHTA is trying to address industry concerns but there should be more upfront transparency on where there is flexibility in the process

	• Greater transparency regarding the criteria for the selection of authors would be valuable
	  • The fact that the lead author is also from an EMA Rapporteur/Co-Rapporteur country has been beneficial – this should also be considered moving forward
	  • Authors selection should be made considering the potential for a meaningful use of EU REAs

	• The role of the dedicated reviewers should be clarified at the initiation of the assessment • Dedicated reviewers' use of EU REAs should be encouraged
	• More structure is required on the process for inclusion of external experts (as well as avoiding conflict of interests) and patient organisations
Scoping	• Need for better consideration of EMA process timelines • EUnetHTA could generate confusion by publishing information prior to the regulatory approval
	• There should be a systematic process to involve external stakeholders (external experts and patients organisations) at the scoping meeting

Assessment	• Some improvements have been made on the involvement of external experts but there need to be a more structured and transparent process regarding:
	  • Role and input of dedicated reviewers
	  • Role and input of external experts
	  • Role and input of patient organisations

Methodology	• Need to improve the clarity of the assessment
	  • Authors should provide more description and justification of the methodology
	  • Need to ensure that intention is for a consistent methodology to be applied across different authors for similar products and how this feeds into other work packages

	• Need of improving the methodological aspects of indirect safety comparison and clarifying the objectives of this section
Outcomes	• There appears to be some inconsistency between authors regarding the scope of the report. The presentation of the results could be "too judgemental" in some cases • Some assessments appear to be on the borderline between assessment and appraisal
	• Need for a mechanisms to ensure that learnings are implemented in the subsequent assessments • There is a need to increase the level of transparency around the outcomes from the EUnetHTA technical meetings

Usage	• Need to proactively emphasise usage
	  • Need to appoint authors that are likely to adopt the EUREA and seek their commitment to use them
	  • Product selection should consider the possibilities for use of EUREAs

Source: CRA analysis

Appendix A: Recommendations for improvement of the EU REA model following the analysis of JA 2 assessments

Table 10: 15 recommendations for improvement of the EU REA model following the analysis of JA 2 assessments

	Recommendation
1	The industry should propose the current timetable should be followed. Only pilots where there is an expectation of this being met should be initiated in JA 3
2	A project alignment meeting 60 days prior to the scoping meeting should be introduced
3	The lead author should be chosen on based experience and should be planning to assess the product in their own market. This would imply that the lead author is directly involved in a national HTA process. The role of lead and co-author should be made explicit
4	To understand the benefits in terms of re-use, the pilots in JA 3 should reflect different types of product. This should be more explicit than JA 2
5	Voluntary participation should improve if pilots based on re-use offer benefits to participating companies, however, the process for including pilots should be made more transparent
6	The inclusion of patients and physicians should be piloted in JA 3
7	The primary objective of JA3 pilots should be re-use but other process and methodological issues still need to be resolved
8	The objective of different pilots, at least at a high level, should be transparent and discussed with the MAH
9	Feedback should be a formal part of the process and lessons from the pilots shared with MAH and WP5 members
10	The EUnetHTA methodology should continue to a best practice model and not a collation of all the methodological approaches used by the national HTA frameworks
11	The guidelines should be incrementally improved and where authors take a different position, there should be a requirement to explain the rationale
12	The role of safety analysis needs to be reconsidered and tested in JA 3
13	The tracking of re-use requires consistent definitions, a focus on whether this reduces duplication and more consistent reporting
14	If re-use is to occur, all stakeholders need to commit to encourage its use. This includes EUnetHTA, authors and reviewers and the industry
15	The pilots under JA 3 should investigate the value of explicitly defining where the Rapid Assessment should replace elements of the national assessment. It seems most realistic this could be through a coalition of the willing

Source: CRA for EFPIA (2015)[34]

34 CRA for EFPIA (2015), "An analysis of the EUnetHTA pilot assessments". Available at [last access 10 January 2018]: https://www.efpia.eu/media/25486/an-analysis-of-the-eunethta-pilot-assessments.pdf

Appendix B: Comparison between the EPAR and the EU REA of the first two assessments

Table 11: Midostaurin: the efficacy and safety sections of the EPAR and EU REA

	EPAR	EU REA
Conclusions on efficacy	Both assessments conclude primary endpoints are met. The EU REA uses a language similar to the EPAR, conducts an indirect comparison and notes the lack of evidence on HRQoL	
Example:	*The primary endpoint OS … was met, with a HR of 0.774 (95% CI: 0.629-0.953, p=0.0078), corresponding to a relative risk reduction of 23% in favour of midostaurin… Comparison of the median OS values (midostaurin:75 months; placebo: 26 months) is not informative since the Kaplan-Meier curves plateau around the median and estimates of the median are therefore not precise (p. 149/ 150)*	*Midostaurin in combination with standard induction and consolidation chemotherapy improved OS in patients aged 18–60 years who are fit for chemotherapy (HR= 0.77, 95%CI: 0.63–0.95, p=0.0078). … the risk of death was reduced by 23% during follow-up for midostaurin versus placebo. … Median OS was 25.6 months (95% CI: 18.6–42.9) for placebo and 74.7 months (95% CI: 31.5–not estimable) for midostaurin-based therapy. … Given this evident plateau effect, the absolute OS gain cannot be reliably determined. We, as authors, do not consider interpreting 49 months' difference in OS medians as a reliable estimate for OS gain. (p. 65/66)* *No evidence on HRQoL or disease-specific quality of life was available. … severe evidence gap from an HTA perspective... (p. 67)*
Conclusions on safety	Compared to the EPAR, the manufacturer was able to submit the safety results from an additional on-going single-arm study (IIT trial, AMLSG 16-10). Otherwise, the language in the EPAR and the EU REA is similar	
Example:	*Over 75% of patients in either treatment group experienced at least one grade 3/4 AE suspected to be related to treatment. These AEs occurred at similar frequencies in both treatment groups. (p. 184)* *The safety profile of midostaurin is manageable…. (p. 190)*	*Approximately 50% of the patients in both groups experienced a SAE. 78% of patients in the midostaurin group and 75% of patients in placebo group reported at least one grade 3-4 AE considered related to treatment… 23 (6.7%) patients in the midostaurin group and 17 (5.1%) patients in the placebo group discontinued therapy because of grade 3–4 AEs…. AEs were balanced between groups but rates of grade 3–4 AEs were high…. this is typical considering the health condition. (p. 67)*
Overall conclusion	Both the EPAR and the EU REA come to the conclusion that midostaurin has a positive effect on OS versus safety	
Example:	*Given the poor prognosis of patients with AML, the treatment effect of midostaurin is considered clinically relevant, and has been robustly demonstrated in the overall population in the single pivotal study that was submitted. The safety profile of midostaurin was manageable and is acceptable in view of the therapeutic context and given the observed benefits. (p. 204)*	*Midostaurin in combination with standard induction and consolidation chemotherapy is considered more effective than standard induction and consolidation chemotherapy alone in terms of improved OS in patients aged 18–60 years who are suitable for intensive chemotherapy* *Based on indirect comparison, there was insufficient evidence to determine whether midostaurin treatment was more beneficial than high dose daunorubicin …in terms of OS. (p. 70)*

Source: CRA analysis

Table 12: Regorafenib: the efficacy and safety sections of the EPAR and EU REA

	EPAR	EU REA
Conclusions on efficacy	Whilst EU REA states key information on the primary endpoint (mOS) which is also available in the EPAR, the EU REA builds on the EPAR by raising a point regarding the health related quality of life (HRQoL), deemed " a critical efficacy outcome" alongside mOS by the "reviewers, authors and co-authors".	
Example:	*"… significant improvement in OS for regorafenib compared with placebo (HR 0.627, 95% CI 0.50-0.785, p=0.00002), with a gain in median PFS of about 2.8 months in favour of regorafenib (median OS 10.6 vs 7.8 months, respectively)" (p.52)*	*"This study met its primary endpoint: the median OS time was 10.6 months (95% CI 9.1, 12.1 months) in the regorafenib group and 7.8 months (95% CI 6.3, 8.8 months) in the placebo group…" (p.51)* *"Conclusions on PFS and HRQoL are, however, limited in the absence of adjustment for multiplicity analysis performed in the trial. …The exploratory analysis of HRQoL as measured by the EQ-5D and FACT-hep scales suggested the absence of a clinically relevant difference between the two study groups for these criteria. However, an important amount of missing data was observed limiting the conclusion on HRQoL" (p.50/p.51)*
Conclusions on safety	The EU REA does not add additional observations regarding the safety of regorafenib compared to the EPAR	
Example:	*"Grade 3/4 drug-related events were reported at a higher frequency for regorafenib than for placebo. The most common grade 3 AEs in the regorafenib arm were…"* *"…limited long-term safety data is available in HCC"* *"Drug-related SAEs were reported at higher frequencies for regorafenib (10.4% vs 2.6%)" (p.78)*	*"… more Grade ≥3 AEs were seen in the regorafenib group than in the placebo group: 51.9% versus 17.6%. Similarly, SAE rates were higher in the regorafenib group: 10.4% versus 2.6%. Dose modifications due to AEs (interruption or reduction) were more frequently required in the regorafenib group (68.2%) than in the placebo group (31.1%)." (p.51)*
Overall conclusion	Whilst EPAR is stating the conclusion in a non-judgemental way, the choice of words by the authors in the EU REA is aimed at and conveys an overall judgemental assessment	
Example:	*"The observed 2.8 months gain in median OS, confirmed by the updated analysis (cut off 23 January 2017) and supported by consistent improvement in PFS and TTP, is considered of clinical benefit and able to outweigh the substantial treatment related toxicity." (p.89)*	*"The addition of regorafenib to BSC induced a **modest** gain in terms of OS (+2.8 months in median) at the expense of a **worsened safety profile**, notably in terms of Grade ≥3 drug-related AEs, drug-related SAEs and dose reduction or discontinuation due to AEs." (p.52)* *"… insufficient evidence to determine the relative impact of regorafenib on HRQoL in comparison with placebo. As clinical management of end-stage patients must aim to improve or maintain quality of life, this is **particularly regrettable**." (p.52)*

Source: CRA analysis

Table 13: Alectinib: the efficacy and safety sections of the EPAR and EU REA

	EPAR	EU REA
Conclusions on efficacy	Both assessments conclude primary endpoints are met. The EU REA uses a language similar to the EPAR, conducts an additional indirect comparison	
Example:	*"The study met its primary endpoint with a risk reduction for disease progression or death with 53% compared with crizotinib (HR=0.47, 95%CI:0.34, 0.65, p value < 0.0001) and the estimated median PFS was 11 months in the crizotinib arm whilst not yet reached in the alectinib arm. […] PFS by IRC (key secondary endpoint) is consistent with the findings from the primary endpoint (HR 0.50 [95% CI: 0.36-0.70; stratified log-rank p < 0.0001]). The median PFS was 10 months in the crizotinib arm and approximately 26 months in the alectinib arm. " (p.45)*	*"Alectinib therapy resulted in a substantial and statistically significant increase in PFS (the primary outcome) compared with crizotinib therapy in the ALEX study. While the median PFS was not reached in the alectinib arm for the investigator-based PFS, the IRC showed a difference in medians of 15.3 months (25.7 vs 10.4 months, respectively).The PFS curves for alectinib and crizotinib from the ALEX study did not separate until 6 months" (p.60)*
Conclusions on safety	The EU REA replicates the direct safety comparison provided in the EPAR and adds an indirect comparison not included in the EPAR	
Example:	*"In the first line setting, ceritinib also showed a statistically significant benefit over chemotherapy in delaying disease progression (PFS) with HR of 0.55 (95% CI: [0.42, 0.73]; p < 0.001) and medians of 16 months and 8 months respectively." (p.7)* *[There is no reference to the safety profile of ceritinib]*	*"The MAH performed a Bayesian fixed effects NMA and an indirect comparison [versus ceritinib] according to the Bucher method […] The NMA performed by the MAH indicates: [s]ignificantly fewer grade 3 or 4 AEs with alectinib than with ceritinib." (p.55)*
Overall conclusion	Both the EPAR and the EU REA come to a similar conclusion on the superiority of alectinib over crizotinib. The EU REA adds a statement on the patient relevance of the delayed CNS progression	
Example:	*"The data available from the primary analysis of the global ALEX study using the EU-approved alectinib dose of 600 mg BID, showed superiority of alectinib over crizotinib in the 1st line treatment-naïve patients with advanced ALK-positive NSCLC. The treatment effect of alectinib on CNS metastases is compelling and of high clinical relevance." (p.75)*	*"From direct comparison, based on high quality evidence, alectinib demonstrated a substantial and statistically significant increase in PFS. It is also associated with a statistically significant longer time to CNS progression compared to crizotinib. This is of high clinical relevance as CNS metastasis and progression affects both the symptoms and the quality of life, as well as the prognosis of the patients." (p.63)*

Source: CRA analysis