

Prepared For:

EFPIA

Leopold Plaza Building, Rue du Trône 108

B-1050 Brussels (Belgium)

An analysis of the EUnetHTA pilot assessments

Prepared By:

Tim Wilsdon, Michele Pistollato, Lilian Li and
Artes Haderi

Charles River Associates

99 Bishopsgate

London EC2M 3XD

Date: December 2015

CRA Project No. D21304-00

Table of contents

Executive Summary	1
1. Introduction	9
1.1. Background.....	9
1.1.1. The goal of rapid REA pilots.....	10
1.1.2. The rapid REA pilots	10
1.2. The approach	11
1.3. Terms used throughout the report.....	12
1.4. Structure of the report.....	12
2. Process	13
2.1. Overall process and timeline.....	14
2.2. Expression of interest	15
2.2.1. The choice of the particular pilot product	15
2.2.2. Participation of the company	16
2.2.3. The objective of the pilots.....	18
2.2.4. Timing.....	19
2.2.5. Lessons regarding the initiation of the pilots	19
2.3. Activities prior the scoping meeting	20
2.3.1. Selection of the pilot team	21
2.3.2. Guidance on the draft submission	23
2.3.3. The possibility of discussing methodological issues prior to the scoping meeting 23	
2.3.4. Lessons regarding activities prior to the scoping meeting	24
2.4. Scoping meeting.....	25
2.4.1. Agreeing the scope	25
2.4.2. Timing of scoping meeting.....	26
2.4.3. The finalisation of the submission dossier.....	27
2.4.4. Lessons regarding the scoping meeting	28
2.5. Assessment.....	29
2.5.1. The role of the parties involved and their interactions	29
2.5.2. The timing of the assessment.....	30
2.5.3. Lessons regarding the assessment	35
2.6. The process post publication	36

2.6.1. Publication of the report	36
2.6.2. Feedback on the pilot process.....	36
2.6.3. Lessons regarding the process post publication	37
3. Methodology and outcomes of the pilot	38
3.1. Health problem and current use of technology	38
3.2. Description and technical characteristics of technology	39
3.3. Clinical effectiveness	39
3.3.1. Selection of comparators.....	40
3.3.2. Selection of outcomes.....	41
3.3.3. The use of direct and indirect comparisons.....	46
3.3.4. Levels of evidence	50
3.3.5. Lessons on clinical effectiveness.....	54
3.4. Safety.....	54
3.4.1. Objective of safety analysis	54
3.4.2. Safety analysis methodology and data	59
3.4.3. Lessons	62
4. Re-use	63
4.1. The definition of re-use.....	63
4.2. External re-use.....	64
4.3. Lessons.....	68
5. Reform of the rapid REA	69
5.1. Improvements to the REA process.....	69
5.1.1. Timing.....	69
5.1.2. Stages in the process.....	71
5.1.3. Authors	72
5.1.4. The types of products that are included in the Rapid REA process	72
5.1.5. Participation	73
5.1.6. Stakeholders included in the process	73
5.1.7. The goal of Joint Action 3.....	74
5.1.8. The goals of each pilot	75
5.1.9. Feedback.....	76
5.2. Improvements to the methodology	76
5.2.1. Develop a methodology consistent with the aim of the rapid REA	76
5.2.2. The application of guidelines	77

5.2.3. The goal of the safety analysis	78
5.3. Improvements required post publication to encourage re-use.....	78
5.3.1. Reporting of re-use	79
5.3.2. Responsibility to re-use by authors vs EUnetHTA.....	79
5.3.3. Binding vs flexible use of REA at national level.....	79
Appendix 1: List of EUnetHTA documents consulted	81

Table of Figures

Figure 1: Process timeline.....	2
Figure 2: Scoping phase – timeline from EUnetHTA perspective	13
Figure 3: Assessment phase – timeline from EUnetHTA perspective.....	14
Figure 4: Process timeline.....	15
Figure 5: Timing of the expression of intent	19
Figure 6: Timing of the scoping meeting	26
Figure 7: Timing of the final submission	28
Figure 8: Assessment timeline from EUnetHTA perspective	31
Figure 9: Timing for the publication of the first draft with respect to the CHMP opinion	32
Figure 10: Timing for the publication of the first draft with respect to the scoping meeting	33
Figure 11: Timing of the assessment process with respect to the CHMP opinion	34
Figure 12: Timing of the assessment process with respect to the scoping meeting	35
Figure 13: Purposes of usage, as at September 2015	66
Figure 14: Pilot 1 Rapid REA by national HTA bodies.....	67
Figure 15: Process timeline including two formal meetings between MAH and EUnetHTA ...	71

Table of Tables

Table 1: The five Rapid REA Pilots conducted under JA 2 by EUnetHTA for pharmaceutical products	1
Table 2: The five Rapid REA Pilots conducted under JA 2 by EUnetHTA for pharmaceutical products	10
Table 3: Composition of the pilot teams.....	22
Table 4: Comparators by pilot	40
Table 5: Endpoints by pilot	42
Table 6: Comparison of endpoint selection and reporting in Rapid REA reports and published national assessments	43
Table 7: Type of comparison(s) by pilot.....	47
Table 8: Indirect comparisons by pilot	47
Table 9: Quality assessments by pilot	51
Table 10: GRADE evidence profile for direct evidence and effectiveness outcomes (example from Pilot 4)	53
Table 11: Safety analysis by pilot	55
Table 12: Comparison of the research questions between the rapid REA reports and the EMA EPARs	57
Table 13: Comparison of the number of pages between the Clinical effectiveness and the Safety sections across the pilots.....	59
Table 14: Methods used and evidence gaps highlighted in the rapid REA reports.....	60

Executive Summary

EFPIA asked Charles River Associates (CRA) to prepare an analysis of the five EUnetHTA pilot assessments of relative effectiveness.¹ In particular the objective was to:

- Provide a comprehensive review of the five rapid relative effectiveness assessment pilots undertaken under JA 2 WP5 that have been conducted by EUnetHTA to date
- Review the extent to which the reports are consistent in terms of process, methodology and outcomes and the underlying reason for the differences
- Assess the degree to which these assessments have been “re-used”, i.e. the outcome in terms of national and regional HTA processes

The ultimate objective is to provide a report outlining the conclusions as a contribution to a workshop involving the industry and the EUnetHTA in October 2015.

Background and approach

The EUnetHTA Joint Action 2 (JA2) programme aims to strengthen the practical application of tools and approaches to cross-border HTA collaboration. In particular, the Work Package 5 (WP5) Strand A has the objective of applying the HTA Core Model for rapid Relative Effectiveness Assessment (REA) of pharmaceuticals and testing the ability of national HTA bodies to jointly produce HTA information and apply it in national context. An important component of JA2 WP5 is a series of rapid REA pilots. EUnetHTA has completed five pilot assessments of pharmaceuticals between 2012 and 2015 as described in Table 1 below.

Table 1: The five Rapid REA Pilots conducted under JA 2 by EUnetHTA for pharmaceutical products

Molecule	Indication	Manufacturer	Publication date
Zostavax (pilot 1)	Prevention of herpes zoster and postherpetic neuralgia	SP-MSD	September 2013
Canagliflozin (pilot 2)	Type II diabetes mellitus	J&J	February 2014
Sorafenib (pilot 3)	Thyroid carcinoma, refractory to radioactive iodine	Bayer	March 2015

1

The sixth EUnetHTA pilot, to review new pharmaceuticals for the treatment of chronic hepatitis C, is currently being undertaken but is excluded from this analysis. The pilot undertaken under JA1 was not included in the scope of the project.

Ramucirumab (pilot 4)	Advanced gastric or gastro-oesophageal junction adenocarcinoma	Eli Lilly	May 2015
Vorapaxar (pilot 5)	Reduction of thrombotic cardiovascular events in patients with history of MI	MSD	June 2015

Source: EUnetHTA

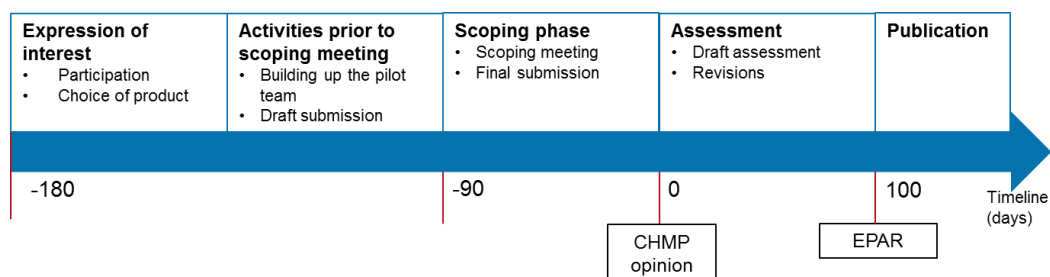
In order to gather the lessons from the five rapid REA pilots, CRA has undertaken two structured interviews with the companies involved in the five pilots (the first one focusing on the process, the second focusing on methodology, outcomes and re-use) and with five companies that did not complete pilots but had initial discussions with EUnetHTA; reviewed documents provided by the companies involved in the pilots, the guidelines provided by EUnetHTA and the final REA reports; reviewed existing publications on the lessons from the assessment; and undertook two workshops with the EFPIA steering group on EUnetHTA pilots to discuss the lessons from the pilots.

It should be noted that the report is based on interviews and documentation provided by the industry participants, and there was not the opportunity to interview the EUnetHTA WP5 coordination team, rapid RE pilot authors or reviewers. The report therefore does not incorporate their perspective unless it is reported in public documents.

Process

To compare the process used in the five pilots and whether this is consistent with the EUnetHTA guidance we simplified the process and distinguished between the expression of interest, activities prior to the scoping meeting, the scoping phase, the assessment and post-publication as in Figure 1.

Figure 1: Process timeline



Source: CRA analysis

There are a series of lessons associated to each of these stages:

- Expression of interest
 - From the outset participation was intended to be voluntary. This was welcomed by the industry. However, in practice some pressure was applied to participate and the possibility of undertaking pilots without the company's participation increased.

This meant companies participated to prevent a pilot being undertaken without their participation rather than because the product represented a good product to pilot the process.

- The overall goal of the pilots is stated explicitly but there is still confusion. It is unclear if usability refers to using the model or using the results of the pilot. In reality, it would appear that testing the process was prioritised over re-use (even though there was a target number of re-uses and examples of re-use were published on the website). If the focus on the process had been clearer participation from the companies might have been considerably less challenging and the choice of authors would have been less of an issue (discussed below), making initiation more straightforward. As the team from the MAH have to justify the use of scarce resources internally, often when the company is focused on launching an important new product, absolute clarity on the goal would have been beneficial. A greater level of transparency on this would help improve participation and collaboration. The goals of individual pilots should be clearly specified (i.e. the reasons why a product is selected for the pilot should be explicit). This would help companies and the authors.
- Timing has been a considerable challenge for the pilot process. The publication of the REA reports occurred later than planned and this can be traced back to starting the process much later than planned. The result of this is that alignment with the EPAR process has worsened considerably. The original plan was for the published report to occur soon after the publication of the EPAR, presumably to increase the potential for re-use. Given the timing of the last three pilots, testing this part of the process was clearly de-prioritised. However, this was not made explicit.
- Prior to the scoping meeting
 - The submission template, which was still under development in the first pilots, has provided some guidance in the later submission, however, there is a concern that the template collates all the potential questions that HTA agencies request rather than focusing only on common issues that should be discussed in the rapid REA.
 - The choice of authors caused considerable concern for MAH during the author selection. In particular, concern was raised about the role of HTA agencies that were not commonly involved in national HTA processes. In practice, manufacturers were able to submit suggestions but due to a number of reasons (including interest and resourcing) the suggestions were rarely influential but did delay the process. The process for the choice of the authors can be improved by (1) starting the pilot on time (2) more transparency on the role of the authors (3) dedicated reviewers involved in the earlier stages of the pilot
 - In practice the MAH is submitting a full submission prior to the scoping meeting. We conclude it would be beneficial to all stakeholders to have a project alignment meeting between the manufacturer and the authors prior the draft submission to facilitate the scoping process and have a high level discussion of methodological issues. The project plan should be agreed immediately after the project alignment meeting and include both the manufacturer's and the EUnetHTA's commitments.

This would mitigate the risk of unnecessary delays (for instance, by planning to account for holiday periods). This should be tested in the next pilots and, unless it is proven to be detrimental, it should be included into the rapid REA process.

- The scoping meeting
 - The content and the timing of the scoping meeting can be improved. The lack of author preparedness in the scoping meeting detracts from discussion and can lead to uncoordinated requests for additional data or data analyses. This probably reflects the delay in the decision on the authors. The scoping meeting would be improved if it focused on completeness of the evidence and was consistent with the minutes of the project alignment meeting
 - An a priori confidentiality agreement (i.e. at the time of initiation of the pilot) would accelerate the provision of confidential data without the need to discuss this during the scoping phase. For instance, a clear understanding of the information required from the EMA submission and a confidentiality agreement between EUnetHTA and the manufacturer could accelerate timelines if defined at the beginning of the process
- The assessment phase
 - Following the scoping meeting, the process timetable was largely adhered to. Although difficult for the MAH to assess, it appears that the division of the responsibilities between the authors worked well and used the capabilities and resources of the authors. However, for re-use the reference to EPAR timeline is more important and this was not met.
 - None of the pilot included any input from external stakeholders. The perspectives of patients and physicians would provide useful insight for the assessment. However, the additional complexity this add to an already complex process would need to be managed.
- Publication
 - For the pilots, 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 learnt in subsequent assessments is vital.

Overall, the process does not differ depending on the type of product. Although there were improvements in some areas (timing of the assessment post the scoping meeting), in other areas the process diverged from the original plan (particularly the alignment with the EPAR process).

Methodology and outcomes

In order to investigate the methodology, we have structured our analysis according to the four domains of the REA report (health problem and current use of technology, description and technical characteristics of technology, clinical effectiveness and safety). For each domain, we

compare the methodology recommended by the HTA Core Model for rapid REA and the nine EUnetHTA methodology guidelines to the methodology used in each of the pilots

There were not significant issues affecting the first two domains (health problem and current use of the technology, description and technical characteristics) but there are issues with both clinical effectiveness and safety.

- Clinical effectiveness

- The selection of comparators was agreed between MAH and authors. Looking forward, it would be good to maintain the process ensuring that comparators are agreed between the authors, the manufacturer and the reviewers (ideally at a project alignment meeting prior to the scoping meeting) and the chosen comparator is representative of European practice whenever possible. As discussed in the previous chapter, this agreement should occur earlier in the process.
- Regarding the selection of the endpoints, overall there is agreement between the MAH and the authors regarding the choice of end-points and the acceptance of surrogate endpoints is generally positive. Some issues were highlighted on the appropriateness of the selection of primary endpoints, their hierarchy and the interpretation of the composite endpoints. In particular, manufacturers recommended that the selection of primary endpoints should be put in the context of the disease, and their choice should be more flexible and pragmatic rather than meticulously following the HTA core model. For the composite endpoints, the author should comment on the contribution of each component. Where the EUnetHTA guidelines are not followed, additional communication between the MAH and the authors appears important.
- Regarding the (indirect) comparisons, the MAH saw it as positive that EUnetHTA uses “cutting-edge” methodologies (e.g. NMA). However, it is important to have greater clarity in reporting and consistency in the application of EUnetHTA guidance for assessment of comparisons. In particular, the authors should provide a critical and detailed analysis of the methodology of the studies included for the indirect comparison.
- Regarding the quality of evidence, there is a need for standardisation so that similar products would be treated in the same way but also flexibility so that issues associated with small patient populations are allowed for. The approach used to assess data quality should be transparent and discussed taking into account the type of product under review.

- Safety

- There is a need for clarification of the objectives of the safety section. In particular, there is a significant concern that the first two objectives of the safety domain duplicate the EPAR. The focus on relative safety could potentially add value but it is unclear if this is of interest to national HTA bodies.
- There is a need for clarification and improvement of types of data and analyses recommended for relative safety assessment. Although EUnetHTA guidelines

require a comparison, the analysis should be put into context: phase III clinical studies are designed for this purpose and there is a risk that “missing” statistical significance is misinterpreted by national agencies, possibly leading to delays in (or no) access.

- There is a need to keep the methodology applied to the safety assessment consistent with EUnetHTA guidelines while allowing sufficient flexibility to adapt to different products/contexts. This should be a standard methodology, reflective of a pan-European assessment rather than the specific practices of individual EUnetHTA authors.

More generally, it was noted that the reports need to have an appropriate balance between the relative efficacy/effectiveness analysis and the relative safety. In particular, the final results should be presented in a pragmatic form, reflecting the fact that the focus of the report is the REA rather than being an academic assessment of each domain. In addition, there is an unsolved issue in the identification of an optimal balance between the flexibility that would allow authors to make pragmatic decisions and the standardisation of the decision process that would make decisions more predictable and easily transferable.

Overall, although the pilot products are very different (vaccines, cancer drugs, orphan drugs, retail products) and the HTA agencies involved in the assessment (the authors) also varied across pilots, there are many common lessons across the pilots. The issues with clinical effectiveness are relatively minor but there is still room for improvement. The experience with the assessment of safety is generally less satisfactory and significant work needs to be done.

Re-use

We have examined the limited published evidence on the use of REA reports by national and regional HTA and interviewed the MAH. There are a number of lessons:

- The first issue with assessing the extent of re-use is the definition. EUnetHTA has defined national adaption but this does not require that the national process substitutes information from the REA report. Without a more useful definition of re-use it will be difficult to assess if there are efficiency improvements or this is simply adding to the information requirements in Europe.
- The existing evidence of re-use of EUnetHTA assessments is limited and until recently, there was very little data on re-use. A recent survey by EUnetHTA however has shed some light on this issue. This indicates national HTA referencing the REA reports to a greater degree than is apparent to the companies but does not allow us to determine whether this has improved efficiency. Significantly more effort need to go into reporting re-use and the lessons published as the pilot develop.
- There has been little analysis on why re-use to date has been limited. Some participants suggested that to date the priority has been on testing the process and re-use has not been prioritised. Nevertheless, industry participants have unanimously suggested that timing is one of the most important barriers to re-use of the assessments. It is not a realistic expectation that national HTA bodies will be able to refer to the REA report unless the latter is conducted within the given timeframe and is available prior to the start of the national assessment. In addition, there are no

requirements on national HTA processes to accept information from EUnetHTA rapid REAs. Even the authors of the REA report are not under any obligation to consider its use in the national assessment. It is therefore inevitable that it is used as a supplementary piece of evidence rather than replacing any part of the existing submission. This is clearly important if one of the key objectives of this initiative – the reduction of duplicative efforts – is to materialise. Finally, it appears that EUnetHTA currently does little to encourage re-use, in terms of making national HTA aware of the timing of the assessment publication or helping national authorities use the report.

In conclusion the initial five pilots has shown the WP5 partners can collaborate on rapid REAs. However, it has not been proven that WP5 partners can collaborate on rapid REAs in a fashion that is sustainable and timely enough to reduce duplication and improve efficiencies for all stakeholders.

Reform of the rapid REA

Finally, we have considered what would need to change in order to establish a sustainable rapid REA model going forward based on the experience of the five pilots. It is important to distinguish between recommendations for further pilots under Joint Action 3 and for any permanent form of rapid REA. We have 15 recommendations:

- The current timetable should be followed. Only pilots where there is an expectation of this being met should be initiated in JA3. This would allow explicit re-use of the report only in countries that start the HTA process after the EPAR is issued. For any future pilot process it will be important to consider how many pilots can realistically be completed within the given timeframe to ensure that all the main objectives (e.g. alignment with the EMA process, re-use and completion of the number of the pilots established in the Grant Agreement) are achieved.
- A project alignment meeting 60 days prior to the scoping meeting should be introduced.
- The lead author should be chosen based on their 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.
- To understand the benefits in terms of re-use, the pilots in JA3 should reflect different types of product. This should be more explicit than JA2.
- Participation should continue to be voluntary while the process is being piloted. In order to encourage company participation, pilots should explicitly aim at adopting the report in participating agency processes. A transparent process of horizon scanning and selection would also increase the willingness of companies to engage. The decision of companies not to participate should also be made more transparent.
- The inclusion of patient and physician representatives in the process should be piloted in JA3.
- The primary objective of JA3 pilots should be re-use but other process and methodological issues still need to be resolved.

- The objective of different pilots, at least at a high level, should be transparent and discussed with the MAH.
- Feedback should be a formal part of the process and lessons from the pilots shared with MAH, industry stakeholders and WP5 members. A debrief meeting should be timely scheduled to allow lessons learnt from a pilot to be input in the subsequent pilot(s).
- The EUnetHTA methodology should continue to be a best practice model and not a collation of all the methodological approaches used by the national HTA frameworks. The implication of this for the re-use of the pilot assessments is that the focus should first be on those countries which have a methodology consistent with the EUnetHTA guidelines, so that direct integration is possible while other countries have time to adjust
- The guidelines on clinical effectiveness should be incrementally improved (with a focus on endpoints and assessment of quality of evidence) and if authors take a different position, there should be a requirement to explain the rationale (however guidelines needs to be sufficiently flexible and pragmatic to accommodate the divergent types of innovation and their contexts that will be subject to review)
- The role of safety analysis needs to be reconsidered and tested in JA3
- The tracking of re-use requires consistent definitions, a focus on whether this reduces duplication and more consistent reporting
- Re-use requires all stakeholders need to make commitments. This includes EUnetHTA, authors and reviewers. Re-use should be a clearly stated objective, agreed in a “contract” with the sponsor for a defined set of countries (e.g. authors and reviewers)
- The pilots under JA3 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. This would involve an explicit plan developed as part of the scoping phase for how the re-use will be piloted in the country (this should include the modification to the national submission template and a transparent approach to replacing some national elements of the assessment with the outcomes of the REA)

1. Introduction

EFPIA asked Charles River Associates (CRA) to prepare an analysis of the five EUnetHTA pilot assessments of relative effectiveness.² In particular the objective was to:

- Provide a comprehensive review of the five rapid relative effectiveness assessment pilots undertaken under JA 2 WP5 that have been conducted by EUnetHTA to date
- Review the extent to which the reports are consistent in terms of process, methodology and outcomes and the underlying reason for the differences
- Assess the degree to which these assessments have been “re-used”, i.e. the outcome in terms of national and regional HTA processes

The ultimate objective is to provide a report outlining the conclusions as a contribution to a workshop involving the industry and the EUnetHTA in October 2015.

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. The network aims to provide a common platform for different countries to share and access scientific information, communicate with stakeholders, promoting transparency, objectivity, independence and fairness.³ 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. The HTA core model was adapted for use in the rapid relative effectiveness assessment (rapid REA) process. The objective of work package 5 (WP5) is to:⁴

- Test the capacity of national HTA bodies to produce structured core HTA information together and apply it in national context
- Implement, pilot and further develop models and tools as well as production processes to support collaborative production of core HTA information with reinforced secretariat and coordination function

² The sixth EUnetHTA pilot, to review new pharmaceuticals for the treatment of chronic hepatitis C, is currently being undertaken but is excluded from this analysis. The pilot undertaken under JA1 was not included in the scope of the project.

³ <http://www.eunetha.eu/about-us/mission-vision-values>

⁴ EUnetHTA webpage [last access 2 September 2015]: <http://www.eunetha.eu/activities/EUnetHTA%20Joint%20Action%202012-15%29/ja2-wp5-applying-hta-core-model-rapid-assessment-nation>

- Develop and test a methodological basis for European cooperation on HTA including guidelines for distinct methodological issues and quality improvement of evidence generation for HTA.

This model was initially used to perform a joint assessment on diagnostic technologies and medical and surgical intervention.⁵ However, for the first time EUnetHTA developed and tested the HTA Core Model for rapid relative effectiveness assessment for pharmaceuticals in 2012. This has been followed by five further rapid REA pilot projects as part of JA2.

1.1.1. The goal of rapid REA pilots

The purpose of the rapid REA pilots is to:⁶

- Produce rapid assessment reports based on cross-border collaboration
- Test the usability of the model for rapid REA including guidelines

As part of the JA2 Grant Agreement between EUnetHTA and the EU Commission, signed in 2011, there was a requirement for ten rapid REAs for pharmaceuticals to be produced by 2015.⁷ In the EUnetHTA 3-year Work Plan, it is additionally indicated that 20 local/national reports based on the HTA information from the pilot assessment should be generated.^{8,9}

1.1.2. The rapid REA pilots

There have been five rapid REA pilots (which we commonly refer to as pilots) completed as at August 2015. As set out in Table 2, these vary in terms of the type of product (the first product being a vaccine while the subsequent four were medicines), the timing and the companies involved.

Table 2: The five Rapid REA Pilots conducted under JA 2 by EUnetHTA for pharmaceutical products

Molecule	Indication	Manufacturer	Publication date
Zostavax (pilot 1)	Prevention of herpes zoster and postherpetic neuralgia	SP-MSD	September 2013

⁵ The first rapid REA pilot was applied to medical devices, specifically “Duodenal-jejunal bypass sleeve for the treatment of obesity with or without Type II Diabetes Mellitus”. There have now been four rapid REA pilots undertaken for medical devices.

⁶ EUnetHTA WP5 Joint Action 2 (2015), “Procedure manual WP5 Strand A: Rapid Relative Effectiveness Assessment of Pharmaceuticals”, V4 April 2015

⁷ EUnetHTA website “Technical Annex of the EUnetHTA JA2 Grant Agreement” [last access 24 August 2015]: <http://www.eunetha.eu/outputs/technical-annex-eunetha-ja2-grant-agreement>

⁸ EUnetHTA WP5 Joint Action 2 (2013), “EUnetHTA Joint Action 2 on HTA 2012-2015, 3-year Work Plan”, May 2013

⁹ JA2 WP5 aims to apply the HTA Core Model for Rapid Assessment to both pharmaceuticals (strand A) and non-pharmaceuticals (strand B). The goal for non-pharmaceuticals (e.g. medical devices, interventions, diagnostics) is to complete 4 pilots by 2015 and re-use them in 10 local/national reports.

Canagliflozin (pilot 2)	Type II diabetes mellitus	J&J	February 2014
Sorafenib (pilot 3)	Thyroid carcinoma, refractory to radioactive iodine	Bayer	March 2015
Ramucirumab (pilot 4)	Advanced gastric or gastro-oesophageal junction adenocarcinoma	Eli Lilly	May 2015
Vorapaxar (pilot 5)	Reduction of thrombotic cardiovascular events in patients with history of MI	MSD	June 2015

Source: EUnetHTA

The application of the HTA Core Model for Rapid Relative Effectiveness Assessment in these pilots is still at early stages. There is considerable variation between the pilots, understandably given their purpose, the methodology has evolved over time but equally, the products being reviewed are different resulting in differences in application.

1.2. The approach

The approach involved a variety of different tasks:

- Two structured interviews with the companies involved in the five EUnetHTA pilots, the first one focusing on the process, the second focusing on methodology, outcomes and re-use¹⁰
- Interviews with five companies that did not complete pilots but had initial discussions with EUnetHTA
- A review of documents provided by the companies involved in the pilots. This included email correspondence, minutes of scoping meeting, project plans, comments on draft assessments, presentations at conferences, and the feedback survey
- A review of the guidelines provided by EUnetHTA (the list of document reviewed is provided in the appendix)
- A review of existing publications on the lessons from the assessment. However, to date there has been relatively little analysis of the significant developments and changes to the scope, methods, process and outcomes from the earliest pilot in 2012 up to the most recent just published in June 2015

10

Interview guides are provided in the Appendix. As some of the products are still undergoing national HTA assessments, the interviews were undertaken with the agreement that we would not report product specific information and some experiences could not be attributed to particular pilots.

- Two workshops with the EFPIA steering group to discuss the lessons from the pilots

It should be noted that the report is based on interviews and documentation provided by the industry participants, we did not have the opportunity to interview the EUnetHTA WP5 coordination team, rapid REA pilot authors or reviewers during this project. The report therefore does not incorporate their perspective unless it is reported in public documents.

1.3. Terms used throughout the report

For the sake of consistency, we have used the following terms throughout the report:

- MAH: we refer to the companies involved in the pilots as the marketing authorisation holder or MAH (as in EUnetHTA reports)
- Pilots: we refer to each of the five pilots by number only referring to the product or specific company where this is relevant and this does not conflict with confidentiality
- Rapid REA reports: we refer to the final report published for each pilot as the pilot report¹¹
- Coordination Team: the EUnetHTA JA2 WP5 Lead Partner (ZIN, formerly CVZ) coordinating the whole process
- Re-use: we distinguish between the outcome of the report (the conclusion on relative effectiveness) and the use of the report by national or regional HTA, which we refer to as re-use

1.4. Structure of the report

The rest of the report is structured as follows:

- Chapter 2 reviews the process for undertaking the EUnetHTA pilots, how this was intended to work, how it worked in practice and the lessons can be drawn
- Chapter 3 considers the methodology applied in the assessment and the outcome of the assessment, how this was intended to work, how it worked in practice and the lessons can be drawn
- Chapter 4 considers the extent to which the reports were re-used by national HTA agencies and the lessons that can be drawn
- Chapter 5 we consider what would need to change in order to establish a sustainable rapid REA model going forward based on the experience of the five pilots

11

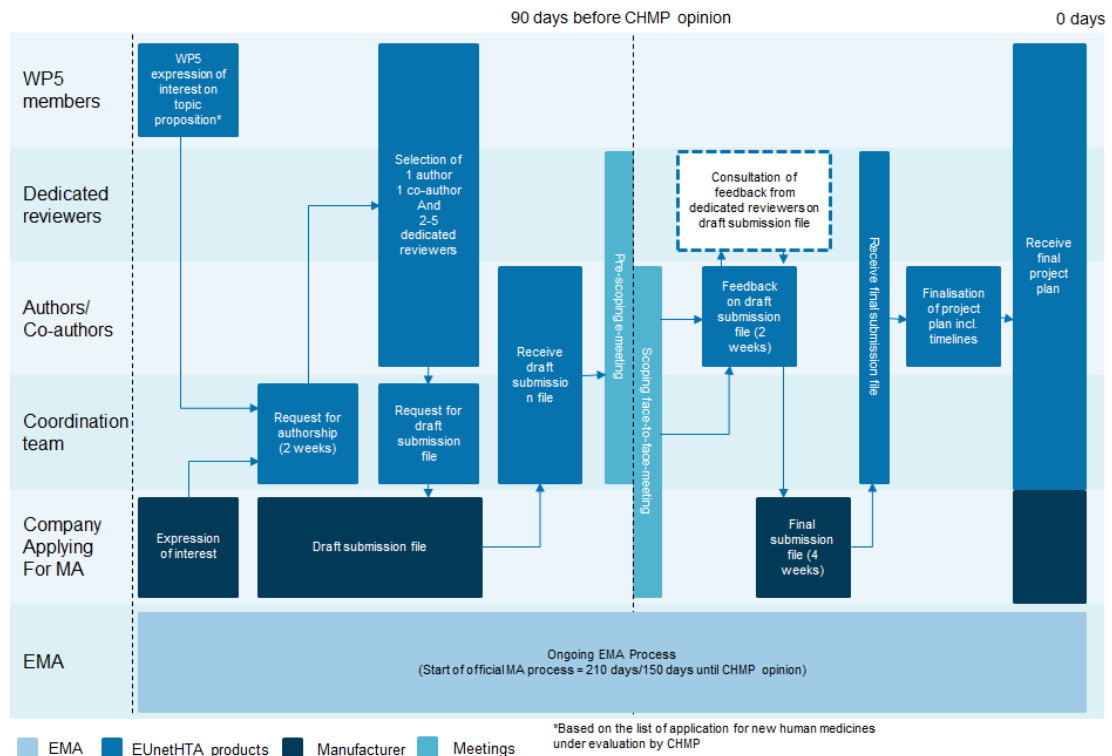
These are all published in the EUnetHTA website. <http://www.eunetha.eu/>

2. Process

One of the objectives of the WP5 of EUnetHTA JA2 is to “test the capacity of national/local HTA bodies to collaboratively produce structured rapid core HTA information on pharmaceutical (Strand A)”.¹² This implicitly involves setting up and testing a procedure to initiate and conduct the rapid REAs. This section analyses the experience in terms of the process and the lessons from the companies’ perspective.

How the Rapid REA pilot process is meant to work has been set out in considerable detail in the Procedure manuals.¹³ This is illustrated in Figure 2 for the scoping phase.

Figure 2: Scoping phase – timeline from EUnetHTA perspective



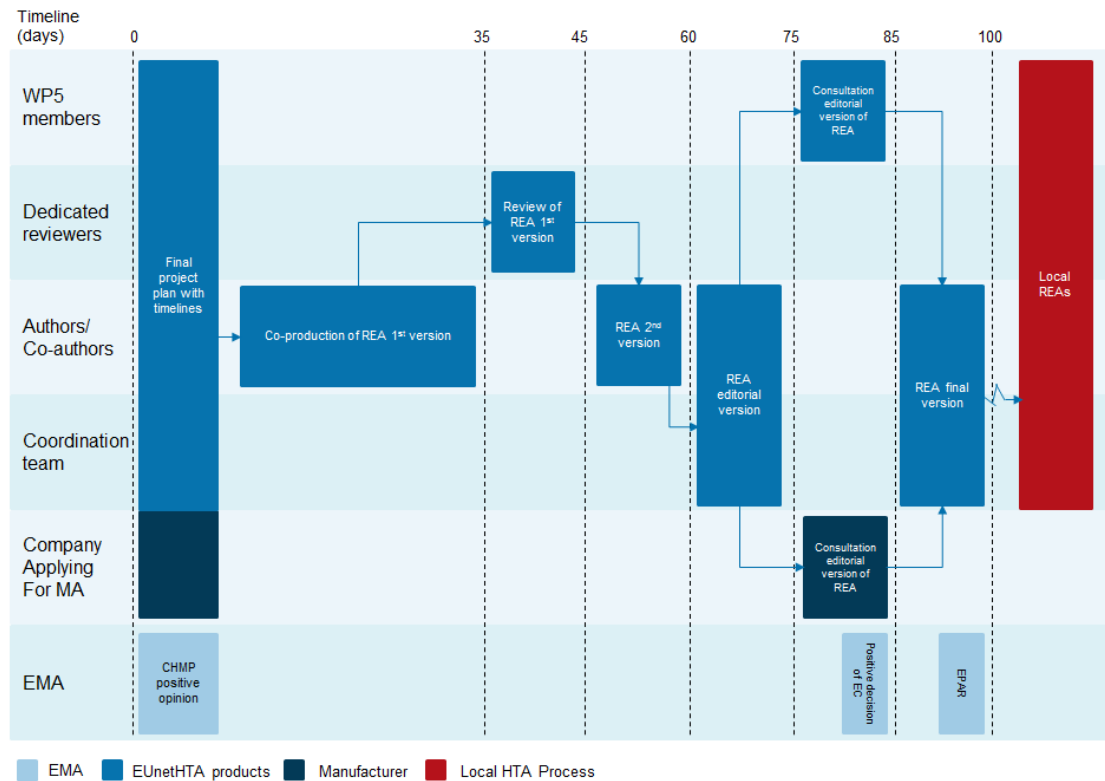
Source: Drawn from EUnetHTA procedure manual v4

And Figure 3 for the ‘assessment’ phase.

12 EUnetHTA webpage [last access 1 September 2015]: [http://www.eunetha.eu/activities/EUnetHTA%20Joint%20Action%20\(2012-15\)/ja2-wp5-applying-hta-core-model-rapid-assessment-nation](http://www.eunetha.eu/activities/EUnetHTA%20Joint%20Action%20(2012-15)/ja2-wp5-applying-hta-core-model-rapid-assessment-nation)

13 Two version of the EUnetHTA Procedure Manual have been made public: v3 was published on 27 May 2013 (but it is no longer available on EUnetHTA website) and v4, which was published on 1 April 2015 (available on EUnetHTA website)

Figure 3: Assessment phase – timeline from EUnetHTA perspective



Source: Drawn from EUnetHTA procedure manual v4

To make comparison easier we first consider a simplified version of the overall process and then we use this to go through each of the steps.

2.1. Overall process and timeline

An overview of the organisation of the process from the manufacturer’s perspective is provided in Figure 1. According to EUnetHTA, the rapid REA should be aligned with the EMA assessment so that the assessment starts following the CHMP opinion¹⁴ and the publication of the REA report is immediately after the EPAR.¹⁵ According to the EUnetHTA procedure manual¹⁶ this requires initiating the process 180 days before the CHMP gives the (positive) opinion with the aim of submitting the final dossier for assessment immediately after the CHMP

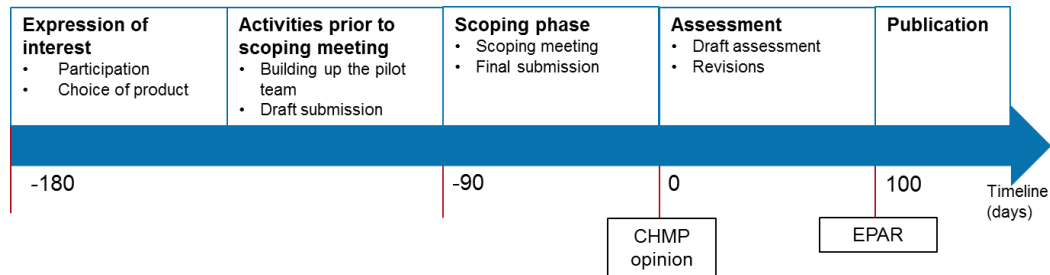
14 Committee for Medicinal Products for Human Use (CHMP) is a committee of the EMA, which provides an opinion on whether a product should be given a marketing authorisation. This is submitted to the European Commission.

15 EPAR is European public assessment reports published by the European Medicines Agency at the completion of the marketing authorisation process.

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

opinion. It should then take no longer than 100 days for the assessment so the rapid REA is available for publication shortly after the EPAR is issued.

Figure 4: Process timeline



Source: CRA analysis

It is important to note that the alignment with the EMA assessment was not an objective of the first pilot, as the product had already been approved by the EMA in 2006.¹⁷ Consequently, it is not appropriate to analyse the timeline for the EUnetHTA assessment with reference to the regulatory process in the subsequent analysis.

2.2. Expression of interest

There are four important aspects regarding the initiation of a pilot:

- How the product for the pilot is chosen
- Participation of the company
- The objective of the pilot
- The timing in practice.

2.2.1. The choice of the particular pilot product

In theory, both the manufacturers and the WP5 members can propose a pilot rapid REA.¹⁸ In practice, the process for initiation varied across the five pilots:

- In the three early pilots, the manufacturers voluntarily suggested products to be included in the process and approached EUnetHTA to be considered for participation. After an initial discussion between the MAH and the Project Leader of WP5 EUnetHTA JA2 (Wim Goettsch, ZIN), an expression of interest was sent by the companies

¹⁷ As mentioned in the EUnetHTA first pilot report, this was due to a complex manufacturing process which led to limited supply capacities and restrictions in the amount of doses available for European countries.

¹⁸ EUnetHTA WP5 Joint Action 2 (2015), "Procedure manual WP5 Strand A: Rapid Relative Effectiveness Assessment of Pharmaceuticals", V4 April 2015

- In the two later cases, a letter identifying the company was sent to the manufacturer (in May and June 2014 respectively). These letters appear to have been sent to many companies expecting a marketing authorisation between 2013 and 2015.

We found no evidence in the first five pilots indicating that WP5 members (other than the Coordinator Team, ZIN) expressed their interest in a specific topic.¹⁹

The EUnetHTA guidelines do not discuss the criteria use to select particular products to be included in the pilot process. The only reference is in the Grant Agreement, which required that “based on the proportion of European market authorisations of pharmaceuticals for orphan diseases”, two or three orphan pharmaceutical should be selected for a pilot assessment.²⁰

In terms of the experience from the pilots, EUnetHTA did not provide the companies with an explanation of the choice of the products. The initial products were chosen through a process of discussion between EUnetHTA and the MAH. However, the later products appear to have been chosen because they were going through the market authorisation process (however, it is not possible to verify this from public documents).

In practice, we conclude that EUnetHTA looked for medicines where the MAH was willing to participate to the pilot (some companies were also able to discuss the indication chosen for the pilot with EUnetHTA and this determined the indications reviewed). Two orphan products were selected, and it is believed that they were chosen to satisfy the requirements of EUnetHTA agreement with the European Commission. The reason why particular products were chosen was not made explicit in any of the published report and the MAH was not aware of the rationale for the choice of the products.

2.2.2. Participation of the company

In terms of participation of the MAH, the EUnetHTA work plan and procedure manual does not mention whether the manufacturer’s consent is needed in order to consider a product for a pilot, but in 2012 EUnetHTA suggested that “MAH that have products for which it is foreseen that they will receive market authorisation between 2013 and 2015 [will be] asked to voluntarily participate in these pilots”.²¹

19 As noted above, the Coordinator Team sent a letter to invite participation in the last two pilots. However, it appears that this letter was sent to all the possible candidates for a pilot, given the timing of their marketing authorisation, rather than reflecting an interest of ZIN in a specific topic. In the 6th pilot (excluded from this assessment), the WP5 members indicated their interest in piloting a rapid REA of the new treatment options for Hepatitis C as this would be of high relevance and interest across Europe. Source: EUnetHTA website [last access 28 September 2015]: <http://www.eunetha.eu/news/publication-project-plan-eunetha-wp5-sa-6-rapid-relative-effectiveness-assessment-new-pharmace>

20 EUnetHTA website “Technical Annex of the EUnetHTA JA2 Grant Agreement” [last access 24 August 2015]: <http://www.eunetha.eu/outputs/technical-annex-eunetha-ja2-grant-agreement>

21 EUnetHTA Presentation at ISPOR Berlin 2012: “Will the EUnetHTA model for Rapid Relative Effectiveness Assessment of Pharmaceuticals work?”. Available at [last access 5 September 2015]: http://www.ispor.org/congresses/berlin1112/presentations/ip14_goettsch.pdf

In general, the pilots were “voluntary” with the manufacturer choosing to participate after some interaction with EUnetHTA. Indeed, for the earliest pilots, there was an implicit assumption that the pilot could be stopped during the process by the MAH. However, there is a perception amongst the MAH that the process for agreeing pilots changed after the second pilot. The second pilot appears to have highlighted some concerns with the process (discussed below) increasing the risk from the MAH perspective and making participation more difficult. As a reaction to this, to increase the probability of participation, the threat that the pilots could be undertaken without the participation of the company was emphasised. The letters suggested that a negative response from the MAH could lead to a unilateral assessment. In these cases, the manufacturer voluntarily agreed to participate, although it is difficult to determine if pilots would have proceeded if no manufacturers had “volunteered”.

It should be noted that the JA2 Grant Agreement between EUnetHTA and the EU Commission, signed in 2011, required ten rapid REAs for pharmaceuticals to be produced by 2015.²² In addition, as stated in the EUnetHTA JA2 Work Plan, it was expected to have the rapid REAs “transferred” in about 20 national/regional HTA reports.²³ It is therefore plausible that the EUnetHTA letter “inviting” manufacturers to participate was an attempt to stimulate participation to meet the goals in the Grant Agreement and the Work Plan.

Non-participation

There are also a number of cases where, after some initial interaction, it was agreed not to proceed for a pilot assessment. In some cases, it was the EUnetHTA coordination team that chose not to pursue some pilots. In particular, because:

- In one case, after some discussion between EUnetHTA and the MAH, the EUnetHTA coordination team realised that the product characteristics did not fit with the objective of the pilot process
- In another, it was noted that the intended timeline would have not worked because the marketing authorisation was likely to occur too late for the current pilots
- Finally, some products were deemed “too old” for selection

²² EUnetHTA website “Technical Annex of the EUnetHTA JA2 Grant Agreement” [last access 24 August 2015]: <http://www.eunetha.eu/outputs/technical-annex-eunetha-ja2-grant-agreement>. In the most recent procedure manual this has been changed to seven pilots however.

²³ EUnetHTA WP5 Joint Action 2 (2013), “EUnetHTA Joint Action 2 on HTA 2012-2015, 3-year Work Plan”, May 2013. A detailed analysis and discussion on how the rapid REAs have been transferred in local reports is provided in Section 4.

In other cases, although they were invited to participate to the rapid REAs pilots, some companies declined the invitation. In general, the companies provided justification to EUnetHTA that was accepted (Box 1).

Box 1: Reasons why some companies declined EUnetHTA's invitation to participate to the pilot assessments

Based on the five interviews with companies that did not participate in the pilots, there were a number of reasons why the companies decided against participation:

- Participation was considered to be resource intensive, in some cases companies did not have resources to dedicate to the pilot.
- The risks of a poor review were seen to outweigh any benefit from a good review. This was particularly because the authors were likely to be small HTA agencies and sometimes academic groups. Without any process for encouraging re-use, the key national agencies will not make reference to the report
- The timing of initiating a pilot would have implied that the rapid REA could not have any impact on national submission/accelerating market access

2.2.3. The objective of the pilots

According to the procedure manual, the purpose of the pilots was to produce rapid assessment reports based on cross-border collaboration and to test the usability of the model for rapid REA including guidelines.²⁴ There was no discussion of whether the specific objectives of each pilot needed to be explicitly described.

In practice, the objectives were made explicit in the early pilot.²⁵ In particular, the objectives of the first pilot focused on three issues:

- Testing the value of the EUnetHTA as a collaborative project:
 - Internal value: whether the EUnetHTA project worked and whether an assessment could be completed within a timeframe that is competitive with that of national assessments
 - External value: the re-usability of the assessment
- Testing the methodology
- Having a “pilot within a pilot”: in parallel have an assessment for reuse of EUnetHTA report at national level in the Netherlands.

²⁴ EUnetHTA WP5 Joint Action 2 (2015), “Procedure manual WP5 Strand A: Rapid Relative Effectiveness Assessment of Pharmaceuticals”, V4 April 2015

²⁵ Manufacturer communication to CRA

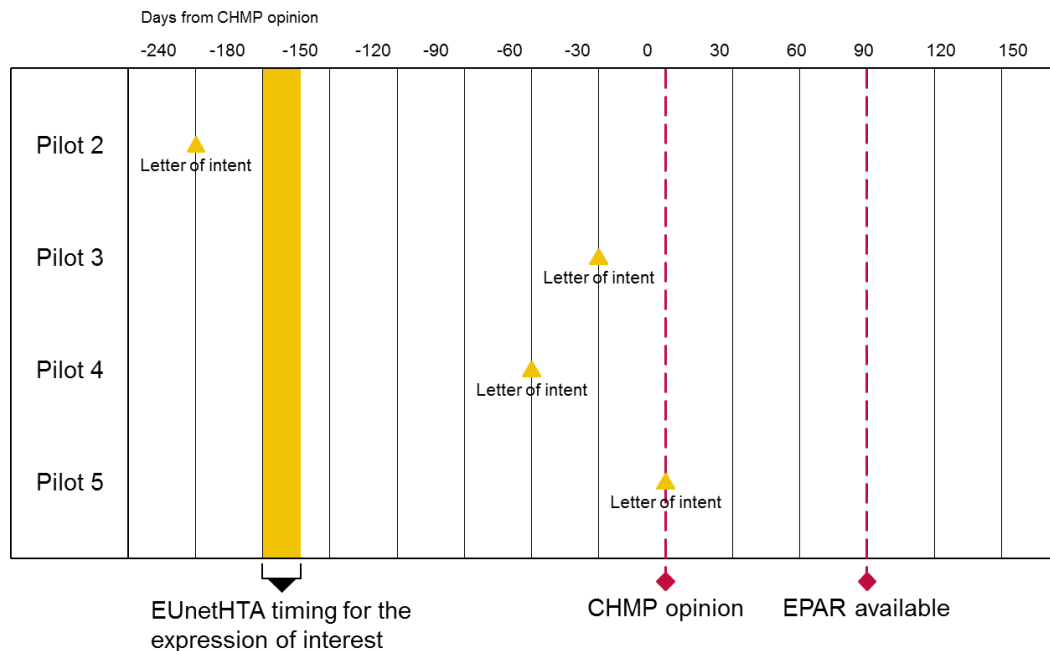
There is no evidence of a discussion regarding the goal of the pilot in any of the future pilots. In particular, the MAH was unclear if the pilot was intended to test any particular issues associated with the type of product or how the process had changed based on the experience of previous pilots.

2.2.4. Timing

To meet the EUnetHTA timeline the expression of interest should occur about 180 days before the CHMP opinion is issued.

In practice, the expression of interest (measured by the date a formal letter of intent was sent to EUnetHTA) varied from 237 days to 0 days before the CHMP opinion (Figure 5). In the second pilot, the letter of intent was in line with the EUnetHTA timeline. In the later pilots the letter of intent was sent between 0 and 60 days before the CHMP opinion. It was clear to the companies involved that starting a pilot so close to CHMP opinion meant that it was not possible to test the ability of EUnetHTA to deliver alongside the EMA timeline and, consequently, it was inevitable that the publication would not occur as intended to allow national re-use. The companies reported that EUnetHTA proceeded anyway given the desire to complete a given number of pilots.

Figure 5: Timing of the expression of intent



Note: Pilot 1 is not included in this analysis as the product received European Regulatory approval in 2006 but was only commercialised in 2012/2013 due to delays with the manufacturing process. Thus an analysis of timing with regards to CHMP opinion and EPAR availability would not draw meaningful conclusions.

Source: CRA analysis

2.2.5. Lessons regarding the initiation of the pilots

There are a number of lessons that can be learnt from this phase:

- From the outset participation was intended to be voluntary. This was welcomed by the industry. However, in practice some pressure was applied to participate and the possibility of undertaking pilots without the company's participation increased. This meant companies participated to prevent a pilot being undertaken without their participation rather than because the product represented a good product to pilot the process.
- The overall goal of the pilots is stated explicitly but there is still confusion. It is unclear if usability refers to *using* the model or *using* the results of the pilot. In reality, it would appear the primary aim was to test the process rather than test its re-use. However, this is complicated by having a target number of re-uses and publishing re-use on the website. If the focus on the process had been clearer participation from the companies might have been considerably less challenging and the choice of authors would have been less of an issue (discussed below), making initiation more straightforward. As the team from the MAH have to justify the use of scarce resources internally, often when the company is focused on launching an important new product, absolute clarity on the goal would have been beneficial. A greater level of transparency on this would help improve participation and collaboration.
- The goal of particular pilots was not explicit. There was little clarity regarding if products were chosen because they were orphan medicines, because they represented a product with a second indication, they were a vaccine, or if they were chosen on methodological grounds, for example because they would test guidance on indirect comparisons, or composite end-points. Understanding the goal and motivation for choosing the product can make participation more attractive to the companies.
- Clearly, starting the process on time is crucial if the publication of the REA report is to be aligned with the EPAR process. The original plan was for the published report to occur soon after the publication of the EPAR, presumably to increase the potential for re-use. Given the timing of the last three pilots, testing this part of the process was clearly de-prioritised. However, this was not made explicit.
- The objective of delivering 10 rapid REA reports within JA2 timeframe has proved to be unfeasible. Given the EUnetHTA timeline, the tenth pilot should have started before June 2015 to achieve this goal. For any future pilot process it will be important to consider how many pilots can realistically be completed within the given timeframe to ensure that all the main objectives (e.g. alignment with the EMA process, re-use and completion of the number of the pilots established in the Grant Agreement) are achieved.

2.3. Activities prior the scoping meeting

There are three important aspects to be analysed regarding the phase between the expression of interest and the scoping meeting:

- The selection of the pilot team
- The guidance in the draft submission
- The (possibility of a) meeting prior to the scoping meeting.

2.3.1. Selection of the pilot team

According to the EUnetHTA procedure manual,²⁶ after collecting an expression of interest, the Coordination Team will send a request for authorship to all WP5 members. A team of a (first or lead) author, one co-author and 2-5 dedicated reviewers will be selected from all members of WP5 STRAND A (authoring organisations will be identified based on their expression of interest). In cases where there is more than one organisation willing to lead the pilot, selection will be made on the experience of appointed authors and co-authors and willingness of a participating organisation to take up this assessment in their national/local assessment. The specific roles and tasks of team members are:

- For first authors: have a leading role in both main phases of the pilot project (scoping and production of the pilot). They are responsible for management of the pilot and together with co-authors take active part in its production
- For co-authors: play supportive role during scoping phase and take active part in production of pilot REAs
- For dedicated reviewers: play supportive role in both phases of the project (scoping and production of pilot REAs).

In general, the manufacturers were able to suggest authors and there was some discussion regarding the ultimate choice. In particular, after the manufacturers expressed their formal interest in participation (letter of intent), initial discussions with the Coordinating Team also covered the process for the choice of the authors and the MAH's preferred agencies.

In practice, the experience with author selection was heterogeneous across pilots and the process became more formal and less open:

- Initially, there was significant discussion between the Coordination team and the MAH regarding the choice of author.
- In the majority of pilots, and in line with the procedure manual, the final decision about the authors was ultimately made by EUnetHTA (and in most cases, the agencies nominated by the manufacturer were not chosen)
- In some cases, the manufacturer had significant influence on the choice of authors (as only some countries would ultimately assess the product) and were significantly involved in the selection.

However, in reality the choice has been significantly constrained by the availability of the agencies (e.g. for summer time or Christmas closure). In line with the procedure manual, in four pilots, two authors were selected; in one case, three authors were involved (Table 3).

26

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

Table 3: Composition of the pilot teams

Pilot	Author	Co-author
1	ZIN (national HTA agency in the Netherlands)	A. Gemelli (Italian hospital conducting HTA and advising regional coverage decisions)
2	FIMEA (Finnish Medicines Agency producing and collating evaluations of therapeutic and economic value)	AAZ (national HTA agency in Croatia) Regione Veneto (regional HTA agency in Italy)
3	AIFA (national HTA agency in Italy)	IMFARMED (national HTA agency in Portugal)
4	NOKC (Norwegian HTA centre providing reports to the national Medicine Agency, NoMA)	AAZ (national HTA agency in Croatia)
5	HAS (national HTA agency in France)	Ministry of Health (national HTA agency in Slovakia)

Source: CRA analysis from EUnetHTA rapid REA pilots

In terms of timing, the choice of the authors has been discussed informally between the MAHs and the coordinator early in the process (i.e. after the expression of interest). However, it was noted that deciding on authors significantly delayed the scoping meeting for early pilots, and this has possibly reduced the willingness of EUnetHTA to dedicate some time for an open discussion.

In terms of division of tasks, the authors covered the different roles as suggested in the procedure manual, with the lead author being the more experienced agency. However, in only three pilots the author was one large HTA agencies (ZIN, AIFA, HAS), while the co-author always was a smaller agency. In general, the manufacturers expressed concern when the authors were not experienced in undertaking HTA and/or involved in national HTA processes. In one case it was necessary to subcontract part of the analysis to a separate institute specialised in HTA.

The roles of lead and co-author were not made explicitly known to the manufacturers, although they were inferred in the majority of the cases. It was also noted that the division of the tasks reflected the interest/competency of the individuals involved and that, in some cases, the apparent division of labour changed through the pilot and the 'senior' partner took over more the assessment.

As for the dedicated reviewers, these were chosen by EUnetHTA without consulting the manufacturers. The manufacturers noted that reviewers mainly focused on providing feedback on the first draft version of the rapid REA and showed limited involvement in the pre-scoping and scoping stages.

2.3.2. Guidance on the draft submission

According to EUnetHTA, the manufacturer should provide a draft submission file to the authors before the positive opinion of the CHMP. This document should provide authors with the information about the topic under assessment and whenever possible the first report of the CHMP. The dossier is intended to serve for further preparation of the scoping meeting.²⁷ A template has been provided to provide information on what should be submitted. Importantly, the submission template is being elaborated in parallel by EUnetHTA WP7 SG4 and a final version is expected to be available in October 2015.²⁸

In practice, given that the final submission template was still under development and was not tailored to highlight the level of detail and the type of information to include, the companies relied on the guidance documents provided by EUnetHTA. These were found to be useful and provided considerable help in how the evidence should be presented. However, there was little clarity on different aspects:

- The PICO (Patient, intervention, comparator, outcomes) structure
- The methodology for analysis
- The expectations of the EUnetHTA/authors

In the later pilots, the template provided significantly more structure on what was required. In addition, in some pilots the authors provided some informal guidance on the relevant sections of the template to be filled in after the Coordination Team suggested this.

In reality, the MAH submitted an extensive submission prior to the scoping meeting. This included analysis on the basis of the patient population, indication, comparator, outcomes. Given that the current scoping only leaves approximately four weeks to the manufacturer to make any changes, the MAH must submit a near complete draft report without any reassurance on whether the underlying assumptions are appropriate according to the authors.

2.3.3. The possibility of discussing methodological issues prior to the scoping meeting

The EUnetHTA process does not consider any formal meeting between the authors and the manufacturers before the scoping meeting.

In practice, there have been some pre-scoping (informal) interactions between the coordinator and the manufacturers within the first 90 days of the process since its initiation. This was particularly the case in the first pilot. In general, these discussions were intended to discuss the authors and the REA timeline. It was not possible to discuss substantive elements of the methodology, i.e. the choice of comparators, the primary outcomes, or the type of comparison.

²⁷ EUnetHTA WP5 Joint Action 2 (2015), "Procedure manual WP5 Strand A: Rapid Relative Effectiveness Assessment of Pharmaceuticals", V4 April 2015

²⁸ EUnetHTA webpage [last access 25 August 2015]: https://eunetha.fedimbo.belgium.be/sites/5026.fedimbo.belgium.be/files/Manufacturer%20submission%20templates_information%20leaflet.pdf

In the third pilot, the Coordination Team also provided some guidance on what should be included in the submission and the part of the template that were most important. However, in the other pilots it was not possible to discuss methodological issues prior to the scoping meeting.

2.3.4. Lessons regarding activities prior to the scoping meeting

There are some lessons that can be learnt about the phase preceding the scoping meeting:

- The submission template, which was still under development in the first pilots, has provided some guidance in the later submission. However, given the final version of the template has not yet been provided and tested, there is a scope for improvement and further testing. In particular, there is a concern that the template collates all the potential questions that HTA agencies request rather than focusing only on common issues that should be discussed in the rapid REA.
- The choice of authors caused considerable concern for MAH during the author selection. In particular, concern was raised about the role of HTA agencies that were not commonly involved in national HTA processes. In practice, manufacturers were able to submit suggestions but due to a number of reasons (including interest and resourcing) the suggestions were rarely influential but did delay the process. The process for the choice of the authors can be improved:
 - Starting the pilot on time to meet the intended timeline means there is less pressure on agreeing authors and planning would allow the capacity of authors to be taken into account. This would prevent predictable issues such as authors lack of availability (summer period, Christmas) affecting the process and avoid unnecessary delays in the process
 - More transparency on the different roles of the authors would help manufacturers identifying those responsible for each section of the report and reduce their concerns regarding the less experienced HTA agency.
 - Ideally, dedicated reviewers should be more involved in the earlier stages of the pilot to avoid discrepancies during the assessment
 - However, if the overall process and methodological issues are improved, choice of author would be a smaller issue in the future.
- In practice the MAH is submitting a full submission prior to the scoping meeting. We conclude it would be beneficial to all stakeholders to have a project alignment meeting between the manufacturer and the authors prior the draft submission to facilitate the scoping process and have a high level discussion of methodological issues. This should be tested in the next pilots and, unless it is proved to be detrimental, it should be included into the rapid REA process.
 - The industry would appreciate more guidance earlier in the process regarding the scope of the assessment. The current scoping meeting happens too late in the process, leaving only approximately two weeks to the manufacturer to make any changes

- In particular, it is important for the industry to ensure that the submission addresses the correct questions, using the appropriate evidence and methodology, before the submission is drafted and not when it is nearly finalised
- Some informal guidance was provided by the coordinator across the pilots, but this should be formalised (and the role of the coordinator strengthened). As the authors are changing from pilot to pilot there is a risk that the lesson learnt in some pilots about the value of some interaction within the pre-scoping period will be lost. This is even more likely given the lack of a formal feedback process.

2.4. Scoping meeting

There are three important aspects to be analysed regarding the scoping meeting:

- Agreeing the scope
- The timing of the scoping meeting
- The finalisation of the submission dossier.

2.4.1. Agreeing the scope

According to the procedure manual, the face-to-face scoping meeting is intended to discuss the manufacturer's REA submission file following the so-called PICO structure. In addition, information regarding the CHMP opinion and the first report of CHMP is expected to be shared by manufacturer as early as possible.²⁹ According to the EUnetHTA timeline, this meeting should happen about 90 days before the CHMP opinion is issued.

In practice, the scoping meeting was divided into two sections to discuss:

- the PICO of submitted dossier
- the completeness of the dossier and the need for additional data.

The discussion was structured around the four domains in the HTA Core Model for Rapid REA of pharmaceuticals (health problem and current use of the technology, description and technical characteristics, clinical effectiveness, safety),³⁰ which also define the main sections of the assessment report.

A significant issue was completeness. Where guidance by the EUnetHTA Coordination Team had been provided prior to the scoping meeting, it was also noted that this was not necessarily respected by the authors. For the majority of pilot assessments, the authors requested additional data (e.g. safety data, data to justify comparator) or additional data analysis (indirect

²⁹ EUnetHTA WP5 Joint Action 2 (2015), "Procedure manual WP5 Strand A: Rapid Relative Effectiveness Assessment of Pharmaceuticals", V4 April 2015

³⁰ EUnetHTA WP5 Joint Action 2 (2013), "HTA Core Model for Rapid Relative Effectiveness Assessment of Pharmaceuticals, V3.0 March 2013".

comparisons, alternative outcomes) during these discussions. Manufacturers have been able to discuss these requests and in some cases the authors agreed that additional data were not necessary. When necessary, manufacturers fulfilled these requests although, in certain instances, they found in retrospect that the additional data were not used in the assessment.

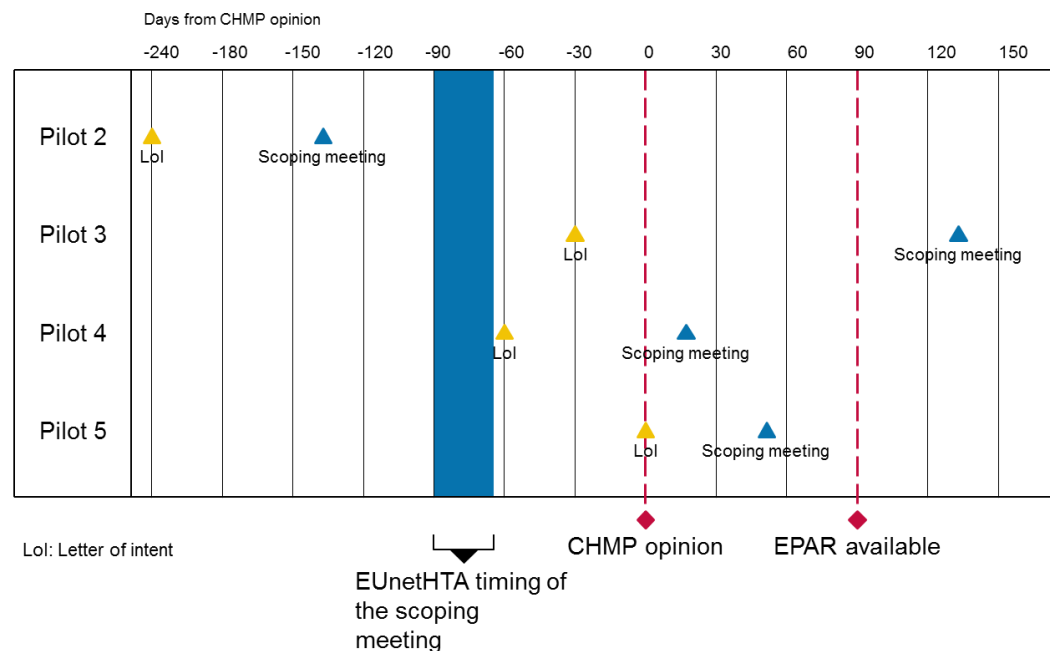
In terms of preparedness of the authors the manufacturers felt that the authors were insufficiently prepared for scoping meetings and that in certain instances they had not formed opinions on the relevant and necessary comparators or the appropriate types of analyses. It has been recognised that the authors did not seem to have sufficient time for preparation: in general, they had 18-36 days to read the draft submission file and prepare for the scoping meeting.

It has also been noted that while the scoping meeting was initially an informal roundtable discussion with relatively little structure, it has evolved during the subsequent pilots into a more formal meeting.

2.4.2. Timing of scoping meeting

In terms of timing, only one scoping meeting was held more than 90 days prior to the CHMP opinion (as it is intended by EUnetHTA process). All the other scoping meetings were held 18-133 days after the CHMP opinion was provided. In the later pilots, the delay of the scoping meeting with respect to the EUnetHTA timeline (with the CHMP opinion as a reference point) reflected the fact that the pilot initiated later than recommended (Figure 6). The scoping meeting usually happened between 50 and 80 days after a formal interest was expressed (with one exception, when the scoping meeting was set more than 150 days after the letter of intent in common agreement between the manufacturer and the authors [pilot 3]).

Figure 6: Timing of the scoping meeting



Note: Pilot 1 is not included in this analysis as the product received European Regulatory approval in 2006 but was only commercialised in 2012/2013 due to delays with the manufacturing process. Thus an analysis of timing with regards to CHMP opinion and EPAR availability would not draw meaningful conclusions.

Source: CRA analysis

2.4.3. The finalisation of the submission dossier

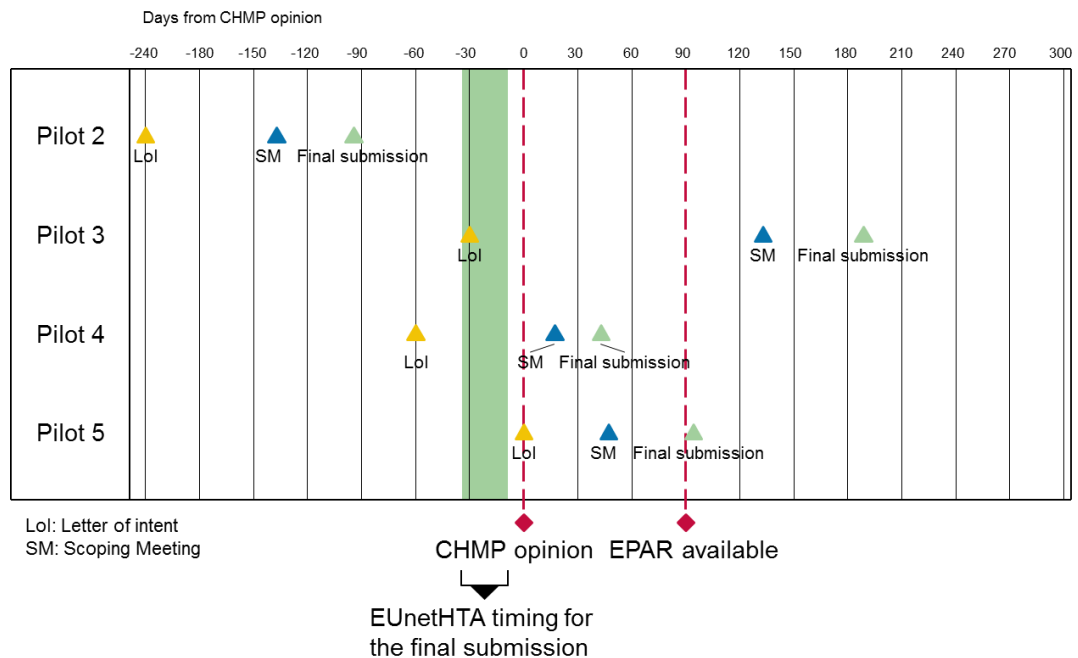
According to the procedure manual, authors are supposed to send their feedback on the draft submission file to the manufacturer within two weeks (14 days) after the face-to-face scoping meeting. The final submission file from the manufacturer is expected within a further four weeks (28 days). If the EUnetHTA timeline is met, this would imply that the final dossier is submitted before the CHMP positive opinion is issued. The final project plan should be elaborated by the authors and shared with the Coordinating Team, the reviewers and the manufacturer within 49 days from the scoping meeting.³¹

In practice, the scoping process has generally been completed within the scheduled timeframe from the scoping meeting (i.e. within 49 days): in three pilots the final submission happened less than 40 days after the scoping meeting, in one pilot there was no significant delay (the submission was 60 days after the scoping meeting) and only one final submission was done 100 days after the scoping meeting. Although the feedback on the draft submission generally took a week longer than the proposed EUnetHTA procedure schedule (i.e. three weeks instead of two), where there were delays, this was often due to holiday periods.

However, it is also important noting that, given the delay accumulated since the beginning of the pilot, the final submission occurred before the issue of the CHMP opinion (as it is intended in the EUnetHTA timeline to have rapid REA reports published shortly after the EPAR) in only one case (Figure 7).

31

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

Figure 7: Timing of the final submission

Note: Pilot 1 is not included in this analysis as the product received European Regulatory approval in 2006 but was only commercialised in 2012/2013 due to delays with the manufacturing process. Thus an analysis of timing with regards to CHMP opinion and EPAR availability would not draw meaningful conclusions.

Source: CRA analysis

2.4.4. Lessons regarding the scoping meeting

There are some main lessons from the scoping phase:

- The content and the timing of the scoping meeting can be improved:
 - The lack of author preparedness in the scoping meeting detracts from discussion and can lead to inappropriate requests for additional data or data analyses. This probably reflects the delay in the decision on the authors
 - A separation of the discussion on scope (in the project alignment meeting) from the discussion on completeness of the evidence (in the scoping meeting) would improve the process. The minutes of the project alignment meeting would also ensure more consistency between the advice provided prior to the scoping meeting and the discussion on evidence completeness
 - An *a priori* confidentiality agreement (i.e. at the time of initiation of the pilot) would accelerate the provision of confidential data without the need to discuss this during the scoping phase. For instance, a clear understanding of the information required from the EMA submission and a confidentiality agreement between EUnetHTA and the manufacturer could accelerate timelines if defined at the beginning of the process
- The scoping meeting is seen as important (although occurring too late in the process):

- The meeting minutes were important and dictated the changes to the draft submission
- The project plan was useful in terms of setting out deadlines and the process that followed the scoping meeting. However, this is being agreed late in the process. It would be better if this was agreed earlier in the process (possibly immediately after the project alignment meeting) and included both the manufacturer's and the EUnetHTA's commitments. This would mitigate the risk of unnecessary delays (for instance, by planning to account for holiday periods)
- The final timelines discussed with the manufacturer and other involved parties at the scoping meeting were challenging for the companies. It is particularly problematic when there are additional data requests to fulfil in a 28 day period.

2.5. Assessment

From the manufacturer's perspective, the process during the assessment primarily affects the authors and the reviewers and is difficult to observe. However, there are two important aspects to be analysed regarding the assessment:

- The role of the parties involved and their interactions
- The timing of the assessment

2.5.1. The role of the parties involved and their interactions

According to the procedure manual, the roles of the different parties are:

- the first author and the co-author draft the report, addressing the comments received by the other stakeholders
- the pool of dedicated reviewers review the authors' version providing comments
- a medical editor, providing an editorial revision.³²

The manufacturer, the other WP5 Strand A members not involved in the pilot and other stakeholders are allowed to comment on a version of the draft that incorporates the comments from the reviewers and the editorial review.

In terms of commenting on the draft, the experience of those involved in the pilots is consistent with the EUnetHTA process. However, in one case, the pilot involved three authoring agencies (due to the complexity of the assessment) and it was also necessary to subcontract part of the analysis to the Dutch Institute for Medical Technology Assessment. In addition, in the early pilot, the editorial review happened before the reviewers commented the authors' version, but this has changed in the subsequent pilots in line with the EUnetHTA intended process. The manufacturer and other WP5 Strand A members provided their comments to the revised version as intended, with all the reviewers (authors, WP5 members, and the manufacturer) providing comments via a template that is published in rapid REA reports. In general, after the

32

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

last set of comments was incorporated/addressed by the authors, the report was published with no opportunity for the manufacturer to view and comment on the final version (although in one case the manufacturer was given the opportunity to view the final draft but only three days before the publication).

In terms of other interactions involving the manufacturer, across almost all the REA pilots the manufacturers did not have any direct correspondence with the authors until their opportunity to comment (in one case, the national affiliate corresponded directly with the authors). In special circumstances where authors/reviewers have questions for the manufacturer, the coordinator mediated the communication between the authors and the manufacturer. This largely worked satisfactorily from the MAH perspective.

2.5.2. The timing of the assessment

The EUnetHTA timeline for the assessment can be looked at in two different ways:

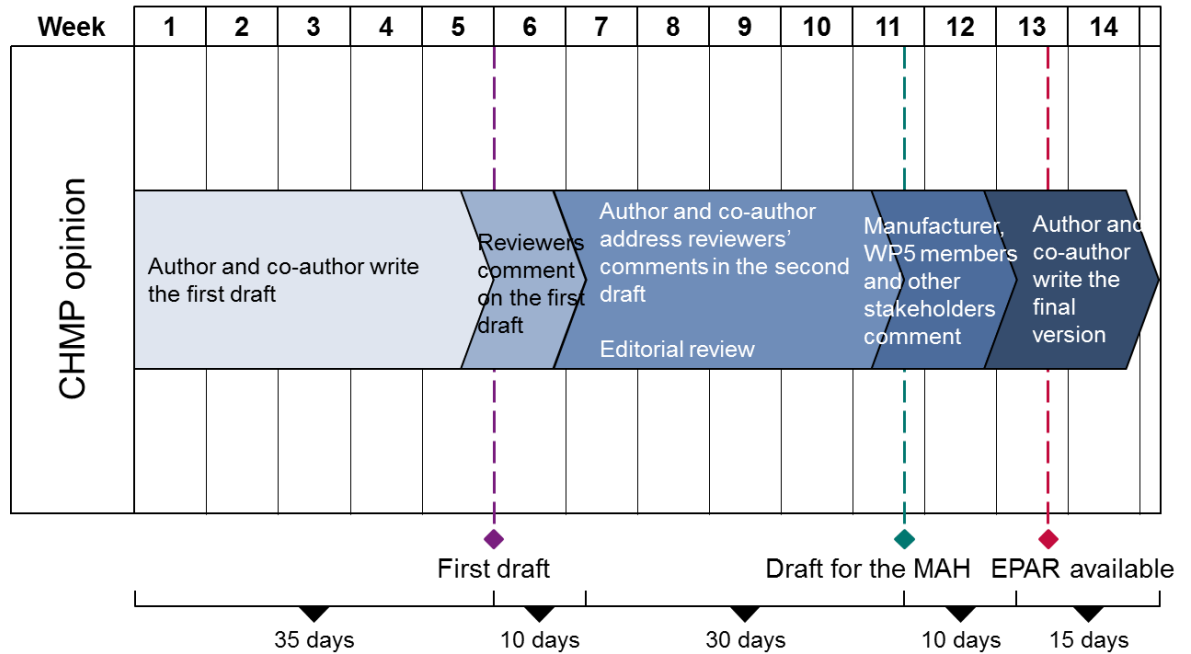
- The CHMP opinion (and the EPAR publication), which could be considered the reference point that is most relevant to allow the intended re-use
- The scoping face-to-face meeting, which could be considered the reference point that is most relevant to verify whether authors can collaborate and produce a *rapid* REA,

If the planned timeline is followed from the beginning of the pilot, the assessment should begin immediately after the CHMP opinion is issued. In addition, it is assumed that the EPAR will be available at day 90 of the assessment, allowing the authors to check (and possibly account) for changes with respect to the CHMP opinion. It is worth noting that according to the EMA, the publication of the EPAR 'takes around two months following the adoption of the EMA scientific opinion'.³³ Hence, it is likely that the EPAR publication happens less than 90 days after the assessment is started.

According to the procedure manual, the authors should start writing the first draft report 49 days after the scoping face-to-face meeting and complete it in five weeks (35 days). The reviewers would have then 10 days to provide comments. After this, there are 30 days for the authors to write a second draft based on the comments from the reviewers and for editorial review. The manufacturer, WP5 Strand A member and other stakeholder have 10 days to comment on the second draft. Finally, the authors have 15 days to respond to the comments and publish the final version.

If the EUnetHTA timeline for the two reference points is met, this means that the final report is published about 100 days after the CHMP opinion is issued. (Figure 8).

Figure 8: Assessment timeline from EUnetHTA perspective



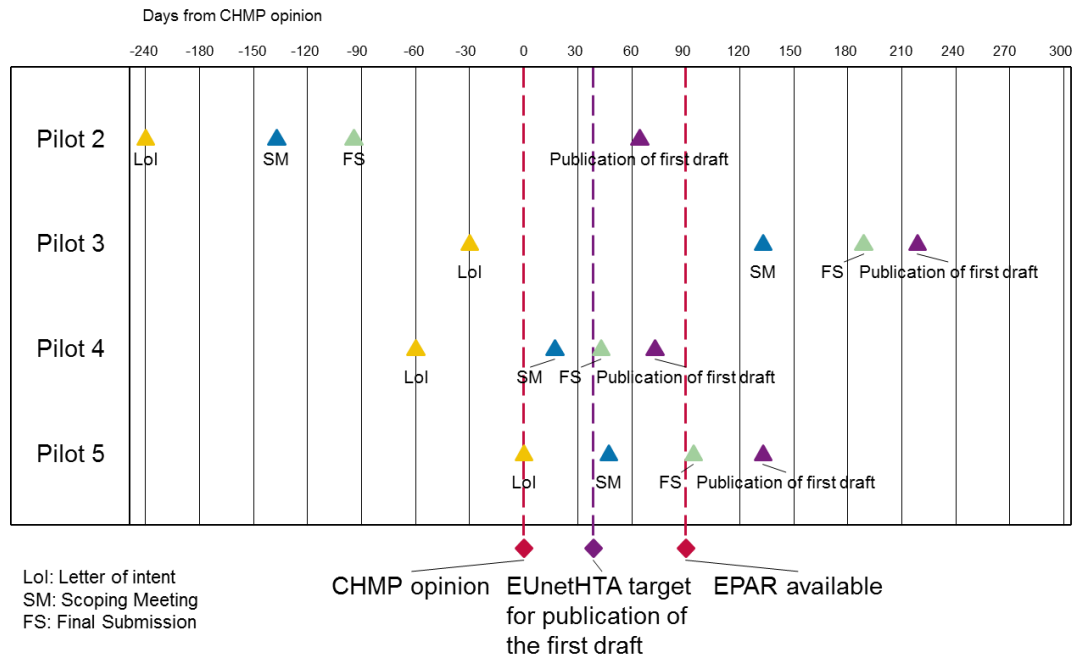
Source: CRA analysis

In practice, the timeline for the scoping phase was not aligned with the CHMP opinion in three pilots and this automatically implied that the assessment phase was delayed with respect to this reference point.³⁴ In addition, for the only pilot that completed the scoping phase within the targeted timeframe, the assessment phase was delayed by the Coordinating Team/Authors (the reason for this is unclear although one possible cause is that there was a lack of clarity about the confidential information from the EPAR requested by the authors and the need for discussions between the MAH and EUnetHTA). Therefore, the first draft of the report was always completed by the authors with some delay (ranging between 25 and 185 days) with respect to EUnetHTA timeframe referring to the CHMP opinion (Figure 9).

34

This statement does not consider Pilot 1, as it was not an objective to align the EUnetHTA process to the regulatory process.

Figure 9: Timing for the publication of the first draft with respect to the CHMP opinion

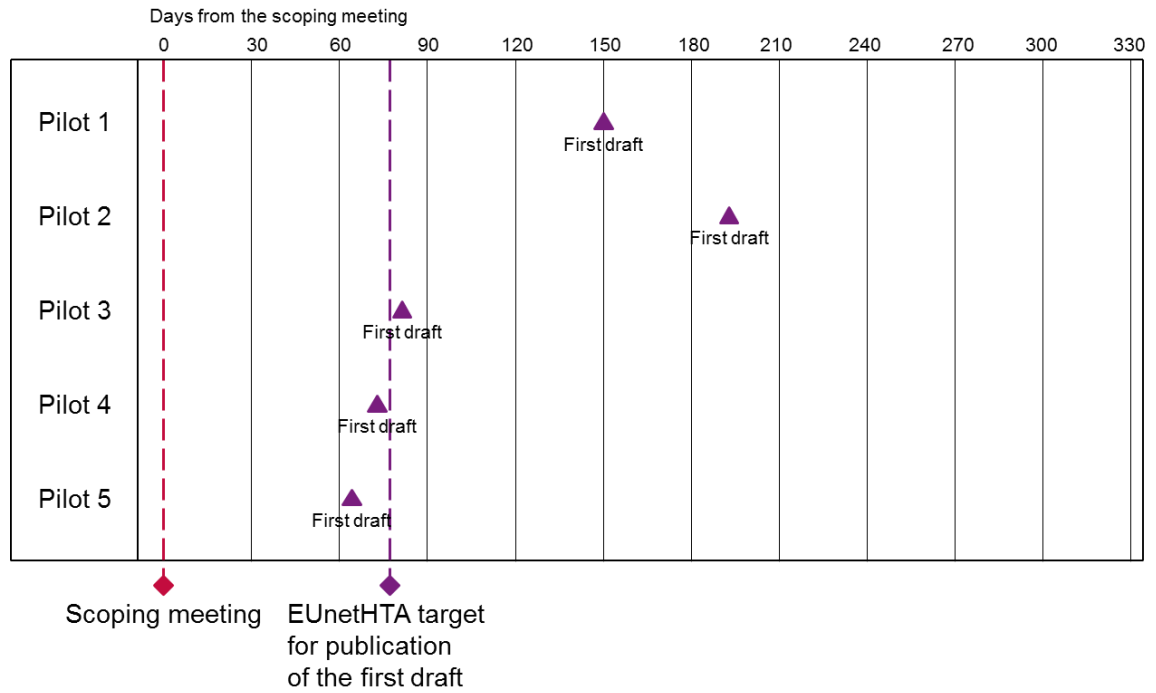


Note: Pilot 1 is not included in this analysis as the product received European Regulatory approval in 2006 but was only commercialised in 2012/2013 due to delays with the manufacturing process. Thus an analysis of timing with regards to CHMP opinion and EPAR availability would not draw meaningful conclusions.

Source: CRA analysis

The experience is more positive when referencing to the scoping meeting: for the later three pilots the first draft was made available within the scheduled timeframe (Figure 10) and for pilot 2 the delay with respect to the scoping meeting was due to the delayed publication of the EPAR.

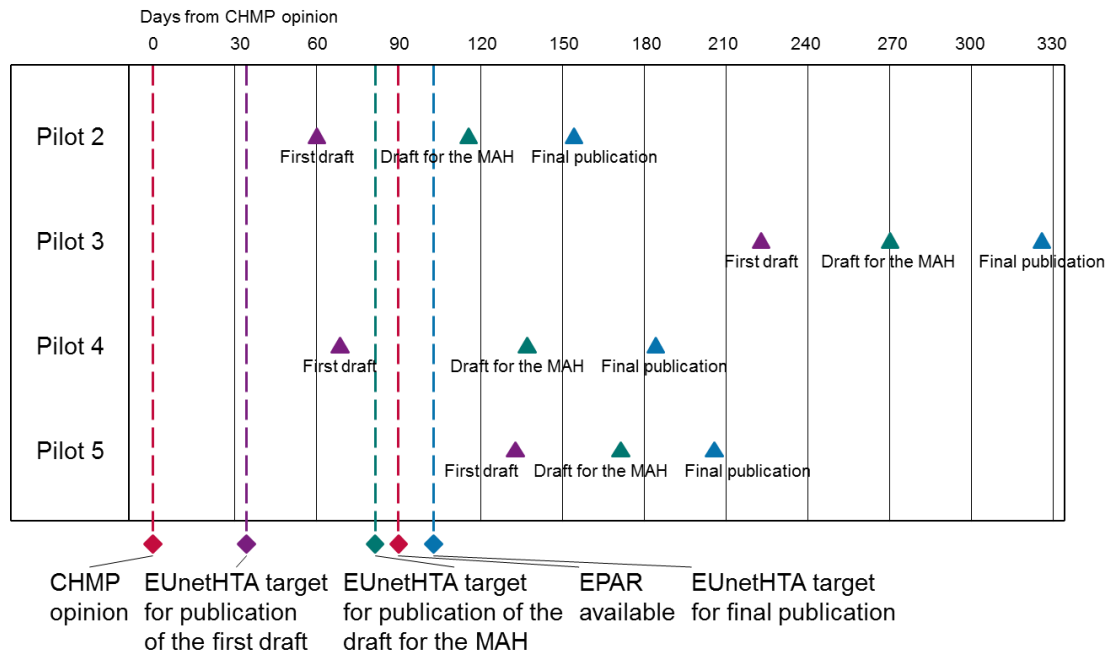
Figure 10: Timing for the publication of the first draft with respect to the scoping meeting



Source: CRA Analysis

The delays accumulated with respect to the CHMP opinion target were also reflected in the next steps of the assessment. The draft for comments of the manufacturer was always made available beyond the EUnetHTA deadline (approximately 30-270 days). Similarly, the final publication happened with a considerable delay with respect to the target (Figure 11).

Figure 11: Timing of the assessment process with respect to the CHMP opinion



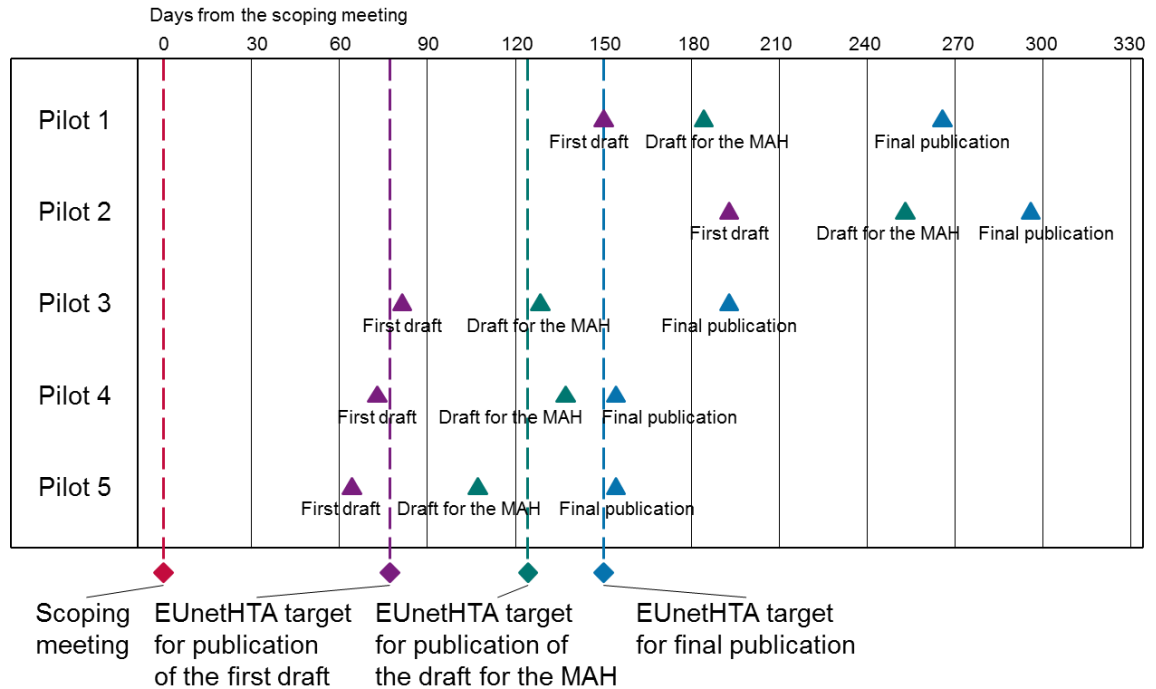
Note: Pilot 1 is not included in this analysis as the product received European Regulatory approval in 2006 but was only commercialised in 2012/2013 due to delays with the manufacturing process. Thus an analysis of timing with regards to CHMP opinion and EPAR availability would not be meaningful.

Source: CRA analysis

The actual timelines for the assessment were more consistent with the target when referencing to the scoping meeting. However, only in the later pilots the version for comments of the manufacturer and the other WP5 members and final publication were in line with the EUnetHTA process (Figure 12). When a pilot did not meet the EUnetHTA timing, this can usually be attributed to an agreed project plan. This is a possibility also considered in the procedure

manual: in particular, EUnetHTA recognises that there is a high possibility of divergence from their timeline, for instance when doing pilots with products that are already on the market.³⁵

Figure 12: Timing of the assessment process with respect to the scoping meeting



Source: CRA analysis

2.5.3. Lessons regarding the assessment

There are some lessons from the assessment phase:

- Following the scoping meeting, the process timetable was largely adhered to. Although difficult for the MAH to assess, it appears that the division of the responsibilities between the authors worked well and used the capabilities and resources of the authors.
- However, for re-use the reference to EPAR timeline is more important and this was not met. Even if the EMA approval timeline is met, in the current environment, the publication of the rapid REA report immediately after the EPAR would be incompatible to allow re-use

35

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

in markets where the national assessment begins before the EPAR is published (e.g. the UK).³⁶

- There was not any opportunity for external stakeholder (i.e. patient associations and physicians) to input in the pilot assessments.
 - The perspectives of patients and physicians would provide useful insight for the assessment. However, it should be considered how the additional complexity this add to an already complex process can be managed.

2.6. The process post publication

Once the report is finalised and the comments incorporated, there are a number of additional steps

- the report is published
- feedback to the EUnetHTA coordinator team could be provided regarding the lessons learnt.

2.6.1. Publication of the report

There are no specific indications from EUnetHTA on how the final report should be published and disseminated. The only mention in the procedure manual says that “authors, dedicated reviewers and other WP5 members [should] put their efforts into adaptation pilot REA into national/local REAs”.³⁷

In practice, REA reports have been published on the EUnetHTA website and a newsletter was sent to EUnetHTA members to inform them about the publication (although this was not transparent to the manufacturers).

2.6.2. Feedback on the pilot process

In terms of steps post-publication, it has been noted that there is no provision for a formal feedback discussion between the manufacturer and the coordinator, although this has occurred in practice (in general, feedback was provided informally, for instance in discussions during conferences). In some cases, the MAH requested to schedule a formal feedback/debrief session, which was eventually scheduled by the coordinator some months after the pilot completion (two debrief meetings already happened and the MAH was able to highlight the main issues from its experience with the pilot).

For the feedback sessions that took place, there were meeting notes setting out the lessons that were shared with the MAH, however, it has also been noted that the lessons from the pilots are not published or documented and manufacturers are unclear how lessons are

³⁶ This issue is discussed in greater detail in Section 4.

³⁷ EUnetHTA WP5 Joint Action 2 (2015), “Procedure manual WP5 Strand A: Rapid Relative Effectiveness Assessment of Pharmaceuticals”, V4 April 2015

communicated to new authors (although EUnetHTA coordinators are likely perform this role) or other stakeholders.

However, recently, a formal feedback survey was sent by the Coordination Team to the MAH. The survey looked for feedback on the experience with: the domains, the summary, the use of the report, the submission file and the procedure. It is expected that the feedback will inform the future improvement of the process but it still unclear how these lessons will be shared.

2.6.3. Lessons regarding the process post publication

There are two main lessons about activities that could occur after the publication:

- A post-publication feedback/debriefing would help to ensure that a manufacturer's view is discussed for incorporation in subsequent pilots. The lessons should be published so that future authors and MAH can draw on this and improve the process. This is particularly important as the authors have changed from pilot to pilot.
- A follow up meeting (after the publication of the pilot rapid REA report) could help to verify how the report has been considered/included into the national HTA process.

3. Methodology and outcomes of the pilot

This chapter looks at the methodology applied in the five rapid REA pilots and the resulting conclusions. This draws on a second set of interviews with MAHs, the rapid pilot reports and the comments provided by MAH and the reviewers.

This chapter is structured according to the four domains of the REA report.³⁸ For each domain, we compare the methodology recommended by the HTA Core Model for rapid REA^{39,40,41} and the nine EUnetHTA methodology guidelines⁴² to the methodology used in each of the pilots. We then summarise the lessons learned.

3.1. Health problem and current use of technology

According to EUnetHTA HTA Core Model for Rapid REA guidelines, this domain has the objective of qualitatively defining the “target conditions and groups” and describing the “condition’s epidemiology and the availability of technologies in question”.^{43,44} Specifically, this section should provide “background information” such as the pathophysiology, natural history, and currently available methods for screening, diagnosing, and available technologies of the condition. Where the technology to be assessed is specified for a subgroup or a special indication, there should be adequate description for these.⁴⁵

38 We order these according to the more recent reports: Health problem and current use of technology; description and technical characteristics of technology; clinical effectiveness and safety. In the first pilot safety came before clinical effectiveness.

39 Versions 1 and 2 of the procedure manual are not publically available. Version 3 and 4 are included as both were available when the rapid REA pilots were undertaken. Version 3 was available in 2013 when Pilots 1 and 2 were started while version 4 was available for the later pilots only.

40 EUnetHTA WP5 Joint Action 2 (2013), “Procedure manual WP5 Strand A: Rapid Relative Effectiveness Assessment of Pharmaceuticals, V3.0 March 2013”.

41 EUnetHTA WP5 Joint Action 2 (2015), “Procedure manual WP5 Strand A: Rapid Relative Effectiveness Assessment of Pharmaceuticals, V4 April 2015”.

42 There are 9 EUnetHTA methodology guidelines – Choice of comparator; Clinical endpoints, Composite endpoints, Surrogate endpoints, Health – related Quality of Life; Direct and indirect comparisons, Safety, Internal Validity, and Applicability. EUnetHTA website [last access 28 August 2015]: <http://www.eunetha.eu/eunetha-guidelines>

43 EUnetHTA (2015), ‘The HTA Core Model ® for Rapid Relative Effectiveness Assessments version 4.1.’ Available at [last access 27 August 2015]: <http://www.eunetha.eu/news/final-version-hta-core-model-and-methodological-guidelines-rapid-rea-pharmaceuticals-now-availa>

44 EUnetHTA (2013), ‘The HTA Core Model ® for Rapid Relative Effectiveness Assessments version 3.’ Available at [last access 27 August 2015]: <http://www.eunetha.eu/news/final-version-hta-core-model-and-methodological-guidelines-rapid-rea-pharmaceuticals-now-availa>

45 EUnetHTA (2013), ‘The HTA Core Model ® for Rapid Relative Effectiveness Assessments version 3.’ Available at [last access 27 August 2015]: <http://www.eunetha.eu/news/final-version-hta-core-model-and-methodological-guidelines-rapid-rea-pharmaceuticals-now-availa>

Based on the interviews with industry their experience for this domain was largely positive. The description presented in the assessment was generally in line with the manufacturer's expectations. The descriptions of the health problem and existing treatment derived largely from the manufacturer submission.

Regarding the indicated population, the majority of MAHs were in agreement with the populations specified. However, in pilot 1, there was some disagreement over the appropriate definition of the population and whether this reflected a 'European' perspective on the use of the medicine. The manufacturer wanted to include people over the age of 50, as this was applicable in most European countries, while the authors initially wanted the indicated population to be over 70 years of age (reflective of the Dutch recommendations). In the end, the final population reflected the requests of the manufacturer. This was seen as a positive reflection that the scope should reflect a European rather than a national perspective.

3.2. Description and technical characteristics of technology

According to the HTA Core Model for Rapid REA,⁴⁶ this domain describes the technology (or a sequence of technologies) and its technical characteristics, e.g. mode of action/mechanism of action, when it was developed, for what purpose(s), who will be using it, in what manner, and at which level of health care.

The guideline states that the issues in this domain should be described in sufficient detail to differentiate the technology from its comparators. The relevant terms and concepts used should be allow those unfamiliar with the technology to get an overall understanding of its use.⁴⁷

Based on the interviews, the description of the technology is in line with their submissions and there is little disagreement between the authors and the MAH on this domain. In one pilot, there have been some minor concerns regarding the description of the biochemical properties of the technology being assessed, some inaccuracies in the qualitative description of the target condition and the inclusion of data of questionable relevance in this section but these were not seen as significant concerns.

3.3. Clinical effectiveness

This domain investigates the "relative benefits of the technology determined under experimental conditions (efficacy data) or under routine conditions (effectiveness data by a physician in a community)".⁴⁸ To undertake this assessment, the authors decide upon the relevant comparators, the appropriate patient outcomes and the assessment of the quality of

46 EUnetHTA WP5 Joint Action 2 (2015), "The HTA Core Model ® for Rapid Relative Effectiveness Assessment. Version 4.1 July 2015"

47 Ibid.

48 EUnetHTA (2015), 'The HTA Core Model ® for Rapid Relative Effectiveness Assessments version 4.1.' Available at [last access 27 August 2015]: <http://www.eunetha.eu/news/final-version-hta-core-model-and-methodological-guidelines-rapid-rea-pharmaceuticals-now-availa>

the evidence. In the next sections we consider each of the following in turn alongside the relevant EUnetHTA guideline(s):⁴⁹

- The selection of comparator(s) – EUnetHTA choice of comparator guideline
- The selection of outcomes – EUnetHTA Clinical endpoints; composite endpoints; surrogate endpoints; Health-related quality of life and utility measures guidelines
- The use of direct and indirect comparisons – EUnetHTA direct and indirect comparison guideline
- The quality and validity assessment of data and analyses -- EUnetHTA Internal validity of randomised controlled trials and Applicability of evidence in the context of a relative effectiveness assessment guidelines

3.3.1. Selection of comparators

EUnetHTA guidelines indicate that in an ideal situation, the comparator is defined “before the assessment begins or in the early phase of assessment” and would be⁵⁰

- “The reference treatment [recommended by] high quality clinical practice guidelines at European or international level
 - With good quality safety and efficacy evidence
 - With an EU or national marketing authorisation for the appropriate indication and line of treatment.”
- Where there are multiple treatments used across Europe, EUnetHTA suggests the use of the “best active comparator” identified by the EMA or the inclusion of multiple comparators in the REA.
- In the case that the REA product is indicated for a rare disease, then the “Orphan Medicinal Designation” can be referenced when choosing the comparator.
- Where a comparator is based on routine use in clinical practice (preferably citing clinical practice as in national reimbursement lists or prescription statistics)

The chosen comparators for the pilot experiences are detailed in Table 4 below.

Table 4: Comparators by pilot

Pilot	Comparator(s)
-------	---------------

⁴⁹ This chapter does not discuss Applicability. We discuss Applicability in Chapter 4: Re-use.

⁵⁰ EUnetHTA (2013), ‘Guideline: Comparator and Comparisons – Criteria for the choice of the most appropriate comparator(s) Summary of current policies and best practice recommendations.’ Available at [last access 27 August 2015]: <http://www.eunetha.eu/eunetha-guidelines>.

Pilot 1	Placebo
Pilot 2	Active comparators in dual, triple therapy, and add-on therapy to insulin
Pilot 3	Placebo
Pilot 4	<ul style="list-style-type: none"> • Three active comparators without market authorisation for pilot product indication • Best supportive care
Pilot 5	Placebo as addition to dual therapy

Source: CRA analysis from EUnetHTA pilots

Comparators were agreed at the scoping meeting and the comparators proposed by the MAH were agreed with the pilot authors. In the cases where placebo was the chosen comparator (pilot 1 and 3), these were in line with EUnetHTA selection of comparator guidelines (as there was no other treatments available, no treatment reflected European practice and no treatment was best supportive care) and industry was satisfied with this choice.

For Pilot 2 and 4, which had active comparators, industry expressed some concern on the methodology applied for comparator selection. In both instances, EUnetHTA made suggestions to include or change the existing comparator in the draft submission. When the manufacturer demonstrated that the suggested comparators were not relevant (pilot 2 and 4), EUnetHTA ultimately agreed their exclusion.

When the selected comparator was placebo (pilot 3), EUnetHTA reviewers suggested additional comparators were necessary and possible through an indirect comparison during the stage of REA report drafting. Ultimately, after the MAH clarified that an indirect comparison was not feasible due to heterogeneity in the data, these comparators remained excluded. Indeed, even where the reviewers questioned the appropriate comparators (Pilot 3) and suggested another comparator, the authors recognised that the suggested comparator was not used across Europe and supported the MAH proposal.

3.3.2. Selection of outcomes

Endpoints describe the positive or negative impact of a treatment on health status.⁵¹ The selection of endpoints is covered by three EUnetHTA guidelines, each looking at a specific type of endpoint – clinical, surrogate, and composite endpoints.⁵²

⁵¹ EUnetHTA (2013), 'Guideline: Endpoints used in relative effectiveness assessment of pharmaceuticals- Clinical Endpoints.' Available at [last access 27 August 2015]: <http://www.eunetha.eu/eunetha-guidelines>.

⁵² EUnetHTA (2013), 'Guideline: Endpoints used in relative effectiveness assessment of pharmaceuticals- Surrogate Endpoints.' Available at [last access 27 August 2015]: <http://www.eunetha.eu/eunetha-guidelines>. EUnetHTA (2013), 'Guideline: Endpoints used in relative effectiveness assessment of pharmaceuticals- Composite Endpoints.' Available at [last access 27 August 2015]: <http://www.eunetha.eu/eunetha-guidelines>. EUnetHTA (2013), 'Guideline: Endpoints used in relative effectiveness assessment of pharmaceuticals- Clinical Endpoints.' Available at [last access 27 August 2015]: <http://www.eunetha.eu/eunetha-guidelines>

From these guidelines, we find that “non-composite final clinical endpoints... measured within a reasonable time frame... and selected based on relevance to disease, reproducibility and validity” are preferred in the REA of pharmaceuticals.^{53,54} Preferred endpoints for non-life-threatening disease are *morbidity* and *Health Related Quality of life (HRQoL)* while *overall survival* and *all-cause mortality* are preferred for life-threatening diseases.⁵⁵

There is a separate guideline for HRQoL which describes basic principles for selecting an instrument to measure HRQoL under the recognition that there is no gold standard for HRQoL measurement. The recommendation is to include both disease / population specific and generic HRQoL measure.⁵⁶

Thus far, each type of outcome has been observed in the pilot experience with clinical and surrogate endpoints more commonly selected than composite endpoints (only selected in two pilots).

Table 5: Endpoints by pilot

Pilot	Type of endpoint	Endpoints in assessment
Pilot 1	Composite endpoint	Burden of disease (incidence, severity and duration of associated pain and discomfort)
Pilot 2	Clinical endpoints Surrogate endpoints	Mortality, long term outcomes, change in HbA1c, change in weight, systolic blood pressure, fasting blood glucose and HRQoL
Pilot 3	Clinical endpoints Surrogate endpoints	Progression-free survival, Overall survival, time to progression, disease control rate, response rate, duration of response and general and disease specific HRQoL,
Pilot 4	Clinical endpoints Surrogate endpoints	Overall survival, progression free survival, objective response rate and HRQoL
Pilot 5	Composite endpoints	Composite endpoint composed of cardiovascular endpoints and death

Source: CRA analysis from EUnetHTA pilots

On the whole, the MAH were satisfied with the selection of endpoints. The selection of endpoints was not a significant issue when the pilot product was for a rare disease (Pilots 3

53 EUnetHTA (2013), 'Guideline: Endpoints used in relative effectiveness assessment of pharmaceuticals- Surrogate Endpoints.' Available at [last access 27 August 2015]: <http://www.eunetha.eu/eunetha-guidelines>.

54 EUnetHTA (2013), 'Guideline: Endpoints used in relative effectiveness assessment of pharmaceuticals- Composite Endpoints.' Available at [last access 27 August 2015]: <http://www.eunetha.eu/eunetha-guidelines>.

55 EUnetHTA (2013), 'Guideline: Endpoints used in relative effectiveness assessment of pharmaceuticals- Clinical Endpoints.' Available at [last access 27 August 2015]: <http://www.eunetha.eu/eunetha-guidelines>.

56 EUnetHTA (2013), 'Guideline: Endpoints used in relative effectiveness assessment of pharmaceuticals- Health-related quality of life and utility measures.' Available at: <http://www.eunetha.eu/eunetha-guidelines>.

and 4), which is not unexpected, considering the greater flexibility in EUnetHTA guidelines for the selection of endpoints in diseases with small populations.

In Pilot 2 and 5, the following issues were highlighted:

- The importance given to mortality as a clinical endpoint for non-life threatening disease (Pilot 2) – Pilot 2 is a diabetes product, a disease that is seen as a non-life-threatening disease given today’s medical treatments. The EUnetHTA guideline states mortality as an endpoint is only applicable for diseases that are life threatening, yet the author criticised the exclusion of mortality as an endpoint in the pilot of a non-life-threatening disease (over the short to mid-term).
- The inadequate discussion around HRQoL data (Pilot 2) -- Both general and disease specific HRQoL measures were submitted but the rapid REA only referenced the general HRQoL measure. The exclusion of specific HRQoL in this instance is inconsistent with the EUnetHTA guidance on HRQoL which purports the inclusion of both disease specific and general measures.
- The interpretation of the composite endpoint (Pilot 5) – In accordance with EUnetHTA guidance on composite endpoints, the assessments of composite endpoints in two pilots were conducted with considerable caution and results were caveated with potential methodological limitations outlined in the section above. In one pilot, EUnetHTA did not comment on the contribution of each component in the composite endpoint on the basis of insufficient data (frequencies of cardiovascular mortality were low across treatment arms).

To test whether the concerns of the MAH on mortality as an endpoint and on the lack of discussion around HRQoL outcomes were valid, we looked at whether other rapid REA reports had the same issues and whether national HTAs have followed the same approach (Table 6).

Table 6: Comparison of endpoint selection and reporting in Rapid REA reports and published national assessments

Assessment Agency	Mortality as an outcome for chronic disease	Reference to HRQoL outcomes
EUnetHTA	Pilot 2 – criticised exclusion of mortality as a clinical outcome for chronic disease.	<p>Pilot 2 – reference to the Short Form 36 Health Survey (SF-36), and EQ-5D, both general HRQoL measures. Concluded that “Canagliflozin or its comparators did not have any relevant effect on functional ability or general health-related quality of life during the follow-up of up to 1 year. “</p> <p>Pilot 4 – reference to results from both general and specific HRQoL instruments. Concluded that treatment provided increased quality of life for a greater proportion of patients than comparator.</p>

HAS	Outcome not mentioned. ⁵⁷	Pilot 2 – HRQoL not mentioned. ⁵⁸ Pilot 4 – assessment mentions both general and specific HRQoL measures. Concludes that there is no difference between the treatment and its comparator. ⁵⁹
IQWiG	Outcome included. Concluded that there was no difference in mortality outcomes between treatment and its comparators. ⁶⁰	Pilot 2 – IQWiG mentioned as an endpoint of the RCT but does not include any discussion. ⁶¹ Pilot 4 – HRQoL measures not mentioned. ⁶²
NICE	Outcome included in scope of Single Technology Appraisal but outcome is not mentioned in published assessment report. Mortality included as safety outcome related to cardiovascular complications	Pilot 2 – NICE HRQoL mentions EQ-5D, a general HRQoL measurement tool. HRQoL fed into health economic analysis. ⁶⁵

57 HAS (2014), 'Commission de la transparence avis INVOKANA 100 et 300 mg comprimé pellicule.' Available at: http://www.has-sante.fr/portail/upload/docs/evamed/CT13512_INVOKANA_PIC_INS_Avis2PostAudition_CT13512.pdf.

58 HAS (2014), 'Commission de la transparence avis INVOKANA 100 et 300 mg comprimé pellicule.' Available at: http://www.has-sante.fr/portail/upload/docs/evamed/CT13512_INVOKANA_PIC_INS_Avis2PostAudition_CT13512.pdf.

59 HAS (2015), 'Commission de la transparence avis CYRAMZA 10mg/mL, solution à diluer pour perfusion.' Available at: http://www.has-sante.fr/portail/jcms/c_2048967/fr/cyramza

60 IQWiG (2014), 'IQWiG-Berichte – Nr. 225 Canagliflozin – Nutzenbewertung gemäß 35a SGB V.' Available at: https://www.iqwig.de/download/A14-12_Canagliflozin_Nutzenbewertung-35a-SGB-V.pdf.

61 IQWiG (2014), 'IQWiG-Berichte – Nr. 225 Canagliflozin – Nutzenbewertung gemäß 35a SGB V.' Available at: https://www.iqwig.de/download/A14-12_Canagliflozin_Nutzenbewertung-35a-SGB-V.pdf, page 14

62 IQWiG (2015), 'IQWiG-Berichte – Nr. 295 Ramucirumab – Bewertung gemäß § 35a Abs. 1 Satz 10 SGB V.' Available at: https://www.iqwig.de/download/G15-02_Ramucirumab_Bewertung-35a-Abs1-Satz10-SGB-V.pdf

65 NICE (2014), 'Canagliflozin in combination therapy for treating type 2 diabetes.' Available at: <https://www.nice.org.uk/guidance/ta315> page 48

	and included in health economic model. ^{63,64}	
ZIN	Outcome not mentioned. ⁶⁶	Pilot 2 – HRQoL not mentioned. ⁶⁷

Source: CRA analysis of HAS, EUnetHTA, IQWiG, NICE, ZIN assessments

We looked at the national assessment reports of HAS, IQWiG, NICE, and ZIN for pilot 2 (Table 6) and found that using mortality as a clinical outcome was indeed uncommon in national assessments. HAS and ZIN did not include mortality as an outcome in their assessments.^{68,69} NICE included mortality in the scope of the Single Technology Appraisal but then made no reference to mortality as a clinical outcome in the published NICE technology appraisal guidance.^{70,71} Rather, NICE discussed mortality as a safety outcome.⁷² IQWiG was the only national agency that considered mortality as an outcome in the comparisons of canagliflozin, sitagliptin and glimepiride. IQWiG concluded that there was no difference in mortality outcomes in all comparisons and discussed “excess” mortality related to hypertension, which implies it is a safety consideration.⁷³

Regarding the concern about HRQoL outcomes. The MAH of Pilot 4 had not highlighted any issues with the presentation of HRQoL outcomes in the EUnetHTA report. Indeed, we find

-
- 63 NICE (2013), 'Final scope for the appraisal of canagliflozin in combination therapy for treating type 2 diabetes.'
- 64 NICE (2014), 'Canagliflozin in combination therapy for treating type 2 diabetes.' Available at: <https://www.nice.org.uk/guidance/ta315>
- 66 Zorginstituut Nederland (2014), 'GVS-rapport 14/08 canagliflozine (Invokana®).' Page 8. Available at: [http://www.zorginstituutnederland.nl/binaries/content/documents/zinl-www/documenten/publicaties/geneesmiddel_beoordelingen/2014/1403-canagliflozine-invokana/1403-canagliflozine-invokana/canagliflozine+\(Invokana\).pdf](http://www.zorginstituutnederland.nl/binaries/content/documents/zinl-www/documenten/publicaties/geneesmiddel_beoordelingen/2014/1403-canagliflozine-invokana/1403-canagliflozine-invokana/canagliflozine+(Invokana).pdf)
- 67 Zorginstituut Nederland (2014), 'GVS-rapport 14/08 canagliflozine (Invokana®).' Page 8. Available at: [http://www.zorginstituutnederland.nl/binaries/content/documents/zinl-www/documenten/publicaties/geneesmiddel_beoordelingen/2014/1403-canagliflozine-invokana/1403-canagliflozine-invokana/canagliflozine+\(Invokana\).pdf](http://www.zorginstituutnederland.nl/binaries/content/documents/zinl-www/documenten/publicaties/geneesmiddel_beoordelingen/2014/1403-canagliflozine-invokana/1403-canagliflozine-invokana/canagliflozine+(Invokana).pdf)
- 68 HAS (2014), 'Commission de la transparence avis INVOKANA 100 et 300 mg comprimé pellicule.' Available at: http://www.has-sante.fr/portail/upload/docs/evamed/CT13512_INVOKANA_PIC_INS_Avis2PostAudition_CT13512.pdf.
- 69 Zorginstituut Nederland (2014), 'GVS-rapport 14/08 canagliflozine (Invokana®).' Page 8. Available at: [http://www.zorginstituutnederland.nl/binaries/content/documents/zinl-www/documenten/publicaties/geneesmiddel_beoordelingen/2014/1403-canagliflozine-invokana/1403-canagliflozine-invokana/canagliflozine+\(Invokana\).pdf](http://www.zorginstituutnederland.nl/binaries/content/documents/zinl-www/documenten/publicaties/geneesmiddel_beoordelingen/2014/1403-canagliflozine-invokana/1403-canagliflozine-invokana/canagliflozine+(Invokana).pdf)
- 70 NICE (2013), 'Final scope for the appraisal of canagliflozin in combination therapy for treating type 2 diabetes.'
- 71 NICE (2014), 'Canagliflozin in combination therapy for treating type 2 diabetes.' Available at: <https://www.nice.org.uk/guidance/ta315>
- 72 This focused on complications from cardiovascular disease and considered the implications of such excess mortality related to adverse safety effects in the health economic model Ibid, page 16, section 3.2.2
- 73 IQWiG (2014), 'IQWiG-Berichte – Nr. 225 Canagliflozin – Nutzenbewertung gemab 35a SGB V'. Available at: https://www.iqwig.de/download/A14-12_Canagliflozin_Nutzenbewertung-35a-SGB-V.pdf.

contrary to the experience of Pilot 2, both general (EuroQol – EQ-5D) and disease specific (European Organisation for Research and Treatment of Cancer Quality of Life questionnaire-EORTC QLQ-C30) measures and findings were discussed in the report for Pilot 4.

The inclusion and reporting of HRQoL of national assessments appear to be consistent with the EUnetHTA assessments. For pilot 2, HAS and ZIN do not mention HRQoL.^{74,75} IQWiG recognises that HRQoL is a RCT endpoint but does not discuss HRQoL further.⁷⁶ Indeed, only the NICE assessment discusses quality of life with reference to a general HRQoL instrument (EQ-5D).⁷⁷ For pilot 4, we found assessments published by HAS and IQWiG. While IQWiG does not mention HRQoL,⁷⁸ HAS provides discussion on both general and disease specific HRQoL and concludes that there is no difference between treatments.⁷⁹

As demonstrated by a study on HRQoL in chronic lung disease, reference to disease specific HRQoL data is important, particularly because general HRQoL instruments may not cover disease specific areas of HRQoL in chronic diseases.⁸⁰ The concern regarding the exclusion of disease specific HRQoL data in Pilot 2 seems justified.

3.3.3. The use of direct and indirect comparisons

After comparators and endpoints are selected, the statistical analysis can occur either with a direct comparison which “combine the results of multiple head-to-head trials” or an indirect comparison which “infers the relative effectiveness in the absence of direct head-to-head evidence”. EUnetHTA recognises that there is “no consensus on the best approach to

74 HAS (2014), ‘Commission de la transparence avis INVOKANA 100 et 300 mg comprimé pellicule.’ Available at: http://www.has-sante.fr/portail/upload/docs/evamed/CT13512_INVOKANA_PIC_INS_Avis2PostAudition_CT13512.pdf.

75 Zorginstituut Nederland (2014), ‘GVS-rapport 14/08 canagliflozine (Invokana®).’ Page 8. Available at: [http://www.zorginstituutnederland.nl/binaries/content/documents/zinl-www/documenten/publicaties/geneesmiddel_boordelingen/2014/1403-canagliflozine-invokana/1403-canagliflozine-invokana/canagliflozine+\(Invokana\).pdf](http://www.zorginstituutnederland.nl/binaries/content/documents/zinl-www/documenten/publicaties/geneesmiddel_boordelingen/2014/1403-canagliflozine-invokana/1403-canagliflozine-invokana/canagliflozine+(Invokana).pdf)

76 IQWiG (2014), ‘IQWiG-Berichte – Nr. 225 Canagliflozin – Nutzenbewertung gemab 35a SGB V.’ Available at: https://www.iqwig.de/download/A14-12_Canagliflozin_Nutzenbewertung-35a-SGB-V.pdf. page 14

77 NICE (2014), ‘Canagliflozin in combination therapy for treating type 2 diabetes.’ Available at: <https://www.nice.org.uk/guidance/ta315> page 48

78 IQWiG (2015), ‘IQWiG-Berichte – Nr. 295 Ramucirumab –Bewertung gemäß § 35a Abs. 1 Satz 10 SGB V.’ Available at: https://www.iqwig.de/download/G15-02_Ramucirumab_Bewertung-35a-Abs1-Satz10-SGB-V.pdf

79 HAS (2015), ‘Commission de la transparence avis CYRAMZA 10mg/mL, solution à diluer pour perfusion.’ Available at: http://www.has-sante.fr/portail/jcms/c_2048967/fr/cyramza

80 Assari, S. et al (2009), ‘Are generic and disease-specific health related quality of life correlated? The case of chronic lung disease due to sulphur mustard. J Res Med Sci 14 (5) pp. 285-290. Available at: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3129097/>.

comparisons, especially when both direct and indirect evidence is available” but when direct evidence is limited, “combining direct with indirect evidence is advantageous.”⁸¹

Irrespective of the methodology used, EUnetHTA guidelines highlight that “a meta-analysis must be preceded by a properly conducted and transparent systematic literature review” and that “heterogeneity, fixed and random effects models, and the presence of bias” should be considered. Specifically for an indirect comparison (including NMAs - Network Meta Analyses), an investigation of inconsistencies between direct and indirect evidence is necessary and the following methods were deemed acceptable for a REA:⁸²

- Bucher’s method of adjusted indirect comparison
- Lumley’s method of network meta-analysis
- Bayesian meta-analysis (sensitivity analysis also needed)

We observed both the use of direct and indirect comparisons across the five pilot REAs (Table 7).

Table 7: Type of comparison(s) by pilot

Pilot	Type of comparison
Pilot 1	Direct comparison
Pilot 2	Direct comparison; Indirect comparison
Pilot 3	Direct comparison
Pilot 4	Direct comparison; Indirect comparison
Pilot 5	Direct comparison

Source: CRA analysis from EUnetHTA pilots

As demonstrated in Table 7, direct comparisons were used across pilots and were the sole comparisons undertaken in Pilots 1, 3 and 5, which had sufficient direct evidence available for the chosen comparator (which was a placebo). As presented by EUnetHTA authors, these direct comparisons were acceptable to the MAH.

In Pilots 2 and 4, EUnetHTA included indirect comparisons and their characteristics are presented in Table 8. As the table indicates, while in both pilots, the NMA was discussed, the discussion did not cover all indirect comparisons submitted in Pilot 2.

Table 8: Indirect comparisons by pilot

Element of NMA	Pilot 2	Pilot 4
----------------	---------	---------

⁸¹ EUnetHTA (2013), ‘Guideline: Comparator and comparisons- direct and indirect comparisons.’ Available at: <http://www.eunetha.eu/eunetha-guidelines>.

⁸² Ibid.

Number of comparators and comparisons	Treatment versus 7 classes of drugs in dual and triple therapy. ¹ For each class of drug, there were 8 endpoints. ²	3 comparators ⁴ , 3 endpoints ⁵
Description of REA discussion	<p>The NMAs were conducted using Bayesian analysis and General Linear Models using fixed and random effects assumptions were undertaken.</p> <p>The REA report discusses the results for 6 endpoints.³</p> <p>The NMA was also used as inputs for the long term outcomes modelling. EUnetHTA found it difficult to verify sources used within the NMA and as such, did not report outcomes from the modelling ⁸³</p>	<p>There was limited evidence available. There were only 4 studies and each of these studies had a small number of patients (from 40 to 223 patients). The REA reports that a series of pairwise analyses using the Bucher method were used because there was no complete/closed network.</p> <p>The indirect analyses found overall survival and the proportion of patients achieving an objective response statistically more favourable for the treatment vs its comparators.</p> <p>There was no significant difference in progression free survival between the treatment and its comparator. 84</p>

Notes: 1= sulphonylureas, GLP-1 agonists, DPP-4 inhibitors, thiazolidinediones, SGLT2 inhibitors, insulin and placebo
2 = HbA1c change, proportion of patients achieving HbA1c target, weight, Body Mass Index (BMI), Fasting Plasma Glucose (FPG), SBP, Long term outcomes and mortality. 3 = change in HbA1c, HbA1c target, weight, BMI, FPG, SBP;

83 EUnetHTA (2014), 'EUnetHTA WP5 Joint Action 2 Strand A, Rapid Relative Effectiveness Assessment of pharmaceuticals Canagliflozin for the treatment of type 2 diabetes mellitus.' (pages 62). Available at: http://www.eunetha.eu/sites/5026.fedimbo.belgium.be/files/WP5_SA-2_canagliflozin_for_the_treatment_of_diabetes_mellitus.pdf

84 EUnetHTA (2015), 'Joint Assessment on Ramucirumab (Cyramza®) in combination with Paclitaxel as second-line treatment for adult patients with advanced gastric or gastro-oesophageal junction adenocarcinoma. (pages 42-44). Available at: <http://www.eunetha.eu/outputs/joint-assessment-ramucirumab-cyramza-combination-paclitaxel-second-line-treatment-adult-pa-0>.

4 = irinotecan, docetaxel, best supportive care; 5 = progression free survival, overall survival, withdrawal due to adverse event (safety endpoint)

Source: EUnetHTA pilot 2 and pilot 4 rapid REA reports

While the MAH involved remarked that the inclusion of a NMA in the REA was appropriate approach and could be useful in other markets (acknowledging that this inclusion could act as a signal to national agencies who currently do not use NMAs), there remained concerns on the assessment of NMAs:

- In Pilot 2, the NMA was assessed in line with EUnetHTA guidelines. However the methodology of the meta-analysis included in the assessment was not discussed in the report. For example, the Vasilakow et al 2013 meta-analysis⁸⁵ was not “measured against the same quality standards.”⁸⁶ The MAH felt there needed to be more consistency in the application of assessment methodology for comparisons. In particular, the authors should assess if the literature review is properly conducted and transparent.
- In Pilot 4, the manufacturer agreed the authors’ conclusions for the NMA were reasonable but reported that the way how conclusions were reached could be made clearer. In particular, the report included some discussion on the rationale behind conclusions but the manufacturer felt that EUnetHTA could further describe data limitations and explain that the indirect comparison results were a direct reflection of poor data quality of studies investigating the efficacy and safety of the comparator products. In particular, the evidence supporting use of one of the comparisons was a single study with only 40 patients⁸⁷ and it was necessary to do an indirect comparison against this study.

From Table 8 we see that the NMAs included in pilots 2 and 4 differ greatly in terms of the number of comparators/outcomes, the amount of data included and the statistical models used. In short, the NMAs in pilot 2 were much more complex than the NMAs in pilot 4, which can be expected given pilot 4 is for a rare disease with limited data availability.

In the absence of other more concrete metrics to evaluate the extent of discussion, we use “pages dedicated to the indirect comparison” as an indirect metric. We observe that the extent of discussion for both pilots is largely similar, there were eight full pages of description for indirect comparisons in Pilot 2 and no more than nine pages in Pilot 4. We observe that the

85 Vasilakou D, Karagiannis T, Athanasiadou E, et al. Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: a systematic review and meta-analysis. *Ann Intern Med* 2013;159:262-74.

86 EUnetHTA (2014), ‘EUnetHTA WP5 Joint Action 2 Strand A, Rapid Relative Effectiveness Assessment of pharmaceuticals Canagliflozin for the treatment of type 2 diabetes mellitus.’ (pages 390). Available at: http://www.eunetha.eu/sites/5026.fedimbo.belgium.be/files/WP5_SA-2_canagliflozin_for_the_treatment_of_diabetes_mellitus.pdf

87 EUnetHTA (2015), ‘Joint Assessment on Ramucirumab (Cyramza®) in combination with Paclitaxel as second-line treatment for adult patients with advanced gastric or gastro-oesophageal junction adenocarcinoma. (page 25). Available at: <http://www.eunetha.eu/outputs/joint-assessment-ramucirumab-cyramza-combination-paclitaxel-second-line-treatment-adult-pa-0>.

similarity in the length of discussions between the two pilots could be, in part, due to the exclusion of the discussion on long term outcomes. Given Pilot 2 is for a chronic disease with many other treatment alternatives, an exclusion of conclusions on long term outcomes (with the exception of mortality) in the rapid REA assessment can be detrimental for the MAH as these conclusions are crucial for pricing and reimbursement decision making.

3.3.4. Levels of evidence

According to the EUnetHTA guideline on *Internal validity of randomised controlled trials (RCT)*, RCTs included in an REA should be assessed for their trustworthiness, that is, their risk of bias. Risk of bias can be disaggregated into many forms of bias, notably: selection, performance, detection, attrition, reporting bias. It is noted that there are many assessments for the quality of evidence, notably including the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework. However, EUnetHTA guidance does not discuss the GRADE approach as it assesses multiple domains: internal validity, external validity, consistency of results amongst other domains.⁸⁸ Also, according to the HTA Core Model guidance, GRADE is recommended for the appraisal of guidelines and the appraisal of diagnostic accuracy studies only.⁸⁹ For the EUnetHTA objective of assessing “internal validity” or “risk of bias”:

- The Cochrane Collaboration Risk of Bias framework (by Higgins et al 2011) should be applied to RCTs.⁹⁰
- The Oxman and Guyatt Index (Oxman and Guyatt 1991, Jadad and Murray 2007) and the AMSTAR instrument (Shea et al. 2007) should be applied to systematic literature reviews.^{91,92,93}

In addition, EUnetHTA highlights that all internal validity assessments should be provided with adequate description to allow for reproducibility.

In practice, as Table 9 details, studies across REA pilots were evaluated against the Cochrane Collaboration Risk of Bias framework, in accordance to EUnetHTA guidance. In addition,

88 EUnetHTA (2013), ‘Guideline: Levels of evidence – Internal validity of randomised controlled trials.’ Available at [last access 27 August 2015]: <http://www.eunetha.eu/eunetha-guidelines>.

89 EUnetHTA (2015), ‘The HTA Core Model ® for Rapid Relative Effectiveness Assessments version 4.1.’ Available at [last access 27 August 2015]: <http://www.eunetha.eu/news/final-version-hta-core-model-and-methodological-guidelines-rapid-rea-pharmaceuticals-now-availa>

90 Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA; Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration’s tool for assessing risk of bias in randomised trials. *BMJ* 2011; 343: d5928.

91 Oxman AD, Guyatt GH. Validation of an index of the quality of review articles. *J Clin Epidemiol* 1991; 44: 1271-1278.

92 Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, Porter AC, Tugwell P, Moher D, Bouter LM. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res Methodol.* 2007 Feb 15; 7: 10.

93 Jadad AR, Murray WE. *Randomized controlled trials: questions, answers and musings.* Malden: Blackwell; 2007.

although GRADE is not recommended by EUnetHTA guidance, it is nonetheless referenced in Pilots 2, 4, and 5.

Table 9: Quality assessments by pilot

Pilot	Quality assessment	
	Cochrane Collaboration Risk of Bias	GRADE
Pilot 1	✓	X
Pilot 2	✓	✓
Pilot 3	✓	X (Only one RCT included in assessment)
Pilot 4	✓	✓
Pilot 5	✓ (only description no table)	✓

Source: CRA analysis from EUnetHTA pilots

The irregular application of the GRADE approach raised a question on what quality instruments should be standard across REAs. It is clear that the EUnetHTA recommended Cochrane Collaboration Risk of Bias assessment is useful for all REAs, on the basis that each REA will include at least an RCT. However, there is less clarity over the role of GRADE and its interpretation.

During interviews, it was noted that GRADE was not applicable to Pilot 3 as meta-analyses of RCTs were not feasible (for Pilot 3, there was only one RCT). Pilot 3 further highlighted that the GRADE might not be useful for rare disease REAs where evidence is extremely limited. However, the manufacturers recognised that the application of GRADE is often inevitable.

More importantly, Pilot 4 reported a need for more explanation and interpretation of the conclusions made from a GRADE appraisal. For Pilot 4, the GRADE table was not initially included in the rapid REA assessment draft report and the involved manufacturer had to request its inclusion. As Table 10 demonstrates, the GRADE table contains particulars on how many RCTs were identified for a specific outcome and describes the number of patients in each study. These details are useful for understanding the more general rapid REA assessment conclusions on the quality of evidence. In the case of Pilot 4, the GRADE table highlighted that for this rare disease, there was only one study for the mortality outcome. Therefore, it was deemed that further explanation of quality assessments is essential for an accurate interpretation of the quality assessment results.

Furthermore, with regards to the presentation of quality assessment conclusions, Pilot 5, due to lack of a table with explanation of the score, supported the presentation of the Risk of Bias in order to clearly understand the rationale behind conclusions on quality. This is also reinstated by the fact that some of the reviewing agencies commented that “the risk of bias is not clearly

reported” and the “quality of data is not sufficiently evaluated”.⁹⁴ This illustrates how lessons regarding the methodology are not necessarily being consistently applied across subsequent pilots, reinforcing the need for feedback on the lessons.

94

EUnetHTA rapid REA of Vorapaxar, page 64:
<https://eunetha.fedimbo.belgium.be/sites/5026.fedimbo.belgium.be/files/Vorapaxar%20for%20the%20reduction%20of%20thrombotic%20cardiovascular%20events.pdf>

Table 10: GRADE evidence profile for direct evidence and effectiveness outcomes (example from Pilot 4) ⁹⁵

Quality assessment								No. of Patients			Effect		Quality
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	Comparator 1	Comparator 2	Relative (95% CI)	Absolute(95% CI)	Quality	
Mortality													
1	Randomised trials	Not serious	Serious	Not serious	Not serious	None	256/330 (77.6%)	260/336 (77.6%)	HR 0.807 (0.678 to 0.962)	75 fewer per 1000 (from 13 fewer to 139 fewer)	⊕⊕⊕○ MODERATE		

Source: EUnetHTA Rapid REA report on Ramucirumab

⁹⁵ EUnetHTA (2015), 'EUnetHTA Joint Action 2 WP5 Strand A, Rapid assessment of pharmaceutical Pilot rapid assessment of pharmaceuticals using the HTA Core Model® for Rapid Relative Effectiveness Assessment Ramucirumab in combination with paclitaxel as second line treatment for adult patients with advanced gastric or gastro-oesophageal junction adenocarcinoma.

3.3.5. Lessons on clinical effectiveness

There are some lessons that can be learnt from the experience of the pilots:

- The selection of comparators was agreed between MAH and authors. Looking forward, it would be good to maintain the process ensuring that comparators are agreed between the authors, the manufacturer and the reviewers at scoping stage and the chosen comparator is representative of European practice whenever possible. As discussed in the previous chapter, this agreement should occur earlier in the process.
- Regarding the selection of the endpoints, overall there is agreement between the MAH and the authors regarding the choice of end-points and the acceptance of surrogate endpoints is generally positive. Some issues were highlighted on the appropriateness of the selection of primary endpoints, their hierarchy and the interpretation of the composite endpoints. In particular, the selection of primary endpoints should be put in the context of the disease, and their choice should be more flexible and pragmatic. For the composite endpoints, the author should comment on the contribution of each component. Where the EUnetHTA guidelines are not be followed, additional communication between the MAH and EUnetHTA coordinators appears important.
- Regarding the (indirect) comparisons, the MAH saw it as positive that EUnetHTA uses “cutting-edge” methodologies (e.g. NMA). However, it is important to have greater clarity in reporting and consistency in the application of EUnetHTA guidance for assessment of comparisons. In particular, the authors should provide a critical and detailed analysis of the methodology of the studies included for the indirect comparison.
- Regarding the quality of evidence, there is a need for standardisation so that similar products would be treated in the same way but also flexibility so that issues associated with small patient populations are allowed for. The approach used to assess data quality should be transparent and discussed taking into account the type of product under review.

3.4. Safety

This section considers two aspects of the safety domain:

- The objective of the safety analysis and
- The methods and data referenced in the safety analysis.

We first examine EUnetHTA’s guidance on safety analyses and then discuss the feedback from the pilot experience.

3.4.1. Objective of safety analysis

EUnetHTA guidance on *Safety* indicates that within the context of an REA, the safety assessment should present both the benefits and adverse effects of the pharmaceutical in a

balanced manner especially considering that these results can influence pricing and reimbursement decisions. Thus there are three objectives relevant for rapid REAs:^{96, 97}

- “Identify adverse effects (no differentiation between safety identified ex-ante or ex-post the start of clinical trial)”
- “Quantify those adverse effects in terms of frequency, incidence, severity (intensity) and seriousness (extent to which it is life threatening)”
- “Compare the safety profile of the pharmaceutical with its comparators...paying special regard to the most frequent serious and severe adverse effects”.

All the pilots covered these three objectives where possible (when the medicine under assessment had no comparator, the third objective was necessarily dropped), although in practice the safety analysis varied significantly across the five pilots. As described in Table 11, the analysis performed in each pilot looked at different measures (frequency, statistical significance, relative effect, relative risk), data (side effects, severe side effects, discontinuation rate, fatal events) and focus (comparison versus active comparator or placebo, analysis for different patient populations).

Table 11: Safety analysis by pilot

Pilot	Safety data reported in REA
Pilot 1	Most frequently reported side effects Severe side effects Discussed relative effect of serious adverse effects versus placebo treatment (4 pages)
Pilot 2	Most frequently reported side effects Severe side effects For different patient populations Discussed statistical significance Presented relative effect (4 pages)
Pilot 3	Most frequently reported side effects Serious adverse events Most severe adverse events Discontinuation rate Fatal events rate (24 pages)
Pilot 4	Frequency of adverse events

⁹⁶ EUnetHTA (2015), ‘The HTA Core Model ® for Rapid Relative Effectiveness Assessments version 4.1.’ Available at [last access 27 August 2015]: <http://www.eunetha.eu/news/final-version-hta-core-model-and-methodological-guidelines-rapid-rea-pharmaceuticals-now-availa>

⁹⁷ EUnetHTA (2013), ‘Guideline: endpoints used in relative effectiveness assessment of pharmaceuticals- Safety’ Available at [last access 27 August 2015]: <http://www.eunetha.eu/eunetha-guidelines>.

	Direct and indirect evidence compared frequency of adverse event; relative risk, statistical significance (9 pages)
Pilot 5	Frequency of serious adverse events and discontinuation with special subgroups Analysed statistical significance between frequency of adverse effects Presented relative effect of secondary safety endpoints (bleeding) (7 pages)

Source: CRA analysis from EUnetHTA pilots

The differences across pilots can mainly be attributed to two reasons:

- First, and more importantly, safety issues depend on the different characteristics of the products under assessment (for example whether it is a vaccine, cancer drugs, or an orphan drugs) and therefore the endpoints and the focus of the analysis can be expected to be different across pilots
- Second, the analysis is limited to the evidence available. As noted in the rapid REA reports, there are cases where the intended analysis was not performed due to lack of data.

However, it does appear that the approach and how the results are presented has varied across the pilots, reflecting different approaches to the treatment of safety. Based on the interviews amongst the pilot companies, the industry had a number of concerns:

- The objective of the safety analysis seemed unclear. The first two objectives seem similar to those of the EMA's assessment in the EPAR.
- The emphasis on safety analysis is similar to, if not more, than the emphasis on clinical effectiveness.
- It is noted that there should be a more comprehensive explanation of how conclusions are reached to put the analysis in context and in balance with the effectiveness data.

The first issue reflects the perceived duplication of the REA safety section and the EMA analysis. Feedback across pilots was that the EMA and REA safety analysis was largely the same and the REA safety section provided little or no added value. There is also the belief that the EMA should be the primary agency to conduct the safety analysis given they are equipped and skilled to do so (and they review over time, which is not the case for EUnetHTA).

To test this we undertook a comparison between the rapid REA report and the EMA EPARs⁹⁸ for the respective products. Table 12 indicates that the EUnetHTA report largely duplicates the research questions already covered in the corresponding EPARs. Thus, while there is a perception that the EUnetHTA analysis should address different "research questions" than the EPAR, this perception is unfounded.

Table 12: Comparison of the research questions between the rapid REA reports and the EMA EPARs

Research question	Pilot 1		Pilot 2		Pilot 3		Pilot 4		Pilot 5	
	REA	EPAR	REA	EPAR	REA	EPAR	REA	EPAR	REA	EPAR
Kind of harms that can be caused to the patient	✓	✓								
Most frequent and serious adverse events	✓	✓	✓	✓						
Relationship between the dose and the most frequent and serious adverse events in special populations			✓	✓	✓	✓			✓	✓
How the frequency or severity of harms changes over time in different settings			✓	Not explicitly provided	✓	Not explicitly provided			✓	Not explicitly provided
Frequency of all adverse events compared to other treatments			✓	✓			✓	✓	✓	✓
Frequency of discontinuation of treatment due to adverse events compared to other treatments			✓	✓	✓	✓	✓	✓	✓	✓
Frequency of the serious adverse events (SAEs) compared to other treatments			✓	✓			✓	✓	✓	✓
Frequency of serious adverse events (SAEs) leading to death compared to other treatments			✓	✓	✓	✓	✓	✓	✓	✓
Most frequent adverse events compared to other treatments			✓	✓	✓	✓	✓	✓	✓	✓
Most frequent adverse events compared to other treatments					✓	✓				

according to Common Terminology Criteria for Adverse Events (CTCAE) grade (grade 3, 4 and 5)									
Susceptible patient groups that are more likely to be harmed	✓	✓	✓	✓	✓	✓	✓	✓	✓
Contraindications and special warnings and precautions for the use									
How the long term safety will be studied/monitored	✓	✓							
Known interactions	✓	✓							
Kind of harms for public and environment	✓	✓							
Need to collect further data on the safety			✓	✓					
Ongoing studies investigating the safety			✓	✓					
Group of patients excluded from the study for safety reasons							✓	✓	
Need of a specific therapeutic management of the patient or a specific education							✓	✓	

Source: CRA analysis based on rapid REA reports and EMA EPARs

Perhaps, reflecting comments from industry, it appears that EUnetHTA have tried to add an analysis of the relative risks (considering confidence intervals derived from direct and indirect comparisons) to meet the third objective stated above. This could help to explain the different length of the safety sections across the analysis (but created its own problems as discussed in the next section).

Regarding emphasis, although it is a rough indicator, the comparison of the number of pages dedicated to the main analysis of the clinical effectiveness and safety sections across the pilots

shows that the safety analysis had a similar weight to the effectiveness analysis (Table 13) with the exception of pilot 3.

Table 13: Comparison of the number of pages between the Clinical effectiveness and the Safety sections across the pilots

Pilot	Clinical effectiveness (number of pages)	Safety (number of pages)
Pilot 1	6	4
Pilot 2	9	6
Pilot 3	18	24
Pilot 4	11	12
Pilot 5	8	7

Source: CRA analysis of rapid REA reports

The final concern is the use of the safety analysis. There is still a considerable uncertainty on how EUnetHTA safety analysis would be re-used by national HTA agencies. This is of particular concern for the pilot companies as there is the risk that any safety information from rapid REA reports that appears to contradict the EPAR would result in confusion and unintended consequences.

3.4.2. Safety analysis methodology and data

The EUnetHTA safety guideline further describes the methodology and data required to meet the set objectives:⁹⁹

- For the first two objectives, the recommendation is to report the absolute frequencies of adverse effects, using primary sources of data as the EPAR, Summary of Product Characteristics, Risk Management Plan, manufacturer's dossier, and RCT data. Data from these regulatory and RCT sources should be quality assessed with the Cochrane Collaboration Risk of Bias tables
- For the third objective, the HTA assessors should evaluate if differences identified in adverse reactions between the products are clinically relevant. The evaluation of the clinical relevance should be performed taking into account the condition for which the treatment is used and the co-morbidities of the population. For instance, in oncology, only serious adverse reactions are seen as relevant but in chronic diseases, non-serious adverse reactions can also have important clinical implications. HTA assessors

99

EUnetHTA (2013), 'Guideline: endpoints used in relative effectiveness assessment of pharmaceuticals- Safety' Available at [last access 27 August 2015]: <http://www.eunetha.eu/eunetha-guidelines>.

should describe limitations of the evidence and analyse how these limitations may affect estimates of the adverse reactions.

EUnetHTA also recognises the methodological complications with relative safety effects and noted that often, “clinical trials are not usually powered primarily to study safety and to that end might render RCT data [on its own] inconclusive for safety”.¹⁰⁰ As such, supplementary data from other sources (observational studies or case studies) might be useful provided their limitations (such as heterogeneity, follow up period) are noted and any necessary adjustments to the results are made (observational data should be adjusted for potential confounding or modifying factors).

In general, the safety analysis was conducted rigorously and missing data or measures (evidence gaps) were reported (Table 14).

Table 14: Methods used and evidence gaps highlighted in the rapid REA reports

Pilot	Method for the analysis	Evidence gaps highlighted
Pilot 1	Comparison of frequency, seriousness and severity with placebo	Different safety outcomes (long term data, interactions with other vaccines, some patient subgroups)
Pilot 2	Analysis of direct data for placebo and comparator controlled trials	p-values and confidence intervals were not available for safety data from RCTs
Pilot 3	Direct comparison with placebo	Further information on vulnerable and insufficiently studied patient subgroups required
Pilot 4	Direct comparison of the frequency of reported adverse events with placebo	No indirect evidence calculations were presented for some outcomes due to lack of available data
Pilot 5	Direct comparison with placebo	Data on frequency or severity of harms change over time or in different settings

Source: CRA analysis of Rapid REA reports

100

Depending on the size and duration, clinical trials may fail in capturing long term and uncommon adverse reactions; in order to identify uncommon adverse reactions they should enrol a larger number of participants impacting negatively on time needed for development of the pharmaceutical

From the pilot experience thus far, there was little concern about the focus on frequency of the most serious adverse events (beyond the concern about duplication with the EPAR discussed above), however there was a concern regarding the data used to assess safety:

- The MAH for Pilot 3 felt that the safety data as presented in the REA report is static and might be misleading as safety data is regularly updated in the EMA webpage. The report should be more explicit on this and indicate that new safety data are likely to be available (e.g. referencing to the EMA webpage)
- In Pilot 4 there was a concern that the safety assessment in the REA report emphasises clinical trial data despite the availability of many other sources of data as the product has been on the market for a significant amount of time.

There was much more concern regarding the relative safety assessment. While the industry was positive about the inclusion of a relative safety assessment and believed this is where a comparison could add value beyond the EMA analysis, the industry had concerns regarding the methodology. One concern was that the relative safety assessment methodology and conclusions would only be a reflection of EUnetHTA author(s) (in other words, specific to one or a few national agencies) rather than a reflection of a pan-European assessment.

Another concern was regarding the request of confidence intervals and p-values of Phase III clinical trials. In these cases, the primary end-points of the study most often reflect clinical outcomes relevant for the assessment of clinical effectiveness. Safety data could be collected in these trials including as primary end points but the latter do not have the required frequencies to undertake statistical analysis. As recognised in the EUnetHTA guidelines, there is a significant methodological issue with the use of statistical tests to test relative safety:

- Trials are designed to test efficacy and relative efficacy and are not designed to allow statistical testing of safety or relative safety.
- The context by which the safety data has been collected needs to be taken into account in the subsequent analysis and appropriate analysis applied. This is particularly the issue if any indirect comparisons are to be contemplated.

Adverse events are clearly important for HTA analysis. There are potential implications for the patient's quality of life (which should already be captured in the quality of life analysis undertaken in the clinical effectiveness assessment) and some HTA will want to take this into account in their economic modelling. However, unexpected Adverse Events are by their nature unexpected and cannot be taken into account in the clinical trial design. The usefulness of the EUnetHTA analysis on relative safety is therefore unclear and potentially misleading.

Unlike relative efficacy where there is a vast literature on the appropriate methods, the statistical tools and how these should be interpreted, the literature on relative safety for relative

effectiveness reviews is immature.¹⁰¹ The tools used for clinical effectiveness cannot be directly transferred and applied to relative safety. The EUnetHTA pilots have illustrated some of the significant challenges in this area. It would appear the academic community should be addressing these methodological issues before this can be applied in pilot assessments of actual products.

3.4.3. Lessons

In general, the assessment of safety has been problematic and there is considerable dissatisfaction from the MAHs:

- There is a need for clarification of the objectives of the safety section. In particular, there is a significant concern that the first two objectives of the safety domain duplicate the EPAR. The focus on relative safety could potentially add value but it is unclear if this is of interest to national HTA bodies.
- There is a need for clarification and improvement of types of data and analyses recommended for relative safety assessment. Although EUnetHTA guidelines require a comparison, the analysis should be put into context: often clinical studies are not designed to perform this types of analysis and there is a risk that “missing” statistical significance is misinterpreted by national agencies, possibly leading to delays in (or no) access.
- There is a need to keep the methodology applied to the safety assessment consistent with EUnetHTA guidelines while allowing sufficient flexibility to adapt to different products/contexts. This should be a standard methodology, reflective of a pan-European assessment rather than the specific practices of individual EUnetHTA authors.

101

However, national HTA agencies have also looked at statistical significance of safety results. For example, the safety assessment does include P values, Cis and relative risks obtained through network meta analyses and logistic regressions. See section 3.13 on here: <https://www.nice.org.uk/guidance/ta336/chapter/3-The-companys-submission#clinical-effectiveness>

4. Re-use

This chapter aims to analyse the re-use of the Rapid REAs produced by EUnetHTA by national and local HTA agencies. In the second set of discussions with the five participants in the pilots, we gathered information and views on how re-use should be assessed and if there has been any indication of the latter in their experience. The views of the companies gathered from interviews have been further complemented with EUnetHTA publications on re-use and research on the assessment of these products across national settings and evidence of re-use in the reports published. The findings of the primary and secondary research and their implications are discussed and lessons drawn. However, it should be noted that we have not spoken to the authors, reviewers on national HTA agencies regarding their use of the reports.

The first question to address is the definition of re-use.

4.1. The definition of re-use

A key part of EUnetHTA's overall vision and mission is the creation of transferable output for implementation in national and local settings.¹⁰² EUnetHTA defines *national uptake* as the general implementation of any of its output including joint assessments, submission templates guidelines the HTA Core Model ® etc. in a national/regional/local setting. *National adaptation* is a particular form of national uptake that concerns the re-use of joint assessment.¹⁰³ The purpose of national adaptation is to avoid duplication of work, and to facilitate the adaptation of information in national HTA reports and promote good practices through the co-production of HTA reports (by multiple HTA agencies). EUnetHTA states that

- The minimum requirement for a national adaptation is inclusion of an explicit reference to the EUnetHTA joint assessment on which the local report was based.¹⁰⁴
- An advanced stage of adaptation i.e. full adoption would require “the use of a joint assessment without making any changes at all in its content (except a potential translation into the national language)”.

JA2 WP5 states that re-use is their main objective, which is applying the HTA Core Model for Rapid Assessment for national adaptation and reporting.¹⁰⁵ This is also stated in one of the conditions of the Grant Agreement for JA2. The EUnetHTA 3-year work plan additionally specifies that the target for rapid REA reports of pharmaceuticals is to be used in 20 national HTA assessment by 2015:¹⁰⁶

102 EUnetHTA website [last access 4 September 2015]: <http://www.eunetha.eu/about-us>

103 EUnetHTA website [last access 4 September 2015]: <http://www.eunetha.eu/national-uptake>

104 Ibid.

105 EUnetHTA website [last access 28 August 2015]: <http://www.eunetha.eu/activities/EUnetHTA%20Joint%20Action%202012-15%29/ja2-wp5-applying-hta-core-model-rapid-assessment-nation>

106 EUnetHTA WP5 Joint Action 2 (2013), “EUnetHTA Joint Action 2 on HTA 2012-2015, 3-year Work Plan”, May 2013

“All WP5 members are expected to put forth an effort towards transferring rapid HTAs or parts of the information produced within WP5 into local (e.g. national or regional) HTA reports. This should result in about 20 national/local reports based on the pilot assessments.”

Additionally, to provide guidance the EUnetHTA procedure manual states that ideally at the 100th day of the process when the final version of the pilot REA is ready, “authors, dedicated reviewers and other WP5 members put their efforts into adaptation pilot REA into national/local REAs”.¹⁰⁷ The guidelines state that the aim of these pilots is to test methodology, procedures and national/local implementation of joint rapid relative effectiveness assessments and further improve tools and procedures through the experience gained in these pilots.¹⁰⁸ However, while delivering a pilot to be re-used by the authoring agency was also one of the three explicit main objectives of the first pilot assessment such an aim was not included in the aims of any of the subsequent pilots.¹⁰⁹

However, it is also important to consider the definition of re-use seen as most appropriate by the industry. Drawing from the interviews, the definition of re-use should require an element of substitution at the national HTA reports. Thus, any re-use that is additional to the national HTAs is viewed as adding to the national process and should not be regarded as re-use.

Building on these definitions, there are a range of different indicators that could be used to assess re-use:

- Anecdotal evidence of the use of the report by authors, reviewers during the assessment (perhaps based on questions requested by the reviewers)
- Direct reference of the EUnetHTA Rapid REA pilot report in the country’s assessment – EUnetHTA would refer to this as minimum required for national adaptation
- Use of a section of the Rapid REA report - EUnetHTA would refer to this as more meaningful national adaptation
- Use of the rapid REA report in replacement for an existing part of the national process – which the industry would see as re-use

4.2. External re-use

There is some direct evidence on the extent of external re-use through EUnetHTA publications and references in national HTA reports and industry reports.

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

108 Retrieved from the individual pages of the EUnetHTA Joint Assessments (2015), [last access 4 September 2015], <http://www.eunetha.eu/document-type/joint-assessment/list>

109 CRA interview programme

EUnetHTA reporting on re-use

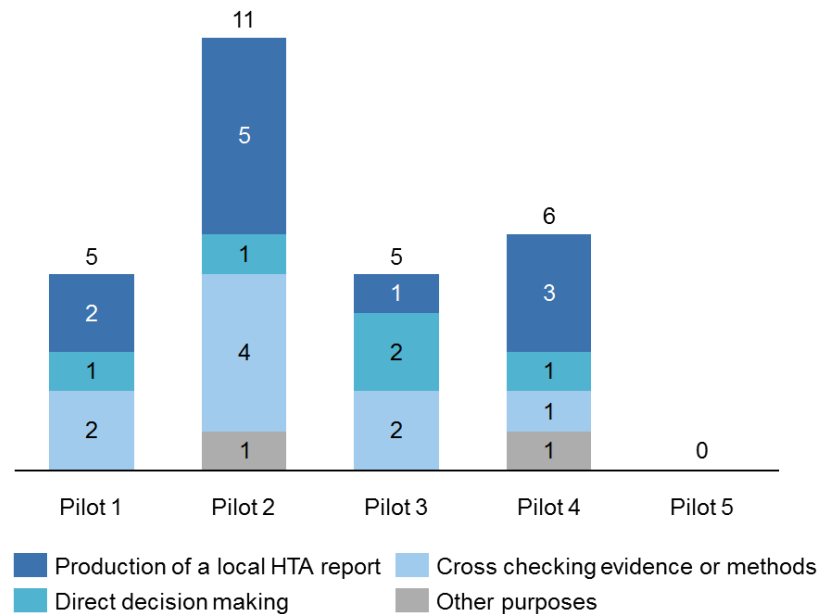
Until recently there was little data on the extent of re-use. Looking at the EUnetHTA dedicated website and the national HTA agencies noted by EUnetHTA, the following national adaptations are noted:¹¹⁰

- In March 2014, ZiN in the Netherlands reference Pilot 1¹¹¹: this assessment refers to the EUnetHTA Rapid REA Report in the analysis of efficacy as per burden of illness. The agency that conducts the analysis is the national HTA body in the Netherlands.
- In November 2014, LBI-HTA and HVB in Austria reference Pilot 1¹¹²: this assessment consists of a translation of the EUnetHTA Rapid REA Report. The agency that has applied this is an academic institution that conducts HTA reports and there is no evidence of this having any impact on reimbursement.
- In March 2014, ZiN in Netherlands re-use of Pilot 2¹¹³: this assessment refers to the EUnetHTA Rapid REA Report in its conclusions regarding the network analysis. It states that the EUnetHTA report confirms the results found by the ZiN assessment. The agency that conducts the analysis is the national HTA body in the Netherlands.

There have been isolated presentations discussing anecdotal evidence on re-use but little consistency. For example, a EUnetHTA presentation suggests pilot 2 was being used in the process or planned to be used in Croatia, Czech Republic, Finland, Ireland, Spain, Slovakia.¹¹⁴

However, more recently EUnetHTA has published a survey in preparation for the conclusion of Joint Action 2, as shown in Figure 13. This distinguishes between four types of re-use: Cross checking evidence; direct decision-making; production of a local HTA report and other purposes.

-
- 110 EUnetHTA website [last access 28 August 2015]: <http://www.eunetha.eu/national-uptake>
- 111 ZiN website [last access 28 September 2015]: [https://www.zorginstituutnederland.nl/binaries/content/documents/zin-ww/documenten/publicaties/geneesmiddelbeoordelingen/2014/1403-herpes-zoster-vaccin-zostavax/herpes+zoster+vaccin+\(Zostavax\).pdf](https://www.zorginstituutnederland.nl/binaries/content/documents/zin-ww/documenten/publicaties/geneesmiddelbeoordelingen/2014/1403-herpes-zoster-vaccin-zostavax/herpes+zoster+vaccin+(Zostavax).pdf)
- 112 Ludwig Boltzmann Institut website [last access 28 August 2015]: http://eprints.hta.lbg.ac.at/1013/1/DSD_73.pdf
- 113 ZiN website [last access 28 August 2015]: <http://www.zorginstituutnederland.nl/binaries/content/documents/zin-ww/documenten/publicaties/geneesmiddelbeoordelingen/2014/1403-canaqliflozine-invokana/1403-canaqliflozine-invokana/canaqliflozine+%28Invokana%29.pdf>
- 114 “Outputs of EUnetHTA joint work applied in HTA Agencies” Mirjana Huic, MD, PhD, Department for Development, Research and HTA, Agency for Quality and Accreditation in Health Care and Social Welfare, Zagreb, Croatia. http://www.eunetha.eu/sites/5026.fedimbo.belgium.be/files/6.%20Mirjana%20Huic_Plenary%20Innovative%20tools%20for%20HTA_HTA%202.0%20Europe.pdf

Figure 13: Purposes of usage, as at September 2015

Sources: Analysis based on EUnetHTA Stakeholder Forum, E-meeting, 8th September

This shows considerably more examples of use than previously published on the EUnetHTA website. Based on the interviews with companies (discussed further below), this also reflects much more significant use of the Rapid REAs than is apparent to the MAH in the markets.

However, looking at these data, despite the division in the four categories, it cannot be determined whether the Rapid REA has replaced any part of the national assessment or whether it has been used as a supplementary piece of information, whether the response reflects a national HTA agency or an academic group or the types of country that have used the reports.

Equally, it is difficult to make any conclusion about the number of “re-use” over time. Three of the pilots are very recent, affecting the number of potential markets, and some pilots assessed products already on the market, where new indications are not assessed in each market. It is therefore very difficult to draw any conclusions regarding the number of composition of re-use.

Industry data on re-use

Looking to the industry evidence on re-use. A study including the majority of the well-established national HTA agencies in Europe, confirms that Rapid REA for Pilot 1 has seen some adaptation at the national/local level (Figure 14).¹¹⁵ However, this uptake was still very limited because:

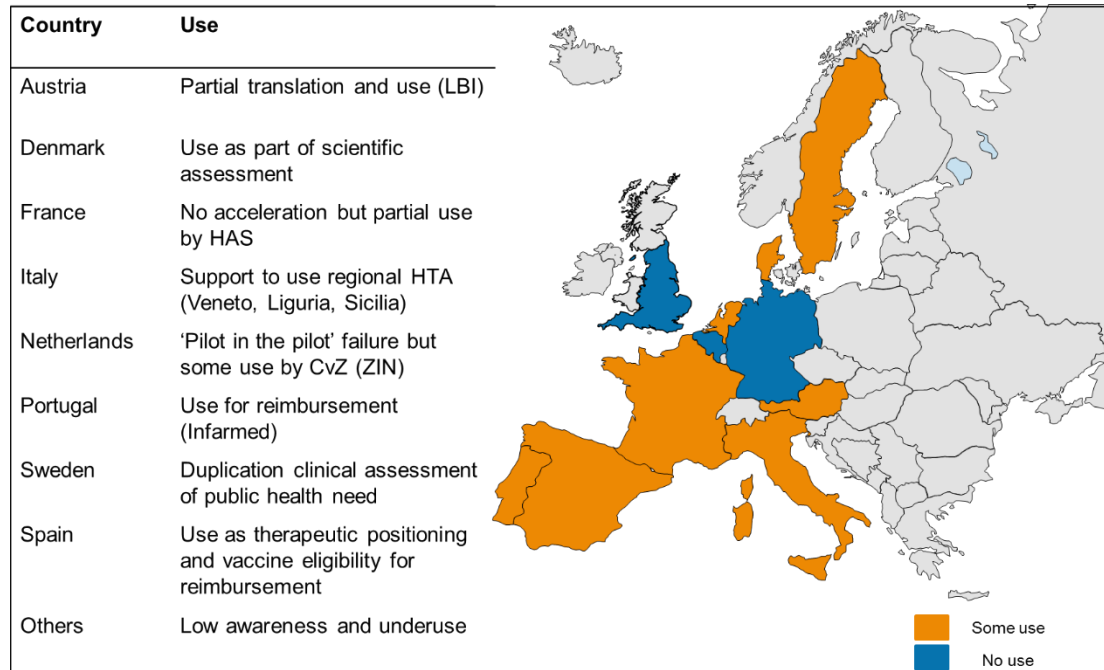
- There is no indication of any of these re-uses reduces duplication by replacing parts of the national assessments, and

115

EFPIA (2014), “Avoiding duplication – using European reports in national processes”.

- Some of the most high profile HTA bodies, such as NICE and IQWiG, have not used this output.

Figure 14: Pilot 1 Rapid REA by national HTA bodies



Source: CRA analysis based on SPMSD presentation (2014), "Avoiding duplication – using European reports in national processes".

Turning to other pilot assessments, in the second pilot there is agreement that the most notable example of reuse is that of ZiN in the Netherlands which references the EUnetHTA report.¹¹⁶ However, the MAH reports that there is no indication that any of the three authoring countries referenced the REA report. In discussions with the rest of the pilot participants, the manufacturers suggest that re-use has not been common. Evidence is limited to the use of the Rapid REA for Pilot 3 by Infarmed in Portugal (the Pilot 3 co-author), but to date the agency has only published the regulatory report and not the HTA one.¹¹⁷ It is indicated that Pilot 5 evidence will be referenced by HAS in France (author) but the report has not been published yet.

116 ZIN website [last access 28 August 2015]: [http://www.zorginstituutnederland.nl/binaries/content/documents/zin-ww/documenten/publicaties/geneesmiddelbeoordelingen/2014/1403-canaqliflozine-invokana/1403-canaqliflozine-invokana/canaqliflozine+\(Invokana\).pdf](http://www.zorginstituutnederland.nl/binaries/content/documents/zin-ww/documenten/publicaties/geneesmiddelbeoordelingen/2014/1403-canaqliflozine-invokana/1403-canaqliflozine-invokana/canaqliflozine+(Invokana).pdf).

117 Infarmed [last access 3 September 2015], http://www.infarmed.pt/portal/page/portal/INFARMED/MEDICAMENTOS_USO_HUMANO/AVALIACAO_ECONOMICA_E_COMPARTICIPACAO/MEDICAMENTOS_USO_HOSPITAL/DL_N_195_2006_3_OUT/RELATORIOS_AVALIACAO_PREVIA/PDF/ParecerNet_Nexavar.pdf

4.3. Lessons

The first issue with assessing the extent of re-use is the definition. EUnetHTA has defined national adaption but this does not require that the national process substitutes information from the REA report. Without a more useful definition of re-use it will be difficult to assess if there are efficiency improvements or this is simply adding to the information requirements in Europe.

The existing evidence of re-use of EUnetHTA assessments is limited and until recently, there was very little data on re-use. A recent survey by EUnetHTA however has shed some light on this issue. This indicates a greater level of usage than is apparent to the companies but does not allow us to determine whether this has improved efficiency. Significantly more effort should have gone into reporting re-use and the lessons published as the pilots developed.

There has been little analysis on why re-use to date has been limited. Some participants suggested that to date the priority has been on testing the process and re-use has not been prioritised. Industry participants have unanimously suggested that timing is one of the most important barrier to re-use of the assessments. It is not a realistic expectation that national HTA bodies will be able to refer to the REA report unless the latter is conducted within the given timeframe and is available prior to the start of the national assessment. In addition, there are no requirements on national HTA processes to accept information from EUnetHTA rapid REAs. Even the authors of the REA report are not under any obligation to consider its use in the national assessment. It is therefore inevitable that is used as a supplementary piece of evidence rather than replace any part of the existing submission. This is clearly important if one of the key objective of this initiative – the reduction of duplicative efforts – is likely to materialise. Finally, it appears that EUnetHTA currently does little to encourage re-use, in terms of making national HTA aware of the timing of the assessment publication or helping national authorities use the report.

5. Reform of the rapid REA

In the previous chapters of the report we have set out the factual experience of the pilots (at least from the perspective of the companies involved), looked at supporting evidence and drawn some lessons regarding the process, methodology, outcomes and re-use. In this chapter, we consider what would need to change in order to establish a sustainable rapid REA model going forward based on the experience of the five pilots.

We distinguish between recommendations for further pilots under Joint Action 3 and for any permanent form of rapid REA.

5.1. Improvements to the REA process

There are a number of potential improvements that could be made to the rapid REA process (up to the point of publication) to make this (1) more efficient (2) increase the potential for re-use. Below we consider:

- Timing: Should the process start earlier in order to make the assessment available at the time of submission to all HTA agencies?
- Stages in the process: Should additional steps – e.g. the project alignment meeting – be introduced to the process?
- Authors: Should the rules on the choice of author be changed?
- The types of products that are included in the Rapid REA process: Should this be limited to certain types of product?
- Should participation be voluntary: Should the manufacturers have a role in the decision to undertake the Rapid Assessment?
- Should other stakeholders be included in the process: Particularly is there a role for physicians and patients?

5.1.1. Timing

In reality, only one pilot was undertaken following the proposed timeline – where the publication of the rapid REA took place shortly after the EPAR. Even so, it seems reasonable to conclude the likelihood of re-use would increase if the report was published earlier.

However, under the current environment, the results of the rapid REA published at the EPAR will never be used in those markets where the national HTA submission and assessment occurs prior to marketing authorisation. Therefore, one could argue that, the EUnetHTA rapid REA needs to be published significantly before the publication of the EPAR in order to be of value to these markets, meaning that the process needs to start earlier or be undertaken more quickly. In general, to be used explicitly in national HTA assessments, this would need to be published approximately 3 to 6 months before the EPAR, meaning the process would start 12 months prior to marketing authorisation (instead of six months as it should today). However, based on experience the case for this seems weak, in particular:

- The dependence on the EPAR in the submission and the duplication in the analysis on safety (but also on relative effectiveness), it is difficult to believe that a rapid REA will ever be published before the EPAR.
- There is clearly a need for the REA to be consistent with the EPAR and therefore it can only be published at the same time.
- The issue of confidentiality would increase. In JA2 pilots, there has been a lag between the MA process and the EUnetHTA assessment, hence few issues regarding confidentiality emerged. However, if the EUnetHTA assessment is published before the EPAR, sensitive information may also be published. However these issues could be addressed in a more formal interaction/discussion between the MAH and the EUnetHTA coordinator at the beginning of the process that would provide any necessary clarification on confidentiality.
- The timeline for the pilot already appears challenging, particularly initiation, but also the other stages.

Based on the experience of the pilots we would recommend keeping to the current timeline for REA publication but enforcing this more diligently. In particular, we recommend only starting a rapid REA where it is possible to meet the planned timeline. The correct timing for pilot initiation and following the prescribed timeline is crucial to achieve the intended objective of re-use. The other steps in the pilot should be set reasonably and accordingly to this objective. In addition, a project plan should be established at the beginning of the process to account for any foreseeable delay (e.g. Christmas break).

This would allow the explicit re-use of the report only in markets that start the HTA process after the EPAR is issued. If there is a requirement for national HTA to use parts of the REA, this could clearly delay the process in some markets where submission occur prior to the EPAR (we discuss this further below).

A final alternative would be to publish the second draft report, so that this can be used in the submission to national HTA agencies (this would allow explicit reference in submission 2 months prior to the EPAR). However, this option clearly introduces complications. For example, there could be conflicts in the case where the EUnetHTA final report reaches different conclusions from the initial draft and the number of comments by the MAH and the WP5 reviewers suggest this could lead to more confusion.

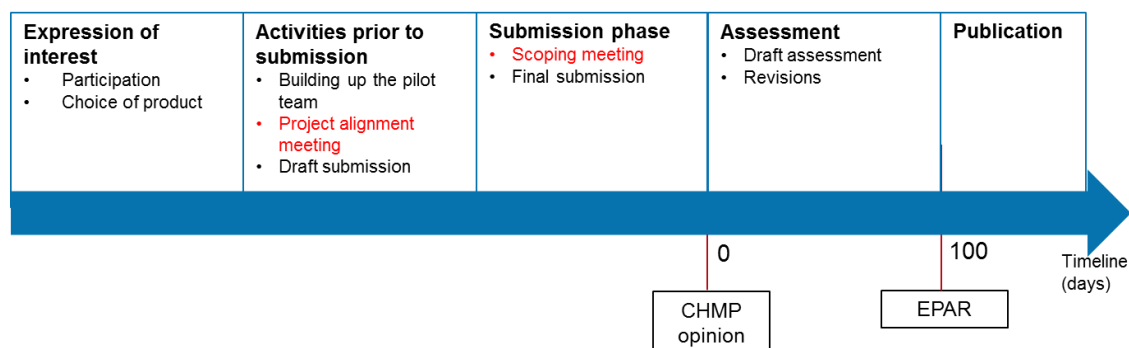
CRA recommendation: The current timetable should be followed. Only pilots where there is an expectation of this being met should be initiated in JA3. This would allow explicit re-use of the report only in countries that start the HTA process after the EPAR is issued. For any future pilot process it will be important to consider how many pilots can realistically be completed within the given timeframe to ensure that all the main objectives (e.g. alignment with the EMA process, re-use and completion of the number of the pilots established in the Grant Agreement) are achieved.

5.1.2. Stages in the process

The current process requires a draft submission without any discussion with the authors regarding the scope of the assessment. In particular, the draft submission is submitted with no agreement on comparators or outcomes. This represents a substantial risk to the company as disagreements and provision of additional evidence need to be addressed later in the process, implying additional and unnecessary use of internal resources and working against tight timelines. This is diminishing the willingness of the companies to participate in the process. To overcome this issue, there should be more formal interaction between REA team and the company before the draft submission to define and agree on the scope of the assessment.

Interaction between the REA team and the company would involve two formal meetings prior to the assessment phase (Figure 15). One meeting (“project alignment meeting”) would take place between the MAH, the EUnetHTA coordinator (and possibly the authors) in the earlier stages of the pilot. This meeting should provide guidance on the draft submission, indicating which information is expected (based on PICO) and the level of details. At this stage, it should also be agreed the definition of the population, the relevant comparators, the main outcomes to be measured.

Figure 15: Process timeline including two formal meetings between MAH and EUnetHTA



Another meeting (currently referred to as the “scoping meeting” by EUnetHTA) should be scheduled before the final submission is due between the MAH and the authors. This meeting should check the completeness of the final submission and be focused on data discussion with the coordination team (and ideally the authors). It should also be scheduled to allow enough time to the company to submit additional data and evidence if this is required.

On the one hand, the benefits of introducing a project alignment meeting appear clear and are in line with other national HTA processes. For instance, NICE develop the remit and the scope (including the definition of the population and relevant subgroups, the comparators, the principal health outcomes) before any evidence is submitted by the manufacturer. Interested parties are also consulted on this and involved in a ‘scoping workshop’ to formalise the final scope.¹¹⁸

On the other hand, this adds another meeting into the process with some administrative complexity. In addition, the agreement of authors is already challenging and this would add to the difficulty. However, as EUnetHTA gains more experience with the process and timing is chosen appropriately, authors' selection could become easier. It could also be argued that there has not been a pilot where comparators or outcomes have been disputed following the scoping meeting, so companies should learn from this. However, as the pilot process is established and authors increase in confidence the risk of choosing different comparators or outcomes increases.

CRA recommendation: A project alignment meeting 60 days prior to the scoping meeting should be introduced

5.1.3. Authors

The choice of authors has caused considerable concern, particularly the role of smaller HTA agencies and inclusion of agencies that do not undertake national assessments. This was due to three reasons. First, the industry believes that non-national agencies or smaller agencies may have limited capabilities (and possibly the adequate resources) to undertake complex assessments involving the use of complex methodologies. Second, and related to the previous point, there is the risk that the quality of the assessments is questioned by bigger agencies and that this could have an impact on national uptake. Third, when the assessment is performed by a regional/local agency, there is the concern that there will not even be uptake or re-use by the country where the author is from.

However, if the authors follow the formal guidance and provided by the EUnetHTA project managers, then who is undertaking the assessment is less important. Indeed, we do not find any compelling evidence that the author affected the quality of the assessment.

It is also clear that every assessment has unique challenges and the authors need to be pragmatic and have the resources to undertake the exercise. The EUnetHTA guidance suggests the authors selected should be based on experience. This should be experience of undertaking national HTA. To understand the challenges of re-use it is clearly preferable that the author is an HTA that will undertake a national assessment (this also helps motivate the industry and the author's involvement). As the pilot process moves from an academic exercise to one focused on the potential for re-use, the experience and reputation of the author becomes more important. This is most important in JA3 pilots.

CRA recommendation: 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.

5.1.4. The types of products that are included in the Rapid REA process

The first five EUnetHTA pilots have shown how the process works for a range of different products including different therapeutic areas (a vaccine, oncology, diabetes, cardiovascular), orphan and non-orphan products, products launching into therapy areas with existing products and those launching without any existing treatments. This suggests that the type of product

included in JA3 is relatively unimportant in terms of process (we return to methodological issues below).

However, the process needs to be tailored to the type of product, particularly if the regulatory timelines are truncated, the time lines for the REA need to be adjusted accordingly.

Finally, although the process works for different types of product, the benefits in terms of re-use for different products are still unclear.

CRA recommendation: To understand the benefits in terms of re-use, the pilots in JA3 should reflect different types of product. This should be more explicit than JA2

5.1.5. Participation

Participation has been an issue in JA2. Although it may be possible to review products on the market without the formal involvement of the MAH, undertaking a review prior to marketing authorisation without the MAH appears very challenging. However, the risk to companies from an REA being published without their involvement appears equally risky.¹¹⁹

The participation of companies will improve if the benefits from the assessment increase. If re-use is an explicit objective then companies will have a much greater incentive to participate. If there is a clear benefit from reduced duplication, then the cost involved will be substantially reduced. However, one could argue that that risk increases for companies if the re-use of REA becomes central to JA3.

One solution is transparency. The EUnetHTA team should publish the products based on a horizon scanning process and a rationale for the product as a pilot and companies should explain their rationale for inclusion or exclusion from the process.

CRA recommendation: Participation should continue to be voluntary while the process is being piloted. In order to encourage company participation, pilots should explicitly aim at adopting the report in participating agency processes. A transparent process of horizon scanning and selection would also increase the willingness of companies to engage. The decision of companies not to participate should also be made more transparent.

5.1.6. Stakeholders included in the process

In the assessment phase of the first five pilots for JA2, no physicians and patients have been involved. The inclusion of other stakeholders would make the EUnetHTA process more consistent with the assessment processes in national HTA processes, which consider patients' and clinicians' views. In these cases, the role of patients and physicians is seen as important in ensuring that the comparators and the outcome measures reflect clinical practice and

119

Some will argue that the position of the industry on this would probably become clearer after the completion of the sixth pilot in JA2. However, this is an ex post assessment involving a number of companies and therefore is not directly applicable.

societal preferences. For instance, NICE invites consultees (including physicians, patients and carers organisations) to comment on the draft scopes of the assessment early in the process of selection of technologies for assessment.¹²⁰

However, there are challenges. First, the views of patients and physicians should take a “European” perspective, rather than national, as the rapid REA reports should be valid and compatible for all the European countries in the EUnetHTA network. The European patient groups would need to develop the capacities to do this as they do for the EMA process. There is a challenge to consider how this can be implemented in practice (for instance, it would appear straightforward to have them as a reviewer of the draft report; however, it could also be considered if there is the need to involve them earlier in the process). Second, the rapid REA process is relatively complex and has tight timelines (failing to publish the report at the time of the EPAR would imply delays or reduce the potential for re-use). The degree to which this would improve or delay the process is unclear.

Therefore, in JA3, it should be considered if patients’ and physicians’ involvement should be a requirement and where in the process they can add most value. In particular, it could also be discussed whether this should be a requirement for all the pilots or for a set of products with given characteristics. In terms of the process, physicians can give input into the standards of care and context around relative efficacy and comparative safety which could be very important for the weightings of these domains. Physicians might also indicate where substantial treatment variation occurs across the EU, which is important to put the conclusions into context. Patients will add value in relation to assessing the Quality of Life and unmet need and also local context and values. This could be in the project alignment meeting (inputting on the PICO) and later in the scoping meeting.

CRA recommendation: The inclusion of patient and physician representatives in the process should be piloted in JA3.

Further implications for the Pilots under JA3

There are some implications from JA2 that should be considered as guidance on how to improve the efficiency and the quality of the process in JA3.

5.1.7. The goal of Joint Action 3

Most of the process issues were resolved in JA2 and it has been shown that assessment can be undertaken by European HTA agencies creating a European assessment. It is therefore possible to argue that JA 3 should focus on re-use which has not been adequately tested.

Although, it was stated as an objective of JA2, in practice re-use was de-emphasised throughout the pilots and the focus was primarily on the process and the methodology. JA3 should clearly put much bigger emphasis on re-use and potentially re-use could be the unique focus of JA3.

120

NICE website [last access 25 September 2015]: <http://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/Guide-to-the-single-technology-appraisal-process.pdf>

However, as set out above there are still unsolved issues on process (the role of stakeholders, the process for initiation, the inclusion of project initiation meeting) and methodology (discussed below) that should be addressed in JA3.

CRA recommendation: The primary objective of JA3 pilots should be re-use but other process and methodological issues still need to be resolved

5.1.8. The goals of each pilot

By stating explicitly which goals each pilot is trying to achieve and why the product has been selected, the manufacturers would have a clearer view of the potential implications of the pilot and the possible downside of participation. This would reduce uncertainty and could help justifying why internal resources are being invested in the pilot. In addition, a clear statement of the objectives could help EUnetHTA's commitment to achieve them and could be used in a debriefing meeting to evaluate the pilot experience.

In particular, re-use should be an objective for each pilot (and the timing of the pilot should be set accordingly to achieve this objective). While on JA2 re-use seems to be a 'secondary' objective, it should be one of the main goals in JA3. Importantly, re-use should be intended as the rapid REA *replacing* part of the national HTA assessment: simple reference to the REA report would not show how the report is used in practice and its outcomes fit into national assessments. Achieving this objective can provide a number of benefits. First, it would resolve the uncertainty on whether the rapid REA report can be used in practice and would provide a better understanding for all the stakeholders of what outcome can be expected from the EUnetHTA programme. Second, it would inform the manufacturers on how the internal submission process will (need to) work once and if the EUnetHTA rapid REA will become the standard. Third, it can justify the manufacturer's effort and resources dedicated to participate to the pilot programme, as the benefit (i.e. partial replacement of the national submission effort) would be more tangible. There is some risk from the manufacturer's perspective in pursuing this objective, as an unfavourable EUnetHTA assessment would have stronger implications in a number of markets. However, this would be a "calculated" risk as long as initial discussions with EUnetHTA, the choice of the authors and the countries for re-use and any other relevant details are able to minimise the uncertainties around the outcomes of the assessment. In addition, in a pilot environment it could be easier for the manufacturer to interact with the different stakeholders to deal with issues arising along the assessment process. In practice, this objective could be implemented by stating in the earlier discussion between the MAH and EUnetHTA which countries should re-use the rapid REA, and how it would be re-used. In particular, an interim objective for JA3 should be to implement a "contract" on re-use with the authors and the reviewers (on a case-by-case basis with the participating countries), which discusses how the pilot assessment will be re-used. This would also help the participating countries to learn how they need to change their internal process to adapt to the EUnetHTA assessments.

CRA recommendation: The objective of each pilot, at least at a high level, should be transparent and discussed with the MAH.

5.1.9. Feedback

In the JA2 experience, feedback from the EUnetHTA coordinator to the manufacturers has been informal and debriefing meetings have usually been scheduled several months after the publication of the reports. There is the need to formalise the debriefing process and consider how feedback can inform and improve subsequent pilots. In particular, establishing a post-publication feedback/debriefing would help to ensure that a manufacturer's view is discussed for incorporation in subsequent assessments. Moreover, industry's views should also be incorporated into the feedback process. In addition, the lessons should be published so that future authors can draw on this and improve the process. Considering the objective of re-use, a debriefing meeting should also discuss how the report has been considered/included into the national HTA process.

CRA recommendation: Feedback should be a formal part of the process and lessons from the pilots shared with MAH, industry stakeholders and WP5 members. A debrief meeting should be timely scheduled to allow lessons learnt from a pilot to be input in the subsequent pilot(s)

5.2. Improvements to the methodology

The changes required in the clinical effectiveness section are largely incremental, whilst there are much larger questions regarding the safety analysis. The methodology can be improved in three main ways:

- Aim: Should the methodology focus on best practice rather than an accumulation of practices?
- The application of guidelines: Should the methodology follow guidelines or is there a need for flexibility in different cases?
- The objective of the safety analysis: Should this focus on ensuring consistency or avoiding duplication?

5.2.1. Develop a methodology consistent with the aim of the rapid REA

There is clearly a discussion in many of the pilots regarding the methodology that the REA should use and whether it incorporates the needs of different national systems – particularly following the comments from the reviewers. Although it could be argued that the Rapid REA should try to anticipate different needs to avoid duplication, the REA should reflect “best practice”.

The principle on which EUnetHTA is founded is that of creating a standardised European system that will reduce duplication if this encourages other HTA to follow this approach and feed in to national HTA and pricing and reimbursement systems. As a result, it is key for the EUnetHTA methodology to represent what a ‘good REA’ or a best practice in Europe should reflect. This has the advantage that this will establish uniform and good standards and methods which could then be adapted in national frameworks.

However, a clear disadvantage is that national HTA systems apply very different methodologies and the differences act as barrier in incorporating the rapid REA reports. Although the reviewers

have the opportunity to make comments on different approaches, i.e. the use of composite end points or surrogate markers, the existing pilots have focused on the EUnetHTA approach. This seems appropriate and should be maintained (with the implication that national HTA systems might need to change to adapt to the EUnetHTA reports). This means that the choice of author and the re-use by some HTA will be limited. This is an inevitable consequence of a European REA model in the short term.

CRA recommendation: The EUnetHTA methodology should continue to be a best practice model and not a collation of all the methodological approaches used by the national HTA frameworks. The implication of this for the re-use of the pilot assessments is that the focus should first be on those countries which have a methodology consistent with the EUnetHTA guidelines, so that direct integration is possible while other countries have time to adjust.

5.2.2. The application of guidelines

Drawing from the experience of the application of the EUnetHTA guidelines in the pilots, the experience has been generally positive. The guidelines on the choice of comparator, outcome measures and quality of evidence are seen as helpful. Our assessment is that these guidelines have been followed in the large majority of cases, helping companies understand the information to be included in the submission.

In some cases the guidelines could be made clearer.¹²¹ It would be beneficial to reconsider and specify more clearly a few methodological issues, most prominently on the use of surrogate and composite endpoints. Drawing from experience during the pilots, an unclear stance on the use of these endpoints can lead to lengthy and burdensome discussions. In addition, there should be clearer guidance on when and how to apply specific instruments to rate quality of evidence (e.g. GRADE) and how to interpret findings.

A drawback of having a definite position, is that there are unique circumstances where a different approach will be appropriate. The EUnetHTA team seem to largely follow the guidance but have on occasions adopted a different position. These will need to be assessed on a case by case basis but where this is occurring, there should be some communication with the MAH and this should be discussed in the final report.

CRA recommendation: The guidelines on clinical effectiveness should be incrementally improved (with a focus on endpoints and assessment of quality of evidence) and if authors take a different position, there should be a requirement to explain the rationale (however guidelines needs to be sufficiently flexible and pragmatic to accommodate the divergent types of innovation and their contexts that will be subject to review)

121

There is currently a public and internal consultation taking place on reviewing the methodological guidelines for REA. More information can be found on: EUnetHTA (2015), "Public and internal consultation of eight adapted methodological guidelines for Relative Effectiveness Assessment": Available at: <http://www.eunetha.eu/news/public-and-internal-consultation-eight-adapted-methodological-guidelines-relative-effectiveness>

5.2.3. The goal of the safety analysis

The most challenging methodological issue in rapid REA methodology is how to perform a relative safety analysis and what this is trying to achieve. It is widely recognised that any value assessment should take into account safety. If the product has an improved safety profile compared to other products on the market then this has implications for the value assessment undertaken at the national process. However, the EMA process assesses safety and determines that the product has a positive risk benefit profile. The question is what should be included in the Rapid REA and the extent to which this needs to be distinct from the EPAR.

It needs to be considered whether the assessment of safety should be significantly reduced. In particular, given the EMA assesses the safety of the medicine, the REA should not question whether the product is safe. Any improvement in safety should be taken into account in the quality assessment for patients (or in national economic assessment as this potentially reduces cost). This implies that the safety section should simply duplicate the analysis in the EPAR, providing national HTA with the safety and clinical effectiveness data in context.

However, others argue that the regulatory assessment focuses on safety but the REA process should focus on relative safety. In the same way that EMA looks at efficacy, often against a placebo, but REA used indirect comparisons to try to compare to standard of care. This means that the safety data should be set out versus the appropriate comparator.

In reality, the EPAR compares the safety profile of the product with comparators on the market. The REA has gone further in making these comparisons, particularly requesting statistical analysis and effectively undertaking indirect comparisons of the safety. The guidelines recognise the problems with undertaking analysis of this kind:

- Safety data from clinical trials focused on assessing clinical outcomes cannot be used in this way as study design is not fit for this purpose.
- Unlike clinical effectiveness, the data on safety is constantly being updated and published. The approach drawing on clinical trials appears perverse. In particular, the quality of the safety data is not the same for products under review and for products that have been longer on the market

There is general agreement that there is a role for the REA putting the safety information into context (without simply replicating the EPAR). The current approach appears to take the toolkit from relative efficacy and apply this to safety. This is scientifically inappropriate and reflects the academic literature of relative safety being at a much more immature state. There appears to be a need to step back from this and ask what national HTA assessment should want from a European assessment of safety beyond the assessment conducted by the EMA.

CRA recommendation: The role of safety analysis needs to be reconsidered and tested in JA3

5.3. Improvements required post publication to encourage re-use

The re-use of the rapid REA has been very limited and this is an area where there could be significant improvements. The pilot process thus far has focused on testing the process and that has reduced the emphasis on how to increase the uptake of the output. However, it is key

to the future success of the EUnetHTA initiative to increase the focus on, and improve, re-use. In addition to changes to the process and methodology, there are other potential changes that would improve the potential for re-use.

5.3.1. Reporting of re-use

If the goal of the pilots under JA3 is to encourage re-use, this needs to be monitored and reported. The current reporting of re-use appears partial and done in an inconsistent manner. This has a number of elements. First there needs to be consistent definitions. Re-use can be categorised in three main pillars: use of any EUnetHTA output, adaptation of any part of the rapid REA report and a full adoption of the rapid REA report. Each of these can be useful, but efficiency also requires that the use of the REA report substitutes for a part of the national process. This should be included in the definition of re-use.

CRA recommendation: The tracking of re-use requires consistent definitions, a focus on whether this reduces duplication and more consistent reporting

5.3.2. Responsibility to re-use by authors vs EUnetHTA

Currently relatively little is done to encourage the re-use of the rapid REAs by EUnetHTA. The reports are published to the EUnetHTA website and may be included in a newsletter. However, if re-use is a focus of the exercise, all the HTA agencies should take greater responsibility in using the reports. National HTA bodies ultimately define what the level of re-use will be. Given the national HTA bodies are authors and reviewers, this could bring some obligation to re-use the report (as mentioned above, signing a “contract” with the manufacturer at the initiation of the pilot). More generally, there could be a commitment of WP5 member to use and report on their experience of the utility of the report.

CRA recommendation: Re-use requires all stakeholders need to make commitments. This includes EUnetHTA, authors and reviewers. Re-use should be a clearly stated objective, agreed in a “contract” with the sponsor for a defined set of countries (e.g. authors and reviewers).

5.3.3. Binding vs flexible use of REA at national level

Thus far, going through the pilot process has served as an academic exercise for both EUnetHTA and participating companies. Given the timing of the REA reports it is inevitable that the use of pilots is weak. There is no agreement on the implications for the national process of HTA.

Therefore this needs to be flexible. As the national process varies from country to country and some processes start prior to the possible publication of the rapid REA, if there are rules, then this will delay processes that are currently occurring prior to MA, delaying patient access.

However, others argue that flexible rules mean that it is inevitable that rapid REA is duplicative and only references in the most superficial way. Therefore there needs to be a commitment by HTA to not duplicate the four domains in the rapid REA.

A third approach is to define the set of markets where the rapid REA is broadly consistent with the current process and form a coalition of the willing to test the re-use within these markets.

This approach seems the most pragmatic for JA3, as other countries need to change their processes in the meantime.

Box 2: Potential course of action to improve national HTA body participation

One approach is to target a number of countries that will be the early adopters and re-use the rapid REA report. Considering the development of HTA bodies across Europe, this could include national HTA that receive submissions at or near the time of the EPAR, specifically:

- The involvement of the coordinating team's national HTA
- Include one major HTA body from the EU5 countries, which has thus far had significant contribution in the process
- Include other mid-size well-established HTA bodies

This is a preliminary suggestions that have emerged during industry discussions, but a final group of markets should be decided in cooperation with EUnetHTA.

For these markets, re-use should incorporate an element of *replacement of some parts of the national assessments* to be regarded successful and a justification of where national assessment differs from the European assessment. However, it is clear that some HTA processes are inconsistent with this approach. For example, some markets do not accept surrogate end-points. Undertaking a pilot of this kind can only be taken where countries are consistent with the REA process.

CRA recommendation: The pilots under JA3 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. This would involve an explicit plan developed as part of the scoping phase for how the re-use will be piloted in the country (this should include the modification to the national submission template and a transparent approach to replacing some national elements of the assessment with the outcomes of the REA).

Appendix 1: List of EUnetHTA documents consulted

EUnetHTA Joint Action 2 on HTA 2012-2015 3-year Work Plan

Available at [last access 2 September 2015]:

<http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/EUnetHTA%20JA2%203-year%20Work%20Plan%20%282013%29.pdf>

Info-Package for the EUnetHTA Stakeholder Group

[Not available online]

Manufacturer submission templates to support production of core health technology assessment (HTA) information (EUnetHTA Work Package 7 Subgroup 4)

Available at [last access 2 September 2015]:

https://eunethta.fedimbo.belgium.be/sites/5026.fedimbo.belgium.be/files/Manufacturer%20submission%20templates_information%20leaflet.pdf

Methodological guidelines for rapid relative effectiveness assessment (REA) of Pharmaceuticals developed in WP5 of EUnetHTA JA:

1. Clinical endpoints
2. Composite endpoints
3. Surrogate endpoints
4. Safety
5. Health-related quality of life
6. Criteria for the choice of the most appropriate comparator(s)
7. Direct and indirect comparison
8. Internal validity
9. Applicability of evidence in the context of a relative effectiveness assessment

Available at [last access 2 September 2015]:

<http://www.eunethta.eu/eunethta-guidelines>

Procedure manual WP5 Strand A: Rapid Relative Effectiveness Assessment of Pharmaceuticals”, V4 April 2015

Available at [last access 2 September 2015]:

[http://www.eunetha.eu/sites/5026.fedimbo.belgium.be/files/2012123627%20-%20Procedure manual REA%20pilots WP5 Strand%20A.PDF](http://www.eunetha.eu/sites/5026.fedimbo.belgium.be/files/2012123627%20-%20Procedure%20manual%20REA%20pilots%20WP5%20Strand%20A.PDF)

Technical Annex of the EUnetHTA JA2 Grant Agreement

Available at [last access 2 September 2015]:

<http://www.eunetha.eu/sites/5026.fedimbo.belgium.be/files/Technical%20Annex1b%20of%20the%20EUnetHTA%20JA%202%20Grant%20Agreement.pdf>

The HTA Core Model for Rapid Relative Effectiveness Assessment of Pharmaceuticals, V3.0 March 2013

Available at [last access 2 September 2015]:

[http://www.eunetha.eu/sites/5026.fedimbo.belgium.be/files/Model%20for%20Rapid%20REA%20of%20pharmaceuticals final 20130311 reduced.pdf](http://www.eunetha.eu/sites/5026.fedimbo.belgium.be/files/Model%20for%20Rapid%20REA%20of%20pharmaceuticals%20final%2020130311%20reduced.pdf)

The HTA Core Model for Rapid Relative Effectiveness Assessment, V4.1 July 2015

Available at [last access 2 September 2015]:

http://www.eunetha.eu/sites/5026.fedimbo.belgium.be/files/news-attachments/hta_core_model_for_rapid_reas_-_public_consultation_2015.pdf