

Are We Moving Towards Collaborative European Rapid Relative Effectiveness Assessments? Insights Gleaned from the EUnetHTA Joint Assessment of Canagliflozin—Approaching Joint Relative Effectiveness Assessments

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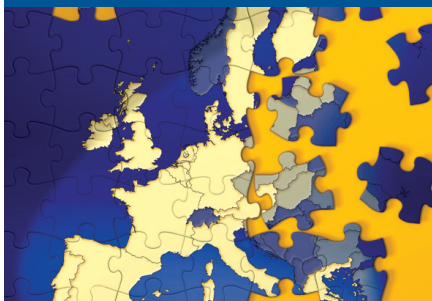


KEY POINTS . . .

Maintaining high levels of consistency regardless of the various participants and assessment topics will be important in ensuring that the highest quality assessments are produced.

A high level of European project management and a high degree of commitment to the project by all participants will be necessary in order to achieve successful outcomes.

EUnetHTA has shown that this can be the way to increase transparency and professionalism in local health technology assessments and to support international collaboration with the aim to decrease duplication and facilitate work for HTA agencies and industry, to generate faster access to market, and to increase the quality of health care.



What is EUnetHTA?

The European Network of Health Technology Assessment (EUnetHTA) is a network that aims to create an effective and sustainable platform for health technology assessment (HTA) with the objective to produce reliable, timely, transparent, and transferable HTA information. Its goal is to decrease duplication of HTA assessments, to use resources efficiently, and to develop methodological guidance and processes for collaborative production of HTA information.

After successful completion of the first Joint Action (JA1) in 2010-2012, a second EUnetHTA Joint Action (JA2) was funded by the European Commission. A key outcome of JA2 has been the jointly produced rapid relative effectiveness assessments (rapid REAs). JA2 will finish in May 2016 and will be succeeded by the JA3 (2016-2019). A kick-off meeting for JA3 will take place in Amsterdam on March 3.

What Is the Aim of Work Package 5 (WP5), Strand A?

WP5 coordinates the development, production, and implementation of joint rapid REAs, focusing on clinical effectiveness (cost-effectiveness will be dealt with on a national level). WP5 aims to test the capacity of HTA organisations to collaborate and produce these joint assessments, as well as apply them in a national context. Generally, one of the EUnetHTA partner agencies acts as author and one as co-author responsible for the production of the assessment.

WP5 is divided into Strand A (assessments of pharmaceuticals) and Strand B (assessments of other technologies). At the end of 2015 Strand A has produced all its 6 planned pilots:

- Zostavax for the prevention of herpes zoster and postherpetic neuralgia.

- Canagliflozin for the treatment of type 2 diabetes mellitus.
- Sorafenib and its use for the treatment of progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma refractory to radioactive iodine.
- Ramucirumab in combination with Paclitaxel as second-line treatment for adult patients with advanced gastric or gastro-oesophageal junction adenocarcinoma.
- Vorapaxar for the reduction of thrombotic cardiovascular events in patients with a history of myocardial infarction.
- New pharmaceuticals for the treatment of chronic hepatitis C.

Experiences from the Second Joint (REA)

In the case of canagliflozin, there were three authoring agencies: FIMEA (Finland), AAZ (Croatia), and Regione Veneto (Italy). The authors collaborated to produce a first draft. This draft was evaluated by dedicated reviewers (which consisted of organisations from Spain, France, Austria, Bulgaria, and the Czech Republic) responsible for providing input and quality assurance. The marketing authorization holder (MAH) and all WP5 members had the opportunity to comment on the editorial draft of the assessment.

The assessment phase of the second pilot (canagliflozin) started at the end of September 2013 and was finalized in February 2014. It was the first rapid REA that had been produced in parallel to the European Medicines Agency (EMA) process (the Committee for Medicinal Products for Human Use [CHMP] granted a positive opinion to canagliflozin on September 20th, 2013). In general, an assessment should be produced within 90 days from the positive opinion of the CHMP.

The Process and the Lessons Learned

Once the topic of canagliflozin was identified and the pilot team completed, the MAH, Johnson & Johnson, submitted a draft submission file. Upon reviewing this draft submission file, a scoping meeting was held.

The scoping meeting—a face to face meeting between the authors, MAH, and the coordination team to discuss the upcoming assessment—was deemed very important and productive by all involved parties, as this helped frame the general focus and generated insights into the production of the REA. The MAH emphasized that the scoping meeting should be held as early as possible in order to agree on the focus of the rapid REA, as this is a different process than making submissions to Member States for pricing and reimbursement of medicines.

The scoping phase was completed upon finalizing the project plan and receiving the final submission file from the MAH. The assessment phase began in September 2013. The three authoring organisations had to produce the first draft of the REA in 35 days. Additionally, a sub-contracted academic group was hired to assist in assessing the extensive Network Meta-Analysis included in the submission from Johnson & Johnson.

The structure of the assessment followed the HTA Core Model®, established during JA1. This model had a three-layer structure consisting of a summary, domain text, and result cards. The HTA Core Model for rapid REA is divided into four domains: 1) Description of the technology and comparators (TECH); 2) Health problem and current use of technology (CU); 3) Clinical effectiveness (EFF); and 4) Safety (SAF). The MAH developed the submission file following the Core Model. They found that not being confined to a template, but addressing questions from the HTA Core Model® gave them flexibility as a manufacturer.

The first draft was evaluated by dedicated reviewers in December 2013. With the quality assurance input from the dedicated reviewers, a second draft was produced and this version underwent editing. Once medical editing was complete, the MAH and all WP5 members had the

opportunity to comment on the draft of the assessment in the consultation phase. The authors noted that this process assured the quality of rapid REAs and led to steady improvements in the quality of the assessments. (Fig. 1).

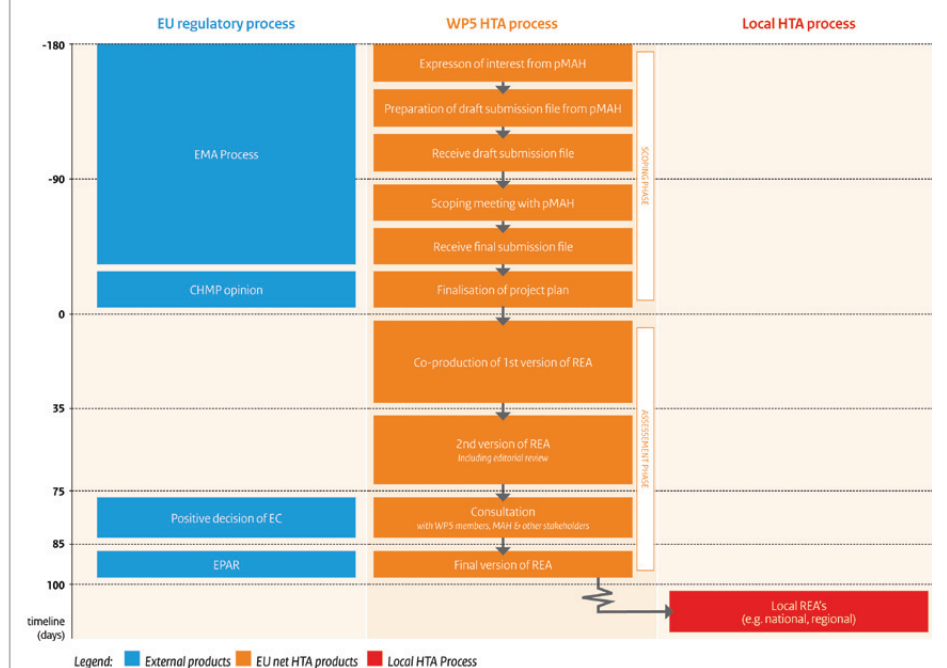
As this second rapid REA was the “first” to be produced alongside an EMA process, timelines played an important role in the discussion. The MAH noted that the timelines given for the scoping and the submission of relevant information were very tight, given the delay in identifying the authors. The CHMP opinion for canagliflozin was delayed by 3 months, which in turn delayed the beginning of the assessment phase. Such a circumstance is not an exception when assessing new drugs; therefore, flexibility in REA timelines should be considered. The final REA was published in February 2014.

The overall experience of this jointly produced assessment was constructive.

In fact, the process was viewed as a positive portent for the future, considering that these rapid REAs aim to develop objective, reliable, transparent, and transferable data which should be implemented into national settings.

With regards to the structure of the rapid REAs, the involved parties agreed that the use of a structured format was on the one hand helpful and gave a good orientation, yet on the other hand, the three-layer structure—consisting of a summary, domain text, and result cards—was very “time consuming,” partly producing duplications of text with a high potential for inconsistencies. Furthermore, this structure made it difficult for the MAH to review the assessment in a short period of time. The HTA agencies confirmed that result cards were difficult to use, but were of good quality. Considering that this is only the second pilot, all parties agreed that continuous improvements will be achieved through “iterative prototyping,”—

Figure 1: Schematic Overview of the Organisation of Rapid REAs in EUnetHTA WP5
(it should be noted that these graphs represent the ideal picture; however, divergence is very possible for specific joint REA's).



CHMP indicates Committee for Medicinal Products for Human Use; EC, European Commission; EMA, European Medicines Agency; EPAR, European Public Assessment Reports; EU, European Union; HTA, Health Technology Assessment; MAH, marketing authorization holder; pMAH; REA, relative effectiveness assessment; and WP5, Work Package 5.

improvements from step to step, from pilot to pilot—in future cycles.

To ensure a harmonized and transparent assessment process, EUnetHTA has developed several methodological guidelines on the following topics:

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

(The full list of EUnetHTA guidelines can be found at: <http://eunetha.eu/eunetha-guidelines>)

The use of these guidelines is important for standardizing the production and methods of joint assessments, but is also important

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for the end users who are encouraged to adopt the use of guidelines in their own process.

What Are the Challenges for Future Assessments?

The main challenges of jointly produced rapid REAs are the cooperation, communication, and coordination between all participants.

From the authors' point of view, a high level of European project management is important in order to achieve successful outcomes and to establish a productive atmosphere. Further, a high degree of commitment to the project by all participants will be necessary.

In addition, the diversity within European assessments has been stressed. It is important that participants and users can be reassured that joint REAs are not a lottery, but rather a reliable and valid set of information for decision makers.

Maintaining high levels of consistency regardless of the various participants and assessment topics will be important in ensuring that the highest quality assessments are produced. According to the MAH, EUnetHTA has demonstrated that it is possible to collaborate on generating reports. There are other issues now which need to be addressed, such as reproducibility, impact, and the value of collaboration.

The MAH also underlined the fact that industry is often the sponsor of trials and that this characteristic of trials should be approached in a more general way with regards to the risk of bias. From a manufacturer's perspective, the assurance of consistency and reproducibility of the jointly produced REAs is important, as the biggest issue from their perspective is the risk of a false negative, which has a bigger impact if it is done once at the European level. False negative results could have a high impact with regards to the delay of the process, not just on one country but on several European countries—potentially

impacting patients' access to innovative medicines where there is an accepted unmet need. Additionally, it is important to keep in mind who will be the end users of these REAs—decision makers, not academia—which means the format and questions should be designed with these users in mind. An alignment between the different work packages of EUnetHTA will be important to achieve this. For example, the MAH proposed the submission template should focus on those aspects required for an EU level review of relative effectiveness.

It should be recognised that next to the challenges for authors and industry, there are a lot of regulatory/legislative restrictions in countries regarding the implementation of REAs, such as choice of comparators, language, definition of content, existing procedures, and financial limitations. The HTA agency perspective noted that there will be challenges to find agreement on comparators in order to be able to implement REAs in the national context.

Hurdles will be presented with legislative and methodological criteria.

Suggestions such as integrating the perspectives of patient representatives, physicians, or payers are made to further improve the process and the outcome of rapid REAs. In addition, the idea of a workshop with the industry (manufacturer) and other involved stakeholders was discussed in which potential barriers and solutions could be explored.

Current Situation: Based on the Lessons Learned

The case of canagliflozin was an excellent learning opportunity to test collaboration and the process of developing joint rapid REAs. WP5 has continued to improve the process of HTA collaboration and has taken the valuable lessons learned and applied them to the REAs which have followed throughout the course of JA2.

After completion of two pilots, WP5 made changes based on the experiences and lessons learned. A key change would be the removal of the results cards (thus reducing the three-layer structure). Removal of the results cards shortened the assessments considerably (the 3rd and 4th pilot are about half the length of the 2nd), reduced duplication within the text, and improved the readability of the REAs. Additionally, the second draft writing and medical editing phases were merged to streamline the process.

Another important development is the use of the submission file template. Colleagues at NICE in WP7 of EUnetHTA produced this template, which consists of a collation of evidence requirements for reimbursement decisions from around Europe. The collated requirements are structured in the template based on the EUnetHTA HTA Core Model and it is used by the MAH to prepare the draft and final submission file to be used in the REA. The submission file template was used in the third, fourth, and fifth REA from WP5 Strand A, and led to a harmonized method of collating the information in the MAH's submission.

Closing Thoughts

In conclusion, there is a lot of potential in jointly produced rapid REAs. Such assessments can serve to reduce duplication, improve collaboration among

Europe, and improve the quality of HTA to support reimbursement decisions across Europe.

From the HTA agency perspective, appraisals and decisions are and will be done on a national level. For example, the HTA Core information of rapid REAs and methodological guidelines can be produced on a collaborative level, and as a result, differences between European countries can be reduced. The objective in the future is that joint assessments, with the addition of national/local context-specific information, will be submitted. The national appraisal committees would then appropriately take into account all of these aspects when making a decision.

Developing future joint REAs can be the way to increase transparency and professionalism in local HTA assessments. The process can also help to support international collaboration with the aim of decreasing duplication and work for HTA

agencies and industry, generating faster access to market, and increasing the overall quality of health care.

The question to be asked is whether or not this is the way of the future—is Europe indeed moving towards collaboration in HTA assessments? Indeed it is.

Despite challenges, and many more lessons to be learned, this is not just an academic exercise—it heralds a new model of European collaboration in HTA. ■

(The content has been updated with the current status of WP5 pilots as of June 2015 to keep the information relevant)

Additional information:

The preceding article is based on a panel session, "Are We Moving towards Collaborative European Rapid Relative Effectiveness Assessments? Insights Gleaned from the EUnetHTA Joint Assessment of Canagliflozin," held on the 17th Annual ISPOR European Congress, 8 – 12 November 2014, Amsterdam, and The Netherlands.

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