

Project Title: Next Generation Health Technology
Assessment to support patient-centred, societally oriented,
real-time decision-making on access and reimbursement for
health technologies throughout Europe



Deliverable Title: Overview of the development of the use of
RWD including a review of international consensus
methods currently developed



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Description of the deliverable	<p>Overview of the development of the use of RWD and discussion of methods relevant for decision-making linked to reimbursement, including a review of international consensus methods currently developed (Lead Partner: TLV; Collaborating partners: UU, ZIN, EORTC, SRI, NICE, EURORDIS. (M3-M24))</p> <p>By means of a questionnaire and interviews with a selected number of HTA agencies the HTx team has explored the use and development of RWD in HTA. This overview focusses on identifying HTA agencies that are aiming at a wider use of RWD for establishing effect in clinical practice, or are encouraging, gathering or leading the development of methods for how to use RWD for decisions linked to reimbursement or the use of pharmaceutical products, methods and medical devices. The review will also include an overview of the practical aspects of international collaboration on RWD and on how consensus is achieved on how to use RWD in for example joint assessment reports.</p>
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Key words

RWD, RWE, methods development, HTA, decision-making, consensus making models, innovation, change management, health policy.



ABBREVIATIONS

AIFA: Agenzia Italiana del Farmaco, Italy

AOTMiT: Agencja Oceny Technologii Medycznych i Taryfikacji, Poland

ATMP: Advanced Therapy Medicinal Products

EUnetHTA: European network for HTA, subsidised by the European Commission

EFPIA: European Federation of Pharmaceutical Industries and Associations

ESIP: European Social Insurance Platform

HTA: Health Technology Assessment

IMI: Innovative Medicines Initiative

INFARMED: Autoridade Nacional do Medicamento e Produtos de Saúde, Portugal

MEA: Managed entry agreement

MEDEV: Medicine Evaluation Committee

MOCA: Mechanism of Coordinated Access to orphan medicinal products

NICE: National Institute for Health and Care Excellence, UK

NIPN: National Institute of Pharmacy and Nutrition, Hungary

PLEG: Post-Launch Evidence Generation

RCT: Randomised Controlled Trials

RIZIV-INAMI: Rijks, Belgium

RWD: Real World Data

RWE: Real World Evidence

SMC: Scottish Medicines Consortium

SNOMED: Systematized Nomenclature of Medicine

TLV: Tandvårds och Läkemedelsförmånsverket, Sweden

WP: Work Package

ZIN: Zorginstituut Nederland, the Netherlands

EXECUTIVE SUMMARY

This report aims at giving a picture of what the use of Real World Data (RWD) in European HTA agencies looks like today and what development projects are ongoing when it comes to access to data and interpretation of this data for the purpose of decision-making in HTA agencies.

In order to get a clear picture of this, the project team has performed a questionnaire survey with HTA agencies active in the EU-project EUnetHTA and complemented this with interviews with 10 agencies.

In the process of the work a theoretical framework has been developed. It helps to identify where in the HTA processes RWD can be used and what questions RWD possibly could answer. The framework also looks at what conditions need to be in place in order to facilitate the introduction of methods and decision models based on RWD. Attitudes and leadership are highlighted as important factors that will drive necessary action. Possibly the framework can also be a guidance for those agencies that want to develop their use of RWD.

The review of HTA agencies shows that there is substantial work being carried out in a limited number of agencies, whilst most are yet not actively working on methods for the use of RWD or access to data. There is a considerable will to expand the sources for evidence for decision-making as a complement to traditional RCTs in the agencies taking part in the questionnaire. Development of this is hampered by both attitudes and leadership and by difficult access to data. This is a bit counter-intuitive given the high appetite for using RWD expressed in the questionnaire. No agency states that they are happy with their access to data. However, many agencies seem to be in a “wait-and-see-mode”. Also, in some places, development happens thanks to devoted individual officials with a special interest in data analysis.

The candidates for interviews were selected among the agencies that seemed to have the most use of RWD and the most development work ongoing. Still very few agencies apply different methods for analysis of RWD or collaborate with academia in order to apply and validate methods commonly used in other disciplines than the medical field. The majority of the interviewed agencies still struggle with data access. This is also true for the larger field answering the questionnaire. A few agencies and their governments have taken radical measures to ensure access to data. The framework helps us to see that different parts of the prerequisites for access to data have been addressed in different countries.

There are a number of ongoing EU-projects that can be seen as effort to create a European consensus. EUnetHTA has, with its long process of making agencies work together, made a model of consensus-by-doing. Also, some standardisation efforts like the EH DEN-project are worth mentioning. Apart from EUnetHTA, few HTA agencies are active in these projects and it can be asked if there is a risk of exclusion, that goes beyond the mere participation in these projects. Are many HTA agencies not developing their networks since they do not take part in EU-projects, and do they by that miss out in the learning process and in influencing the debate? Or is it due to not participating in networks that they do not get invited to take part of EU-projects?

In the questionnaire answers, almost all agencies have indicated that they have made negative reimbursement decisions due to high uncertainties in the clinical efficacy. The high rate implies that there's a need to investigate more what consequences this could have on patient access and how access to complementary data such as RWD could reduce the risks, since a large majority of the respondents meant that the possibility to collect data on relative effectiveness and safety could have changed the decision, at least under some conditions. This implies that there is a cost in not using RWD, in lost health or in money spent on medical products that have not been reassessed. Re-assessment based on RWD will likely be a pre-requisite for more advanced payment models for new therapies.

INTRODUCTION

This review has been performed as a deliverable in the Horizon 2020 Project HTx: *Next Generation Health Technology Assessment to support patient-centred, societally oriented, real-time decision-making on access and reimbursement for health technologies throughout Europe*. The aim of the project is described in the Grant agreement in the following terms:

“HTx will create a framework for next generation Health Technology Assessment (HTA) that supports patient-centred, societally oriented, and real-time decision-making for integrated healthcare throughout Europe. HTx will focus on therapeutic areas with high unmet need for which HTA information has to be provided on complex and personalised combinations of health technologies. Based on a select number of relevant case studies, HTx will enhance methods for integrating evidence from RCTs and Real World data (RWD).

HTx will also augment statistical and econometric methods for generating robust estimates of effectiveness and cost-effectiveness in order to support relevant HTA decision-making for these complex and personalised combinations of health technologies.”

The health care systems in the EU are facing challenges as an increasing number of new medical products are reaching the market with expectations from the pharmaceutical companies of high levels of remuneration. Often the same products pass the regulatory processes based on studies that present relatively immature data for measures that are relevant for HTA agencies and especially for evaluation of effectiveness. The difficulties in assessing both budget impact and relations between effectiveness and costs is a challenge for health systems that are forced to increase cost-control as political scrutiny increases and resources are limited.

The main challenges for HTA lie in the immature data of studies presented by pharmaceutical companies and the accompanying uncertainties about the long-term effects of medical products. A detailed study of this has been performed in the HTx project and it shows that data insufficiencies at the time of assessment is the main challenge for HTA-agencies. This is especially true for more complex health technologies, like ATMPs or combination treatments¹. On the other hand, the EU countries' social welfare and healthcare systems generate a large amount of data that can help. An OECD report from 2019², based on a survey answered by respondents from 26 countries, concluded that all these countries do collect data routinely. About half of this group of countries use this data routinely in cost-effectiveness studies. The countries in the report admit that this data is not used to its full potential.

The value of real world data (RWD) is recognised by the EU and through various projects it supports development of the use of RWD from clinical practice. It is not only to support the individual HTA agencies in the member states. RWD can also be an important part

¹ HTx deliverable 1.1 *A gap analysis of the challenges in HTA of complex health technologies*.

² OECD, 2019. *Using Routinely Collected Data to Inform Pharmaceutical Policies Analytical Report, 2019* <https://www.oecd.org/health/health-systems/Using-Routinely-Collected-Data-to-Inform-Pharmaceutical-Policies-Analytical-Report-2019.pdf>

of scientific research and development in the pharmaceutical industry. To have easily accessible registries with relevant data will be a competitive advantage to countries and regions in the future. Many countries have formulated this in Life Science strategies.

Real World Evidence (RWE) based on RWD use has been discussed extensively the last years, and the view of it has also been analysed in an article from October 2020 by several EMA staff members; *Randomised controlled trials versus real world evidence: neither magic nor myth*³:

“The future is not about randomised controlled trials (RCTs) versus real world evidence (RWE) but RCTs and RWE – not just for the assessment of safety but also of effectiveness. Finally, we highlight that, in the era of precision medicine, we may not be able to reliably describe some small treatment effects - either by way of RCTs or RWE.”

They highlight the fact that there need not be any conflict between the use of RWD and RCTs, they complement each other.

It can be discussed if all agencies and countries in the EU can follow the same path. However, it is important to guarantee an equal access to methods and data for the assessment of new medical products and all countries should at least be able to follow the developments and be inspired by others. The importance of access to networks and knowledge-building contexts is discussed in the present report.

The HTx project aims at producing innovative methods for HTA. It is important for carrying out the project to understand what the current use of HTA methods, and especially methods using data, looks like in the relevant countries and agencies. This report aims at providing such a background information. It is also looking at informing the project of the current use of data from clinical practice, and what the main drivers and hindrances for this are. It hopes to clarify what the needs in the HTA agencies are and inspire to exchange of experience. This should also inform the HTx project about what methods are already in use and, by this, avoids duplication.

³ Hans-Georg Eichler, et al., 2020. *Randomised controlled trials versus real world evidence: neither magic nor myth*
doi:10.1002/cpt.2083 <https://ascpt.onlinelibrary.wiley.com/doi/epdf/10.1002/cpt.2083>

METHODS

This study is aiming at giving an overview of the development of the use of RWD in the EU, and provide a discussion on methods relevant for decision-making linked to reimbursement currently being developed. Various methods have been applied to gather a mass of data that makes it possible to analyse and describe this issue. A questionnaire was sent out during the Spring of 2020. It was combined with literature studies looking at both other studies of what RWD work is done in the EU and how it can be implemented, and at change mechanisms and consensus making models currently applied. Using the answers from the questionnaire a number of HTA agencies were selected and interviews performed. This data was then analysed both in a thematic way and through the lens of the models formed after the literature study.

Questionnaire

A questionnaire was sent to 36 HTA organisations, that are members of the EUnetHTA network. Out of 36 invited HTA organisations, 24 organisations from 23 different countries completed the questionnaire (response rate 67%), see Appendix 2. There was a relatively balanced spread of organisations throughout Europe, with a slight overrepresentation from the Nordic countries, as seen in Figure 1. Twenty-one responding organisations (88%) were responsible for assessing pharmaceuticals, of which nine (38%) are assessing solely pharmaceuticals. Ten organisations (42%) were responsible for assessment of non-pharmaceuticals, of which one (4%) solely assesses non-pharmaceuticals. An overview of responding HTA organisations can be found below in Figure 1.

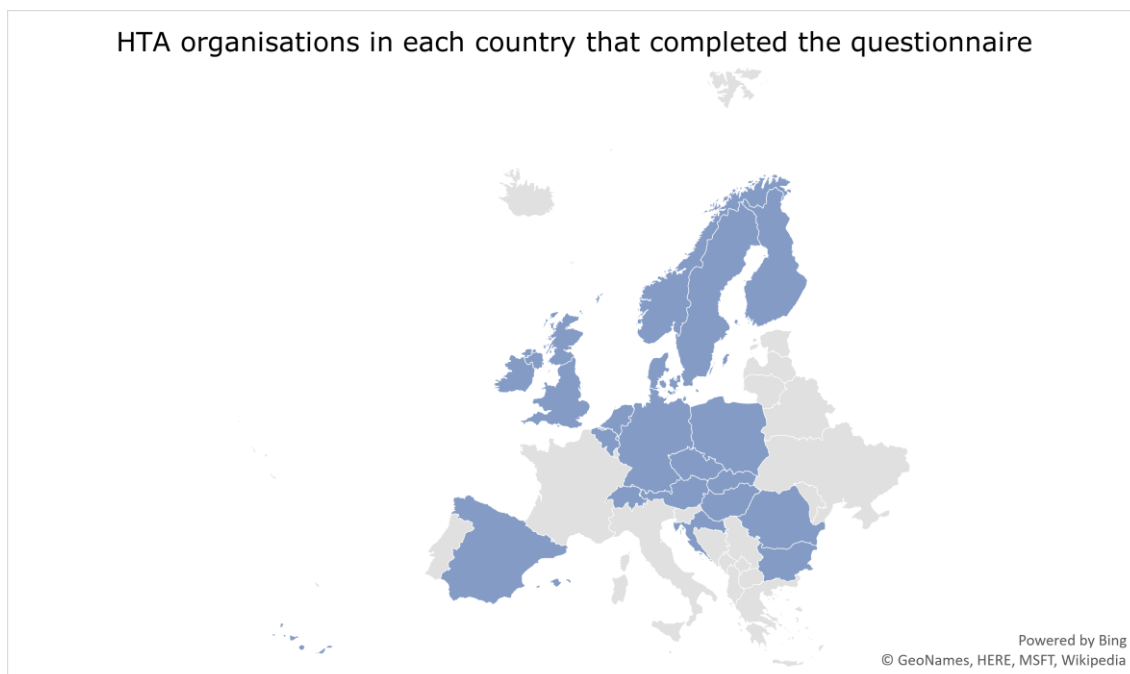


Figure 1 - Map with highlighted countries with HTA organisations that completed the questionnaire

The questionnaire was prepared and sent out in collaboration with two other subtasks of work package 4 in HTx. It made the questionnaire lengthy, but it was deemed more efficient than repeatedly coming back with shorter questionnaires. It also meant that the

questions were audited by a larger group and the whole questionnaire evolved to become a better controlled product with higher quality. The questionnaire was validated and tested for reliability and disseminated via the online tool LimeSurvey⁴. The analysis of closed and quantifiable questions was done in Excel.

The questionnaire was constructed using so called skip logic, meaning that some questions only apply to some respondents, given a certain response to a previous question. This means that not all questions were answered by 24 respondents. Most of the questions also provided the possibility of adding a comment or free-text answer.

Interviews

From the 24 partners that had answered the questionnaire seven authorities were purposively selected for interviews. In addition to that four more authorities were invited to participate and three agreed. In total ten interviews were performed from May to October 2020 and recorded with the consent of the participants. One interview was discarded since it was felt that the content did not become relevant, despite the best intentions on both sides. The interviewee was not working with decisions on HTA, but had a purely academic perspective. When selecting the interviewees, the authors were looking for agencies with the most comprehensive experience of developing the use of RWD or actually using RWD. It was deemed that this approach would contribute most and enable description of best practice. Here, the questionnaire was the prime source of information. AIFA in Italy, INFARMED in Portugal and the National Health Insurance Fund in Estonia were added as their achievements in the field has been presented in many international HTA fora. Also, it was important to include some larger EU-countries and perspectives from the relatively new member states. A list of the interviewed organisations can be found in Appendix 4.

The interviews were subsequently transcribed, and the transcripts shared with the interviewees for comments. All interviewees came back with approvals and some minor clarifications.

The interviews have been analysed using a framework approach. One source describes this method as follows:

“The framework approach offers the researcher a systematic structure to manage, analyse and identify themes, enabling the development and maintenance of a transparent audit trail. It is particularly useful with large volumes of text and is suitable for use with different qualitative approaches”⁵.

Several important topics and themes were explored in the interview guide (appendix 3) for the semi-structured interviews and answers were subsequently grouped into corresponding themes. Also, the Swedish experiences from TLV have been worked into the thematic presentation.

⁴ A detailed description of this can be found in HTx deliverable 1.1 *A gap analysis of the challenges in HTA of complex health technologies*.

⁵ Hackett A, Strickland K (2018) *Using the framework approach to analyse qualitative data: a worked example*. Nurse Researcher. doi: 10.7748/nr.2018.e1580

Literature Review

The literature review has been performed mostly through internet searches or through recommendations. Many papers on RWD issues are circulated between practitioners in this field and are discussed. That partly informed the selection of background literature. The literature review has thus not been structured in a methodical way, but been formed partly ad hoc and within the possibilities allowed by the time constraints of the task.

Three themes have been important in the literature search: previously performed descriptions of HTA agencies, or similar, developing the use of RWD, change mechanisms and consensus making models currently applied, and also, descriptions of EU-projects that have produced tools for RWD use or implementation, or that are currently doing so. The websites of these projects have been most helpful.

Methodological Limitations

The scope of this study has been relatively ambitious and presented the authors with several issues and hard choices. There will always be a limit to how many agencies can be made to respond to a questionnaire. Also, some authorities will find it hard to make time for an interview.

Interviewing is a very time-consuming activity, if interviews are transcribed verbatim. Also, in transcription mistakes can be made due to temporary flaws in conference calls and recordings, or simply due to the language barrier. Giving the interviewees a chance to review transcripts is partly a way to remedy this, but there will inevitably be a time lapse between interview, transcription and review, and the interviewee can miss correcting expressions deemed important at the time of the interview. However, these issues are surely limited, especially since there has been a continued dialogue with the interviewees, with the view to limit misunderstandings.

A more serious limitation is that the answers potentially only reflect the view of one person in the questionnaire, and in the interviews only one, or two, persons' views. The questionnaires were to a large extent sent to known officials in the concerned authorities. The whole WP 4 helped gathering contacts and asking for response, assisted by the main project leader for Htx. That way it was to a large extent controlled that the officials sent the questionnaire and invited to interviews were indeed active in the relevant fields or could channel the questionnaire or interview invitation to the appropriate colleague.

The selection of authorities for the questionnaire was based on the EUnetHTA Joint Action participants. That is a selection that should guarantee that most agencies in the field are reached, but it also means a bias in the fact that agencies participating in EUnetHTA already have a network in which RWD issues are discussed. This can influence the outcome but was also a practical way to go since the EUnetHTA participation covers some 70 agencies and that very few agencies are not represented. For the interview one authority that is not participating in EUnetHTA was chosen. Also, one can see that the response rate was higher in countries being very active in EUnetHTA and that smaller countries in the southern or eastern parts of the EU have a lower response rate to the questionnaire.

Finally, it is worth stating that this has been a work in progress and a discovery journey also for the authors. Had we known what we know now, the questionnaire would have

had somewhat different questions and the interviews would have been more detailed and specific. The growing awareness that came with the interviews inspired the work on the Theoretical Framework. Had that been in place before the interviews, we believe more details could have been captured.

The authors have selected a number of models provided by other studies in order to make it easier to make an analysis of the situation with RWD usage in HTA agencies today. We have also chosen to produce simple models of our own, based on the input from the interviews and the basis for the best practice we have been able to identify in some cases. This framework is presented in the next section and used in the section on analysis.

THEORETICAL FRAMEWORK

In this study, RWD is defined as data collected in a non-randomized controlled trial setting⁶. This permits a broad view of the activities performed by HTA authorities in Europe in order to widen their evidence bases. However, in order to draw conclusions, studies are helped by a theoretical framework that facilitates the understanding of the results and the conclusions. For this purpose, we have considered several studies and formed our own models that are presented below. The purpose of each model presented is to make it possible for the reader and us to distinguish important traits in the work of the HTA agencies taking part in the study. The models complement each other, but do not build on to each other.

In the HTx Work Package 1 a framework has been developed with the title *General Framework Definition for Case Studies*⁷. This conceptual framework is meant to provide guidance on the process of innovating HTA-methods. It takes into account how multiple stakeholder views should be channelled and also helps the developer to check whether they have considered all relevant aspects of innovation of HTA methods. This is a framework that is helpful in the development of new methods and for that reason it is mentioned here. In this part of the report framework refers to the juxtaposition of models that will help us understand how HTA agencies work with RWD today and in a development perspective, when looking at the empirical data from the questionnaire and interviews performed in this task.

HTA Agencies' Views on RWD in Decision-Making

In a study published in August 2020, Facey et al.⁸ discuss actions for stakeholders related to RWD to support decisions for HTA. In their study they start from a stakeholder perspective and describe what the different stakeholders see as necessary for decision-making based on RWD. A proposed list of potential uses of RWD is helpful to us. It provides an exhaustive list of what measures in HTA decision making that could be supported by RWD.

Facey et al. propose three settings linked to uncertainties in determination of value, partly linked to a life-cycle perspective of the pharmaceutical product, where RWD can be used. These are at Initial HTA, for the use in connection with Managed Entry Agreements and at re-assessment. At the Initial HTA, RWD can be used to describe current standard of care; create external comparators to contextualise efficacy; and to populate cost effectiveness and value impact models. For Managed Entry Agreements, there are additional potential use; to evaluate outcome in clinical practice; and resolve uncertainties related to determination of value in the initial assessment. The third category is re-assessment and where RWD can have two potential uses: to complement the clinical and economic evidence base that was available in the initial assessment and

⁶ See Makady A, de Boer A, Hillege H, Klungel O, Goettsch W; (on behalf of GetReal Work Package 1). What Is Real-World Data? A Review of Definitions Based on Literature and Stakeholder Interviews. *Value Health*. 2017 Jul-Aug;20(7):858-865

⁷ General Framework Definition for Case Studies, Next Generation Health Technology Assessment (HTx). Deliverable 1.2.

⁸ Facey KM, Rannanheimo P, Batchelor L, Borchardt M, de Cock J (2020). *Real-world evidence to support Payer/HTA decisions about highly innovative technologies in the EU—actions for stakeholders*. *International Journal of Technology Assessment in Health Care* 1–10.

<https://doi.org/10.1017/S026646232000063X>, <https://pubmed.ncbi.nlm.nih.gov/32878663/>

to monitor utilisation and evaluate budget impact in clinical practice. For a schematic overview see Table 1.

Table 1 - HTA agencies views on RWE in decision making, Facey et al., 2020, adapted by HTx WP 4

Resolution of uncertainties in determination of value	Setting	Potential uses of RWE in decision making
	Initial HTA	<ul style="list-style-type: none"> • describe current standard of care • create external comparator to contextualize efficacy • populate cost effectiveness and budget impact models
	Managed entry agreement	<ul style="list-style-type: none"> • evaluate outcomes in clinical practice • resolve uncertainties related to determination of value in the initial assessment
	Re-assessment	<ul style="list-style-type: none"> • complement the clinical and economic evidence base that was available in the initial assessment • monitor utilization and evaluate budget impact in clinical practice

This model permits us to see what use is discussed at the different European agencies that have taken part in the survey and the interviews. It allows us to discuss if there is a holistic view at an agency when it comes to discussing potential use of RWD or if there is a more tailor-made discussion fitted to the agency's current or future needs and situation.

Schematic Model of The Main Questions that could be Answered Through RWD

In order to complement the views on potential use of RWD in Facey et al.'s article, we find it useful to also analyse what sort of questions RWD can answer. This is discussed in the TLV report on RWD from October 2020⁹.

According to TLV, the questions that RWD can answer can be divided into two overall categories; *How is a pharmaceutical product used?* and *What is the effectiveness of the pharmaceutical product in clinical practice?* The second question is of course more complicated to answer since more advanced methods and competences are needed. Questions that can be relevant to understand how a pharmaceutical is used are, for example, which indication the drug is used for, the dosage regime, duration of treatment, treatment in combination with other medical products and adherence to treatment.

The patient-specific questions concern, for example, which previous treatments the patient has had, the patient's health status and possible comorbidity. This could for instance be measured by previous diagnosis and health care visits. Gender, age and socioeconomic status can also be important patient-specific factors. If an agency has

⁹<https://www.tlv.se/rwd-development>

general access to this sort of data, the number of patients should be clear. Data from these two sub-categories are sometimes referred to as claims data, that is data that can be found in the documentation of insurance systems. Some of the data fields described are more frequent than other in claims data.

The effectiveness of the pharmaceutical product in clinical practice, can be divided in sub-questions on efficacy from the clinical study, clinical values such as death and patient reported values on for example pain. Health-related outcome measures that may be of interest to study regarding drug effect may, for example, be hard clinical outcome measures, such as heart attack or death. Other outcome measures may be those used in the underlying clinical study, which are sometimes surrogate measures. For example, it can be laboratory values such as LDL, that indicate cholesterol levels in the blood or other measured values, such as blood pressure. The questions are visualised in the Figure 2 below from the TLV RWD report 2020.

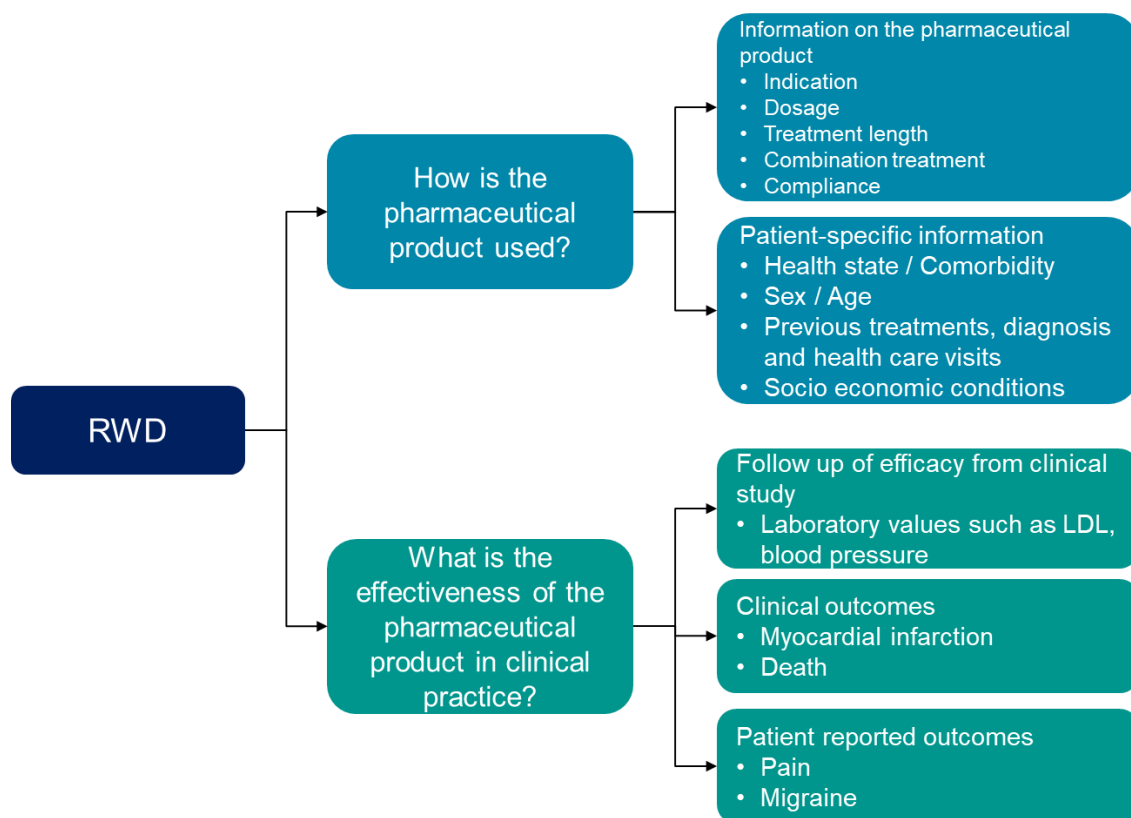


Figure 2 - Schematic model of the main questions that could be answered through RWD and examples on variables that could be needed to respond questions on medical product use and effectiveness in clinical practice, RWD report TLV, 2020, slightly modified by HTx.

The model cover questions that RWD can potentially answer will complement the Facey approach described above and also allow us to better understand the ambition of RWD work in the various agencies and see the scope of what they wish to accomplish. This can be seen as a result of the vision that drives RWD work in the concerned member states.

Data Access and Processing

A fundamental aspect of development of the use of RWD for decision making is the access to relevant data. Very roughly the countries that participated in the survey and interviews can be divided into two categories; Those who have permanent national registries, either for clinical or financial use, and those who put up registries ad hoc, for instance to follow up MEAs. That gives us the ground for a model over the relationship between data registries and RWD analysis.

A number of questions are relevant to look at when it comes to access to data. The first would be if there is a legal requirement to gather data from clinical practice without patient consent. This should allow for data collection for all treatment regardless of reimbursement status at a national level, so that the data or statistics becomes available to HTA agencies and is updated regularly, if not continuously. To override patient consent makes it possible to gather data that covers the whole patient population without selection bias.

The second question is what infrastructure is available to channel, store and treat data. This must allow HTA agencies and academia to access the data continuously. Data in registries must also be updated continuously and the rules for accessing the data need to be transparent. If data is updated too seldom it becomes very hard to follow-up pharmaceuticals and their outcomes in a way that is practical and gives a correct and fair view of treatment at the right time.

If suitable infrastructure is in place it should be possible to decide if the data is accessible in a processable form. In some countries the authorities may only access information that is collected in patient records in text-strings, making it difficult to analyse larger data sets. In this is also included a demand of quality control of the data as well as high granularity and coverage.

A last condition to be able to process the data for decision making, is that there is access to the needed skill sets. Countries with strong traditions of registry research are likely to be ahead here. Agencies can have this knowledge in-house, which is of value, but it can also be present with registry holders or academia collaborating with the HTA agency

This hierarchy of questions leading to useable data for RWD analysis in HTA is visualised in Figure 3. This flow-chart reflects the complex nature of data access and it will be further discussed in the results and discussions parts of this report.

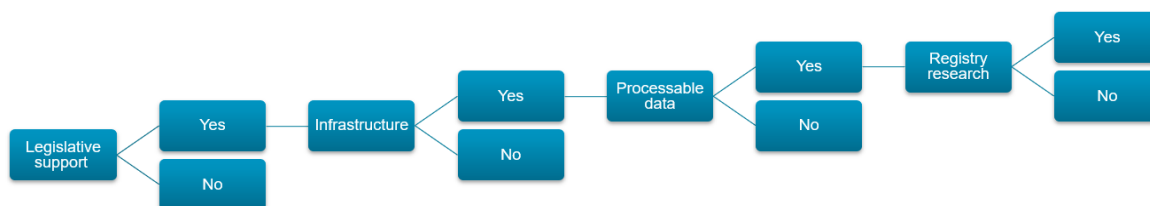


Figure 3 - Data Access and Processing

Review of Change Models in the Context of Use of RWD

In this context it is also useful to think about how implementation of new methods can take place in organisations. This is discussed in detail in the HTx deliverable “Review of change model methods for multi-lateral multi-stakeholder initiatives”¹⁰ from July 2020. The report presents four change management models, namely adaptive space, midstream modulation, developmental evaluation, and knowledge brokering. This is a selection that was deemed useful for HTx purposes, there are of course a great number of possible models.

Adaptive space is “a space that people come together in to provide solutions for the tension between the need to produce and the need to innovate”¹¹ In a certain extent this can be seen as a variant of the “policy sandbox” idea, where innovation can take place firmly separated from the daily running of affairs. When the stakeholders are assembled in the creative space a number of facilitating tools are available to foster the dialogue. For our purpose the idea of working on innovation separated from the activities of the agency is central. Also, the fact that this method aims to foster co-production with other stakeholders is of interest.

Midstream modulation was created to help the scientific world to engage closer with societal and ethical considerations. It was developed for a laboratory environment where for instance a scientist expert in ethics is employed and works among the other scientists, using both observation and various direct engagement tools to ensure a larger perspective as the science project evolves. This has the advantage that this perspective can be taken into account almost instantly and that the expertise assures the project that they have considered these aspects. For RWD innovation, the ethical and societal perspective can be important to cover, but one could also see other disciplines being integrated into the teams. An HTA team could need IT or data transfer knowledge close at hand, and so on. An iterative process of feedback and observation is the key steppingstone here.

Developmental evaluation can be said to be an “approach to conduct implementation research and to support organisational learning and knowledge translation”¹². It is evaluation aimed at supporting the implementation of innovations, from an early stage, and it is also suitable to adapt innovation projects to a rapidly changing environment. Fully applied this method calls for professional evaluators being attached to the innovation programme who can apply an evaluation logic and think systematically, seeing interrelationships and boundaries. Collecting data for the evaluation can be a large undertaking, so the method needs professionally trained evaluators and resources for their work. In counterpart this affords the innovation programme timely feedback and allows for adaptation as the innovation evolves. The method’s focus on complex relations and systems makes it especially useful in complex environments and introducing RWD with many stakeholders involved would be such a complex environment.

Knowledge brokering is another method to support implementation of innovations. Here a special mediator or broker interacts with the scientists or experts leading the innovation

¹⁰ *Review of change model methods for multi-lateral multi-stakeholder initiatives*. 10 July 2020, Next Generation Health Technology Assessment (Htx) etc. Deliverable 4.1.1.

¹¹ *Ibid.* p.14

¹² *Ibid.* p. 19

effort and the decision-makers. The right sort of broker has a knowledge of both worlds; their discourses and their restraints. This is a process of choosing, packaging, and distributing information between the two layers in an organised and coordinated way to achieve best impact. At best, revealing differences in perspectives and expectations, this effort can foster a shared vision and expedite the necessary changes in the organisations involved. The role as broker is challenging and intimate knowledge of both layers are required. The model builds on the assumption that there is a limited understanding of each layer's respective discourse and methods and that the gap can be closed or lessened through sharing of knowledge.

In the discussion of the results of this study, the WP 4 team hopes to discuss what use of change models that can be discovered at the various HTA authorities, and also to see if there are recommendations that can be made from this choice of change models.

Policy Factors for RWD Use in Reimbursement Decisions

Looking at the results from interviews and surveys we identified a number of factors that affect the possibility to use RWD for reimbursement decisions. Based on these observations we propose a model of what are the necessary steppingstones towards tangible results in the use of RWD. We are not saying that the factors build on to one another, or that they are interdependent, but we note that agencies that express that they have achieved results that are useful for them are working in an environment where a critical number of these factors can be observed. We also do not pretend to have made an exhaustive list of factors. However, we perceive that there is a relation between the suggested factors and that they can be seen as a hierarchy, to a certain extent, which is why we have chosen to visualise them in the form of a staircase. This can surely be discussed. However, attitude and leadership can be seen as the basis of all change management needed to work with RWD and legal support is not present in all countries and can be seen as somewhat the last step.

The importance of **stable institutions** for development are often highlighted in economic studies¹³. In this context that means institutions that have a clear role, strong support of and dialogue with the government, good relations and practices for collaborating with other agencies, health care providers, and (public) registry holders. Infrastructure for data can form a part of this, but it can also be established relatively rapidly if the institutions are strong, collaborative and have insights of the needs. RWD can be a national need at many levels, but to fulfil the need of the HTA agencies these agencies should be able to identify and communicate needs and ways to overcome them in the national context.

An important factor is **attitude and leadership**. Some agencies have a clear mission statement, a vision, or a mandate from their government to work on inclusion of RWD in decisions. Also, attitude can reflect the experience of the individuals working in the agencies. If one has no positive experiences of RWD, or lack the insight in what skills and methods that can make RWD work, it is likely that one will be negative to the development of use of RWD. Inversely, some agencies benefit from the engagement and the will of individual staff members that use skills and contacts to work with RWD.

¹³ As an example: Ben Ali, Mohamed & Krammer, Sorin. (2016). The Role of Institutions in Economic Development. 10.1057/9781137480668_1.

This is of course a risk for the activities since they in these cases are not systematic and can lack management support.

Access to European networks is another factor that can have a positive influence on the capacity to develop the use of RWD. In some networks, like EU-projects related to HTA learnings related to RWD are shared. However, the most important factor is that in networks the challenges and needs can be discussed, and good examples will surface even if it is not the purpose of the particular project or network. If an agency is weak in resources, they might choose not to engage in activities like EUnetHTA and will then not be included in these discussions or different spin-off development projects. It is thus not easy to tell what is the hen and what is the egg, but the result is that some agencies risk being left without the positive influence of joint discussions and the influence of a network of practitioners. Once left out they also are unlikely to be included in follow-up projects. Agencies that lack networks are less likely to be forerunners in RWD.

The use of RWD for decision making in reimbursement decisions, as in the potential uses described above, also calls for a special skill set. There needs to be an understanding of how registries are set up and what they contain, as to understand what questions can be answered by what data set, but there is also a need for skills in statistical analysis, just to mention one field. This **competence** does not necessarily need to be in-house at the agency, but can be present in registry holders, or academic partners, with whom the agency collaborates.

The last factor of importance to our model is legislation or relevant **regulations**. Some jurisdictions have a very clear mandate to collect RWD and to use it. There are possible conflicts of interest with integrity issues and research issues, and they need to be clarified in legislation. A detailed legislation can give high impetus to a development process. In other countries governments give agencies assignments that are reported separately, and the development will be done in an environment that can be described as policy sandboxes, apart from the daily business of the HTA authority. This can be a safer way of preparing for legislation, as changes to legislation as development continues can be cumbersome. Here the agencies have a key role to formulate their needs of legislative support, after trying various models of implementation. See an overview of the policy factors below in Figure 4.

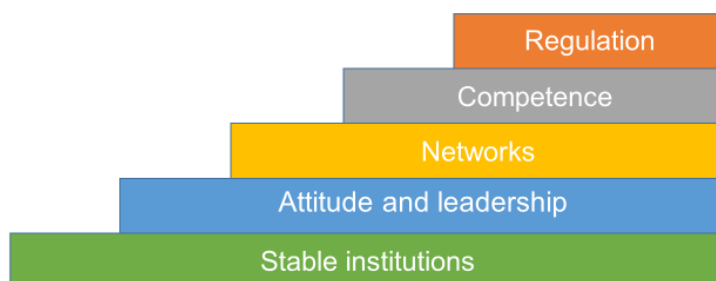


Figure 4 - Policy factors for RWD use in reimbursement decisions. Source HTx.

RESULTS

Results from the Questionnaire Sent to HTA Organisations in the EU

The questionnaire sent to HTA organisations in the EU, selected from the EUnetHTA membership list, as previously described, gave an initial overview of the use of RWD in decision-making for HTA in the EU-countries. In the following text the most informative answers from the questionnaire will be described.

One of the aims of this report was to find out if there is overlapping development of methods to use RWD being done at various authorities in Europe. That includes in-house development or adaptation or collaborations with academia, consultants or other stakeholders. This is part of the mapping of activities in the RWD field, aimed to understand the state-of-play of RWD developments and to avoid duplication in the work done, not only by HTx-partners, but for all relevant stakeholders, including other EU-projects.

A majority of the agencies state that they have projects developing and assessing methods for using RWD for decision (14/24). When going through the free-text answers where respondents detailed what projects they were active in, only very few stated that they made in-house development in order to integrate and assess methods helping RWD analysis. Instead references are made to participation in European projects such as EUnetHTA. In EUnetHTA work package 5 B, post-launch evidence generation, a small number of pilots on use of RWD have been conducted and a tool for assessing quality of data in registries has been developed (REQueST tool). NICE in the UK stands out as they detail a large number of development projects, that seem to be coordinated with academia and an internal development work. See Figure 5 below.

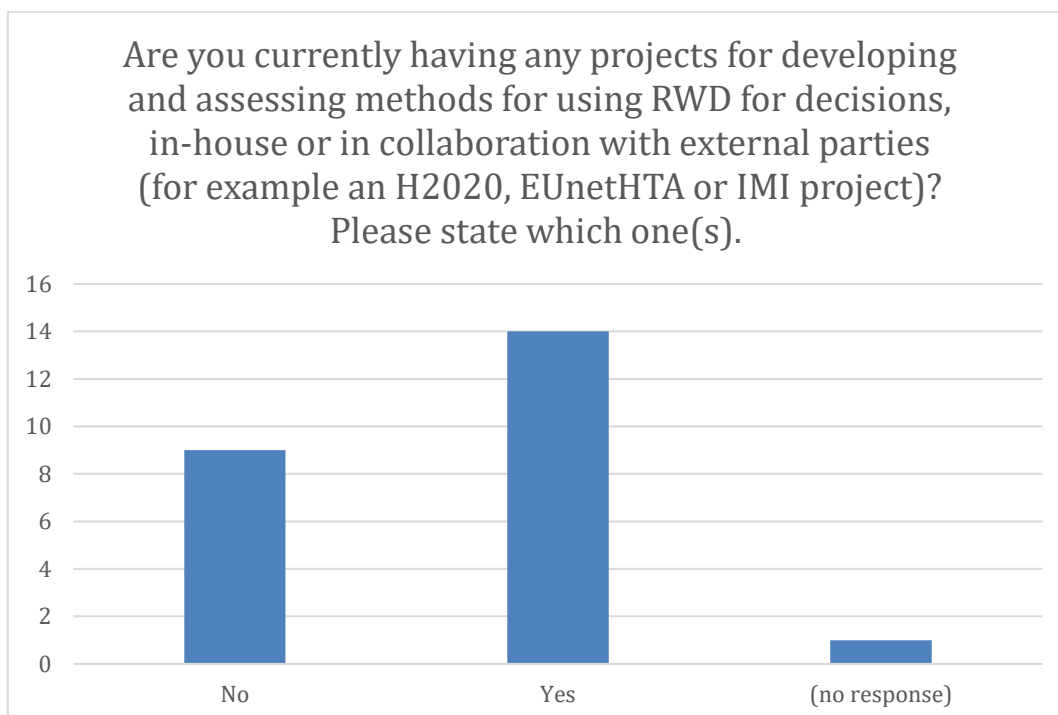


Figure 5. Projects for developing methods for RWD use in decisions

Almost all organisations (22/24) have indicated in the questionnaire that they have made negative reimbursement decision due to high uncertainties in the clinical efficacy. In the follow-up question if the possibility to collect data on effect and safety would have changed the decision, 10 authorities said yes and seven said yes with a condition. The conditions vary, but in general are focused on data quality and effect of the new data for pricing. G-BA in Germany states that

“Until about 2012, a number of negative decisions because of lack of valid evidence for certain technologies have been taken; since then, the laws have changed making it more or less impossible to exclude technologies because of lack of evidence from the benefit package.”

See Figure 6 below.

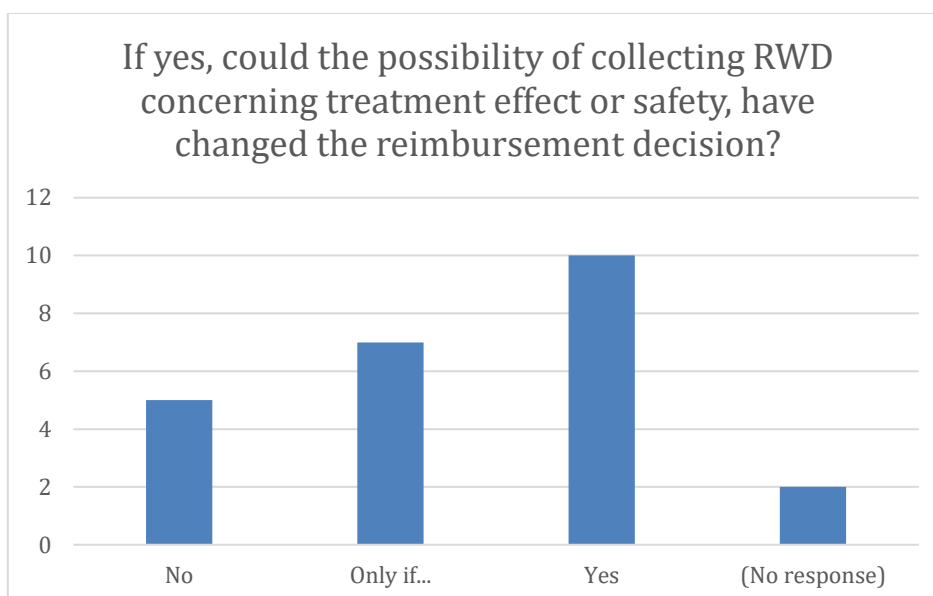


Figure 6 – Potential impact of data collection on reimbursement decision

This could point in the direction of a need to use RWD for decision-making. Only five respondents stated that the possibility to have RWD on these topics would not change their decision.

In preparing the questionnaire it was assumed that RWD is used in a very limited manner for reimbursement decisions. For natural reasons there is none or very limited RWD on the use of a pharmaceutical product at the point of original HTA or reimbursement decision. The agency might use other RWD sources to confirm standard of care or other patient population characteristics. Instead the questionnaire focused on the impact that the possibility for follow-up using RWD might have on a reimbursement decision. This was formulated as several questions on the same theme.

The question “After a first evaluation of a new health technology, do you think that the reimbursement decisions based on your evaluation have been affected by the possibility to follow up on the use and treatment effect in clinical practice” saw 16 positive answers. This is a majority of the respondents. Possibly this indicates the potential for

market entry agreements (MEA) if follow up is possible. It should be noted that there was no option for a conditional answer here, which explains the difference to the previously described questions and the next question on general impact of RWD use on decisions. See Figure 7 below.

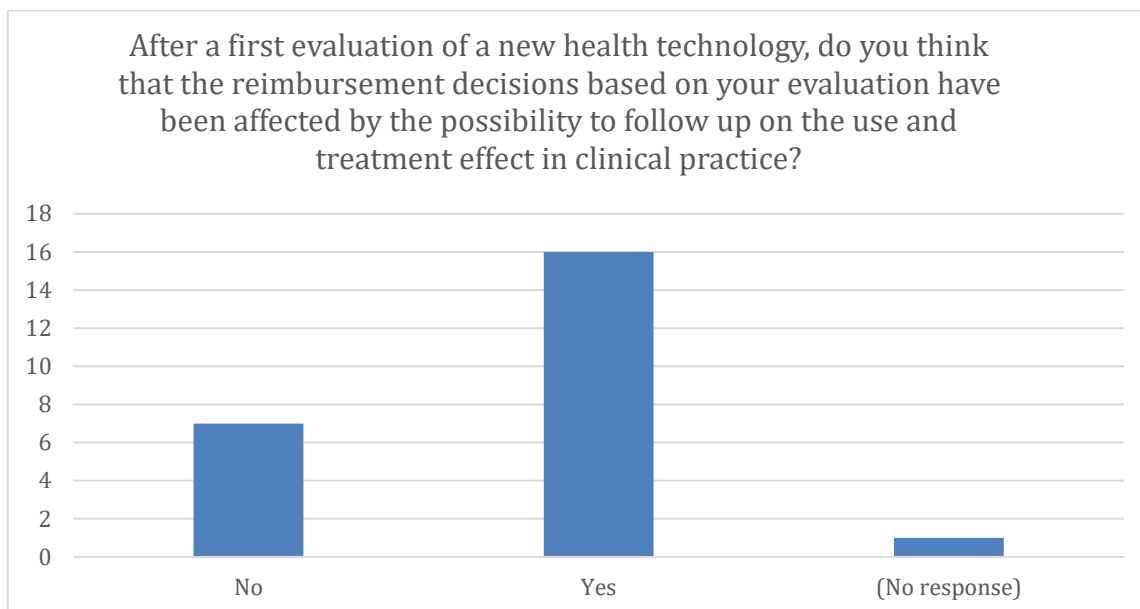


Figure 7 - Potential impact of data collection on initial reimbursement decision

Nine agencies out of 24 responded that they saw that the use of RWD would affect the outcome of reimbursement decisions in their countries in general. Three agencies saw no potential impact on their decisions by the use of RWD. The rest of the agencies mentioned that it would be dependent on several factors such as quality, relevance and accessibility of the data. It would seem from these responses that there is a need for further development of access to data sources and methods to assess the quality and validity of this data. From some authorities the rarity of the disease is indicated as a driver for the use of RWD. It is common in the discussion on RWD in other fora to indicate orphan designations as especially suitable for RWD and joint RWD use, as there would be few patients treated in each country. One authority indicates that they already use RWD for non-pharmaceutical products. See Figure 8 below.

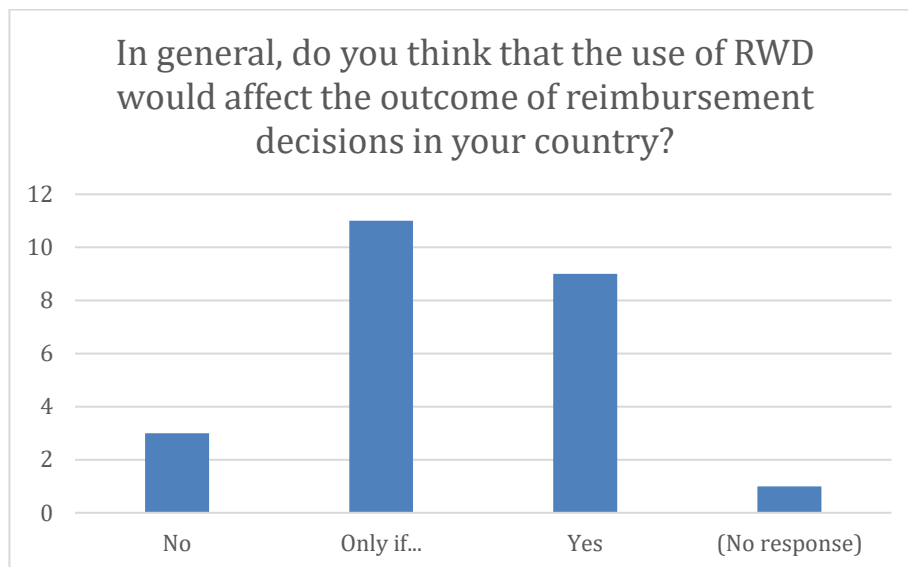


Figure 8 - The role of RWD on the outcome of a reimbursement decision

Regarding re-assessments, where typically RWD would be most relevant for assessment of relative effectiveness, a majority said that they do re-assessments and a majority of the agencies responded that they use RWD in re-assessments but five agencies said that they didn't use it. One of the agencies saying no, also stated: *our decisions generally rely on RCT data because they are considered to be most valid.*

See Figure 9 and Figure 10 below.

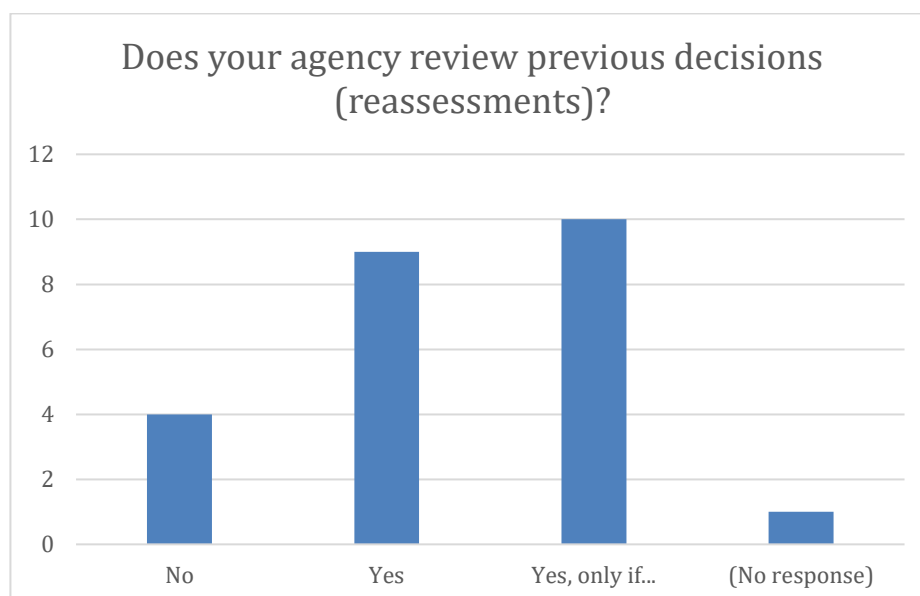


Figure 9 - Re-assessments

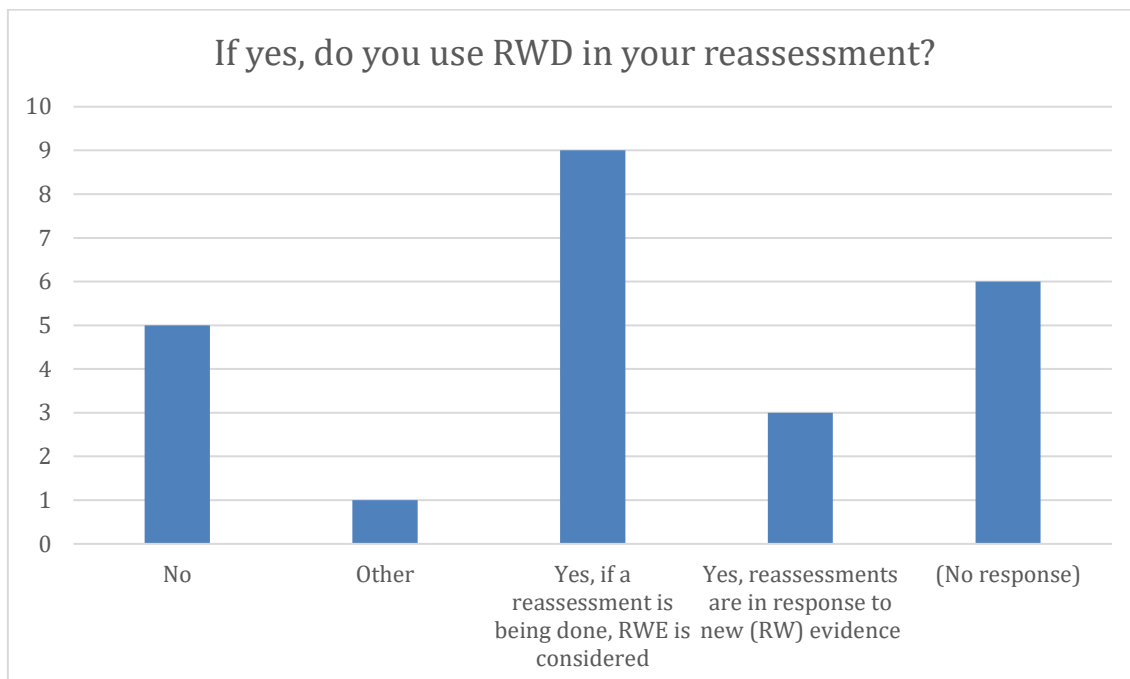


Figure 10 - Usage of RWD in re-assessments

Several agencies answered positively to the question if they consider use of RWD for risk sharing such as managed entry agreements and outcome rebate schemes. About 50 per cent said that they did not use RWD in those situations, and the rest that they did, or had conditions for it. It was mentioned by the agencies that outcome based MEAs are less common than managed entry agreements and they are most common in rare cases in hospital only products. Some agencies said that it is used by the financing agent (payer organisation), not by the HTA agency. This could potentially explain why only half of the group answered yes. See Figure 11 below.

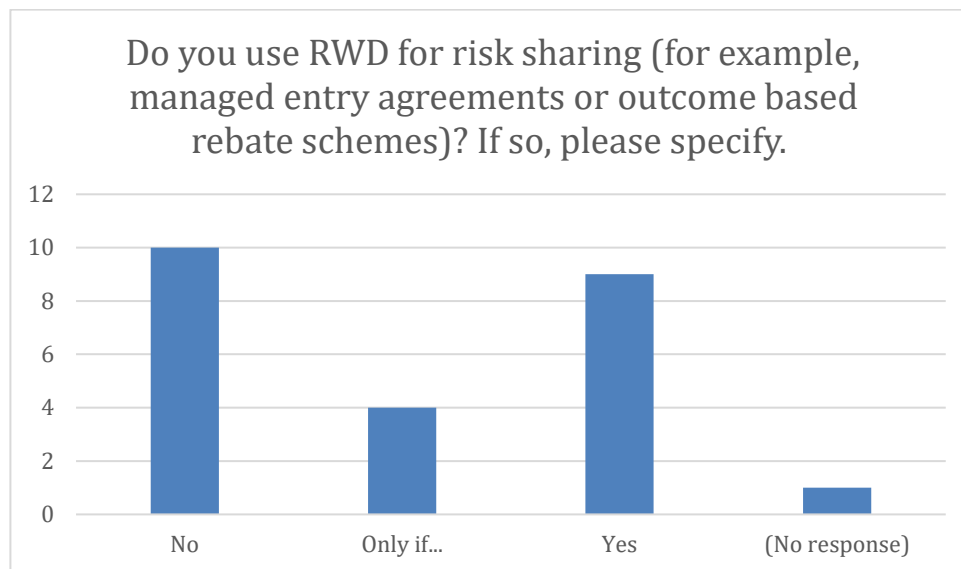


Figure 11 - Usage of RWD in risk sharing

Many decisions are needed to be done for treatments only applicable for a few patients due to rarity of diseases. This has increased the need to access international data in order to increase the patient population and potentially reduce uncertainties in the results. Eighteen agencies meant that they would use RWD generated from other countries, and six said no. Most agencies meant that they need to consider differences in population and treatment pathway and one referred to the Good Practices for Real-World Data Studies (ISPOR).

There was a unified message from the entire HTA community that they were interested in understanding how other agencies use RWD for decisions. Only one agency answered negatively to this question. Comments on the theme were:

- *Do countries have clear rules when/under which circumstances RWD is used; for which questions (Safety vs Effectiveness vs Resource use...)*
- *What data do they use? How do they access it? How do they ascertain its quality? How do they deal with commercial registries?*
- *We are willing to follow up the development in this field.*
- *Interested to know if other agencies have found a way to integrate RWD with other conventional data sources.*
- *Yes, to learn more about how RWD can be used and also for future collaboration.*

According to the comments there seem to be a number of questions related to understanding how other agencies use RWD for decisions. There is an interest in understanding the matter and a need for discussion and shared expertise between the agencies.

Since almost all agencies seem to have an interest in knowing how RWD is used in decisions, it was interesting to take part of the answers on the question with a ranking of main reasons for not using RWD at reimbursement decisions. The reasons to choose from were:

- *Data sources lacking*
- *Existing policy structures / information governance (e.g. rules complicating or prohibiting use of RWD)*
- *Lack methods to use RWD*
- *Lack of statisticians or other relevant analysts*
- *Lack relevant variables in registries*
- *Long time to access data*
- *No possibility to or difficulty with verifying/interpreting data*
- *No possibility/experience to link various data sources*

As the main reasons, rank 1, policy and lack of data sources were the most common responses. This was not surprising since this was a theme that was often mentioned in the interviews. As the second reason, no specific trend was seen, the responses were distributed over all possible reasons, see figures below. “Lacking relevant variables in registries” and “No possibility to or difficulty with verifying/interpreting data” were the main two reasons, marked by eight agencies in total. Three agencies marked “Lack of methods”. See Figure 12 and Figure 13 below.

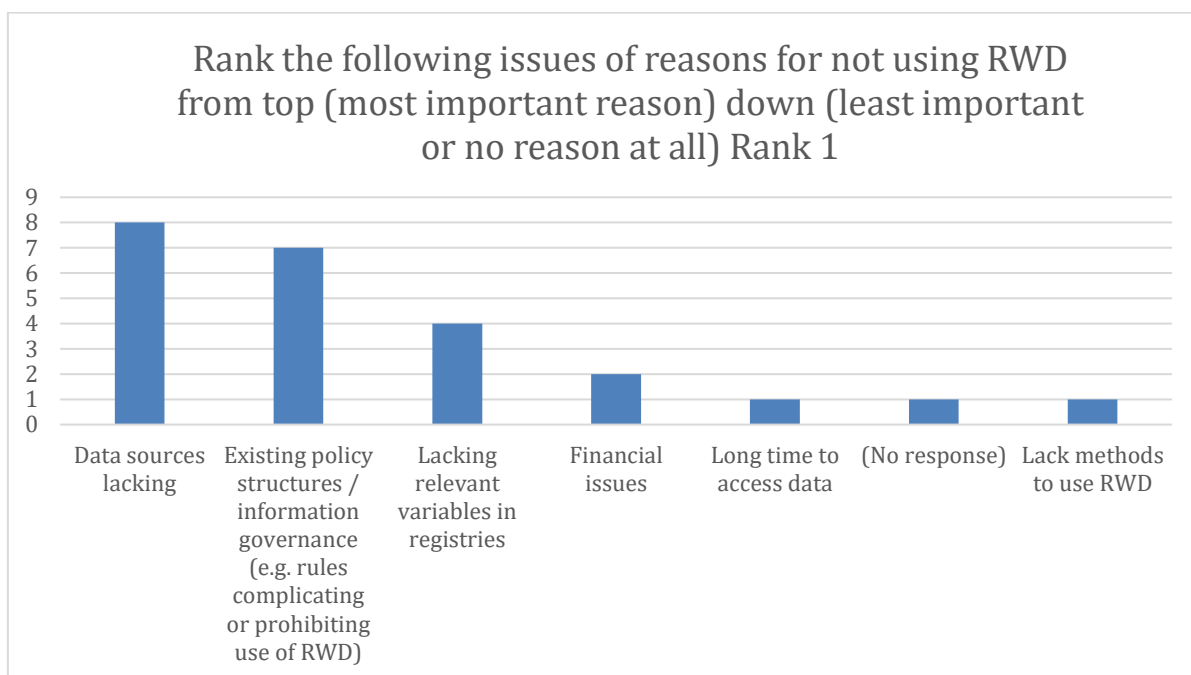


Figure 12 - Reasons for not using RWD - Rank 1

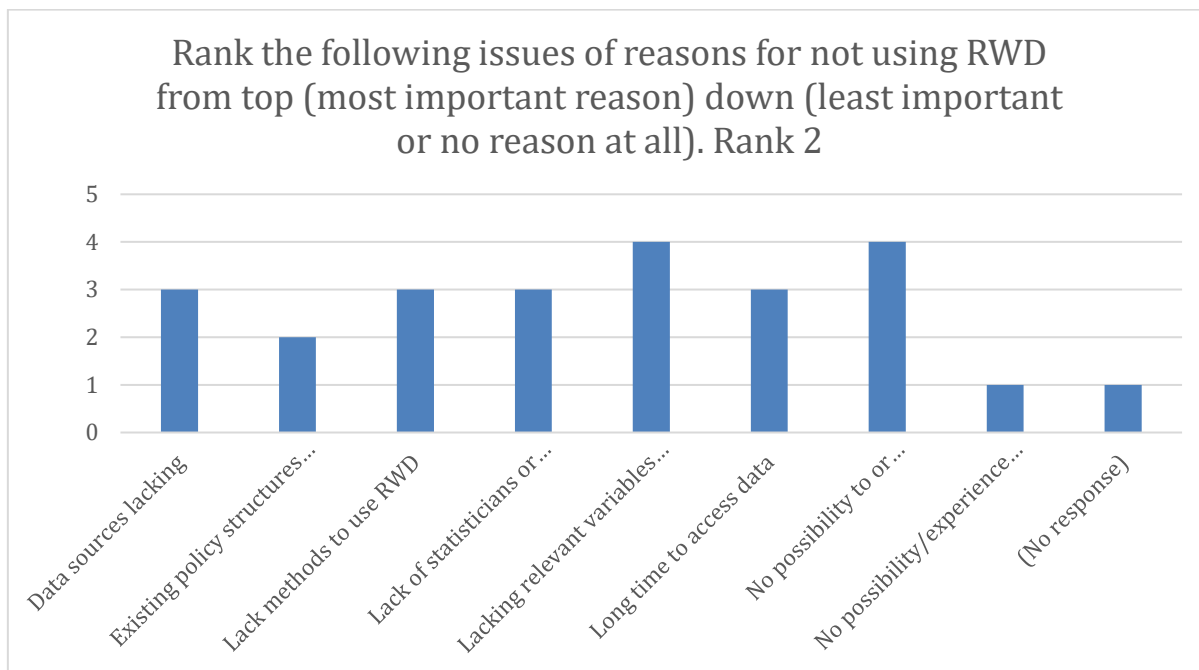


Figure 13 - Reasons for not using RWD - Rank 2

In the report previously cited also developed by the HTx project *A gap analysis of the challenges in HTA of complex health technologies*¹⁴, based on a questionnaire sent out together with the presently presented to the same stakeholder groups these findings are corroborated. Barriers for not using RWD that are highlighted are “*lacking necessary RWD sources*” and “*existing policy structures or information governance*”.

In order to understand the attitudes and willingness to use RWD for reimbursement decisions, three questions were asked on this theme. The first of these was around the need for wider systematic use of RWD in decisions than what is current practice. Eighteen agencies responded yes to the question “Does your agency see a need for a wider systematic use of RWD in decisions than what is your current practice?” indicating that there is a vast interest. Only three agencies responded no, and these agencies seem to have low activity in the field. Comments from the agencies indicated a certain scepticism though: “*Only if used primarily as supportive evidence*” and “*It will give wider picture to use them in assessments*”. See Figure 14.

¹⁴ HTx deliverable 1.1 *A gap analysis of the challenges in HTA of complex health technologies*.

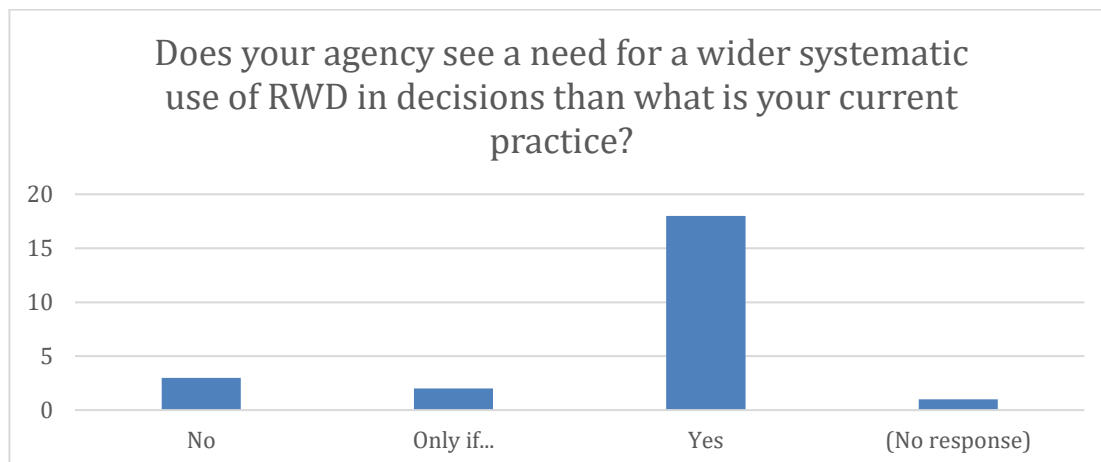


Figure 14 - Need for wider systematic use of RWD

There is a clear signal of willingness among both assessors and decision makers to accept RWD for decision making since 16 agencies answered yes on this question. Two agencies indicated that only the assessors have willingness, and one agency has indicated that only the decision makers have willingness. See Figure 15 below.

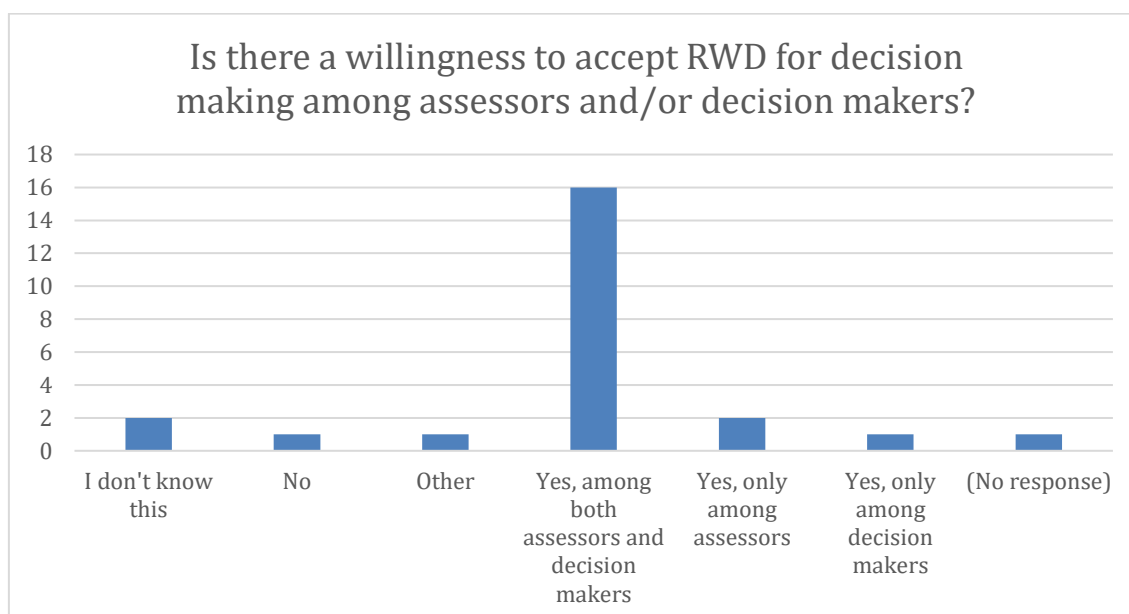


Figure 15 - Willingness to accept RWD for decision

When we asked in which circumstances it would be more likely for an agency to accept RWD for assessments or decision making, the following types of situations were described: lack of robust evidence but promising results on the basis of existing published literature and innovative technologies. It was also mentioned that it would be acceptable when the conditions are very severe, fatal, or alternative treatment is not available or accessible. Another situation was when the data has potential to resolve areas of uncertainty in the clinical use. It was noted though that one agency would not

accept it as the sole source of evidence, it would be acceptable as supplementary to RCT evidence.

Summary of Observations from the Questionnaire Responses

To summarise the overview of the results in the questionnaire given above there seems to be an openness to alternative sources of information, that is RWD. As expected, it is a fragmented situation that is depicted in the answers. There is surely an interest for these issues in the EU, especially against the backdrop of new advanced therapies approved on immature data, or given conditional approval by the EMA. It is evident from the answers that there are large differences between the authorities when it comes to policies, institutional cooperation, infrastructure, data access and need to use RWD.

16 out of 24 agencies state that their reimbursement decisions have been affected by the possibility to follow up on the use and treatment effect in clinical practice. This implies that the possibility to follow up the drug use and effectiveness is of great importance for the HTA agencies.

Almost all organisations (22/24) have indicated that they have made negative reimbursement decisions due to high uncertainties in the clinical efficacy. The high rate implies that there's a need for investigating more what consequences this could have on patient access and how access to complementary data such as RWD could reduce the risks, since about 50 percent (10) meant that the possibility to collect data on effect and safety could have changed the decision and seven said yes with a condition. This theme was also explored in the interviews.

Regarding re-assessments, where typically RWD would be most relevant for assessment of relative effectiveness, a majority said that they perform re-assessments and a majority of the agencies also responded that they do use RWD in re-assessments. Only five agencies said that they did not use RWD in re-assessments. This could mean that RWD in some form already has an established role in re-assessments for a majority of the agencies. However, it is not clear which questions are answered with the RWD in this group of agencies; if it's related to the prescription and use of the medical product or the effectiveness, see section Theoretical Framework.

About fifty per cent of the HTA agencies answered positively on whether they use RWD for risk sharing such as managed entry agreements and outcome rebate schemes. Since some agencies said that it is used by the financing agency, not by the HTA agency, there could be a group with indirect use through their payers.

The entire HTA community answering the questionnaire stated that they were interested in understanding how other agencies use RWD for decisions. There was only one discordant voice. This made it especially interesting to take part of the answers on the question ranking the main reasons for not using RWD at reimbursement decisions. As the main reason, rank 1, policy and lack of data sources were the most common responses. This inspired a more detailed discussion on policy and data sources in the interviews and initiated an overview of types of policy factors that could affect the use of RWD. The result of this process became the model of policy factors in RWD use presented in the section Theoretical Framework. In the second rank lack of methods was lifted by three agencies. This could indicate that methods and competences are on the

mind of the HTA agencies, even though most do not rank it as a primary reason for not using RWD.

The learnings from the questionnaire were important when formulating questions for the interviews and selecting the interviewees. As shown above, the theme is not unimportant, but some agencies are more advanced than others. For the interviews, HTx WP 4 were looking for the most advanced experiences. This will be further developed in the next section giving a thematical overview of the interview results reflected against the questionnaire results.

Thematical Overview of RWD Work at Agencies, from Interviews

To get a deeper understanding of the RWD work at the HTA agencies in Europe, the team decided to perform interviews. The questionnaire served as a basis in selecting suitable agencies for an interview. In the following section, the results from the nine performed interviews are presented theme by theme. Also, the team's knowledge of our own agency, TLV in Sweden, has been channelled into the thematic study. Answers in the questionnaire have been studied to support the reasoning in the presentation.

Based on previous knowledge of the status of RWD work at the agencies, also a few agencies were interviewed that did not take part in the questionnaire. Those agencies were: AIFA in Italy, INFARMED in Portugal and the Estonian Health Insurance Fund.

The questions prepared for the interviews in the interview guide were inspired by our perception of what themes would be relevant. A further analysis of the answers suggests that themes relevant to study are “current use of RWD”, “access to data sources”, “development of methods for using RWD”, “involvement in European collaborations” and “proposals on how to share knowledge between the agencies within the field”.

Current use of RWD

As described in the Theoretical framework section, based on Facey et al., RWD could be used in different steps of an HTA procedure. These are initial assessment, follow up of a MEA or re-assessment. RWD could be used in order to complement the RCT data on relative effectiveness or to validate the inputs or assumptions in the health economic model. It could also be used to estimate the population size, the comparators or the costs associated with the new treatment or the comparator. For estimation of relative effectiveness, it can be assumed that it is more often used in re-assessments than in initial HTA-assessments.

Initial assessment

Three agencies, AIFA (Italy), NIPN (Hungary) and TLV (Sweden) mention that there is a limited but still evident use of RWD to support various modelling aspects, assumptions for calculating budget impact, relevant comparators and sometimes the cost-effectiveness directly in the initial phase.

NIPN seems to seek this information actively through interaction with the Health Insurance Fund. AIFA states that this information is available in the AIFA registries and can be used to confirm use and comparators, for instance.

TLV has over the last three years increasingly started to ask for data from the registries at the National Board of Health and Welfare to analyse the assumptions in the initial application for reimbursement. An internal process has been established where the assessors are supported by experts on data analysis, who advise on what possibilities there are to support the decision with data from clinical practice. In order for this process to be successful the data needs should be identified early in the process by the assessors. This is partly due to the fact that getting the data is still a time-consuming process.

ZIN in the Netherlands are using data to support reimbursement decisions but identifies a number of issues, for instance that data can be outdated and not complete:

“We have different data sources available and we have already used them sometimes, especially for patient numbers and to look at how they are treated now, more for comparator kind of information and patient characteristics. We have information on the use of pharmaceuticals so out-patient pharmaceuticals mostly. The main problem with that information is that some is a bit outdated, for example now we only have data from 2019 and I don’t think it is even complete yet. So it could be a problem and we only know which drug they get but not for which indication so if the drug is given to several indications then it’s difficult to make a distinction.” (ZIN)

For SMC and NICE the situation seems to be the same at both agencies, they do look at RWD, if the company submits the data, either in the application dossier or at a later stage of the initial assessment, or if stakeholders ask for that during the review of the assessment. They will, however, not seek this data actively.

“We provide an initial decision and then send that out for consultation and stakeholders can comment on that. If there are then questions arising from that in terms of evidence gaps, the manufacturer can then choose to submit those. We wouldn’t signal that we want those and we would not bring in data ourselves to answer those questions, it’s down to the manufacturer to submit that to us and to decide what they submit.” (NICE)

It seems like both agencies find it important to work for a more systemic approach to generating, collecting and analysing data going forward.

The Estonian Health Insurance Fund mention that mainly claims data is used in their assessments. They use data from the prescription centre as well as treatments bills, to check whether the budget impact prognosis seem appropriate and to see what the current standard of treatment is. The view of RCT as golden standard lingers in many agencies and there is also an additional workload potentially associated with using RWD.

“I think currently everyone is still a bit in the wait-and-see mood. Because also what we see from the prescription data or data from hospital bills or from health records that all of them have a little bit of quality issues. Because the data is entered by people, there is always risk of incorrect entry. Hence, I think one key issue that has to be tackled with the RWD is the quality check which is really strongly done in the clinical trials where there are clinical research associates double checking the data. I think that something similar must be done also with

the RWD. Why we as a payer are maybe not so eager to do all the work is that we see that it is a lot of additional work that might not give us the quality data that we need. Additional work means also additional costs and then it's a question why we as payers should pay the costs and take the responsibilities of what used to be the responsibilities of the drug developer. Now we have new drugs coming to the market with cheaper studies with less data and payers should basically pay the high price and do all the clinical trial work as well! I think it's a controversy, why should we do it?" (Estonian Health Insurance Fund)

RWD use for assessing Market Entry Agreements, or similar

AIFA's system with one registry per medical product and indication, joined together in the AIFA registries, is designed to allow follow-up of MEAs. There is legal support for the collection of the data and for the compulsory assessment of the outcomes at the end of a 12-24 month period. AIFA states that they compare RWD with RCT when they update their MEAs. They have 56 payment-by-results agreements in place by July 2020, and they can use the information contained in their registries to define if a patient is a responder or not. If there is a new comparator at the re-assessment stage, they gather new data in their registries and do a new evaluation.

RIZIV-INAMI also actively use data to evaluate MEAs but that this is not fully based on data from clinical practice. They depend to a large extent on claims data, which might be incomplete. They still see potential in this data source:

"It's very limited, it's mainly descriptive, budget and numbers of patients, this is not really part of, I would say, research vision, where you would like to assess after a few years clinical outcomes. Claims data have limitations but you can still explore them, they are still underused in my opinion." (RIZIV-INAMI)

TLV has since 2015 been involved in supporting MEAs between the companies and the Swedish regions. As these agreements expire there is a need to reassess the reimbursement decisions and in this context TLV has used RWD to support its decisions. The data has come mostly from national registries.

NICE is performing MEAs, and evidence collections plans implemented as part of the MEAs will have RWD collected. The main onus for setting up this collection is still on the company, but there are structured data collection arrangements to follow.

RWD use for re-assessments

INFARMED in Portugal use RWD for re-assessments, based on data from certain disease-specific registries. This means that this does not take place in a routine manner for all medical products. Cancer is in focus for the Portuguese agency.

Swedish TLV performs re-assessment since a long time. The ambition of their RWD-projects is to secure a steady and easily accessible flow of national data that will allow re-assessment to be a standard procedure that will not be conditioned by the access to data.

Both INFARMED and TLV has had projects where RCT data was compared with RWD for PD1 inhibitors. Data for this comparison was used from the oncology registries. It was

performed both in a policy sandbox setting as for TLV, and for real use in Portugal. In Portugal, the registry holders from the national oncology registry performed a RWD analysis in relation to five (5) drugs to support the re-evaluation safety and effectiveness gap used in a re-negotiation. The oncology registers have a mandate from the government so according to the law they have to collect data and support INFARMED in the HTA. But the definition of the medicine that is going to be analysed is an INFARMED choice. There is a need for more resources though, to do this type of work continuously.

AIFA and RIZIV-INAMI do re-assessment in a similar way as described above for MEAs and mostly in that context.

NICE mentions that they do perform reassessments and that this is planned at the initial publication on guidance. The delay to the reassessment is depending on the status of the current evidence and knowledge of ongoing research. The review will be proceeded by a consultation to relevant organisation on whether an update of the guidance is needed or not.

The Estonian Health Insurance Fund and NIPN do not do re-assessments at all. NIPN is working to create the legal and financial environment for making re-assessments.

“We don’t do this at all but are lobbying for doing this; to actually create the legal environment and the financial environment for this. So, re-assessment is currently not a thing outside of the insurance fund. NIPN is currently not involved in these procedures, which is quite unfortunate. We would like to take a step in this direction.” (NIPN)

The Dutch agency ZIN mentions that they have stopped doing re-assessments due to bad quality of data and difficult access to data:

“No, we used to do it. We stopped doing this because we had a lot of problems in getting the data. Data was also not of enough quality and it was very difficult to say no if it was already reimbursed for two years, so to stop the reimbursement we had a lot of problems with that. One of the issues was also that most of the pharmaceuticals were in oncology. In some fields the development is so fast that your comparator in year one is not the same anymore in year seven or year six so your whole data collection is not relevant anymore after six years.” (ZIN)

The discussion on how to handle the results of a re-assessment that means that reimbursement has to stop, is of course of interest to all agencies, but was only mentioned in this interview with ZIN. Our understanding is that this might be a hindrance in many cases.

Summary of observations on the use of RWD

There is a fragmented landscape of the use of RWD among the interviewed agencies. It should be noted that the agencies selected for the interviews, were selected with the hypothesis that they were the ones that were most advanced in data access and in the use of RWD in reimbursement decisions. One observation is that if it is possible to use RWD in one phase such as initial phase, it leads to better possibilities also in other

phases such as MEAs. This could potentially lead to better possibilities also for re-assessments, that seem to have been downgraded in importance lately.

In the initial phase most of the RWD use is regarding the budget impact, current treatment practice and validation of modelling. A majority of the interviewed agencies use RWD in some way in the initial assessments even if this use is not systematic and not corresponding to the whole picture of possible questions to answer with RWD, as depicted in the theoretical framework.

For MEAs, there is diverse usage, both to answer the question on effectiveness through registry data and the use of the medicines through claims data. Only a few agencies mention that they do this, but only one agency has a system with an own registry made specifically for this reason. The use in the re-assessment phase to answer questions on effectiveness is less common since the access to data is limited. Three agencies mention that they compare RCT with RWD in the re-assessment setting, either in a test, or in a real case setting. Three agencies do not perform re-assessments, and of those three agencies one is working to create legal support to be able to do it.

The interviews suggest that claims data is an important and possibly the most used source in the three situations.

Access to data sources

There's data regarding the patients' treatments and use of medical products in the patient records in all countries, but this data often stay with the health care provider, or is gathered only in disease specific registries. In some countries, data are at least in part centrally gathered, sometimes by a central health authority, sometimes by a national insurance authority or fund, and then more for financial purposes surrounding treatments. This centrally gathered data is not available to all HTA agencies; in fact, it is rather exceptional that access to centralised data is institutionalised and systematic according to our interviewees.

Several systems have been developed nationally to access data regarding the use and the effectiveness of medicines, each country creating a system to serve their needs and purposes and according to their infrastructure. Many countries have national health databases with different coverages, some are based on insurance claims to the national health insurance schemes, others are more comprehensive as the Swedish registry of prescribed pharmaceutical at the National Board of Social Welfare with compulsory registration of all drug use in outpatient care. Patient records can be electronic in many countries, but that is no guarantee that this information is channelled to a national repository and subsequently accessible for HTA agencies.

In the interviews it was mentioned by several agencies that disease specific registries have been set up nationally either by the agency, the ministry of health or a health care provider. This can be for specific illnesses such as cancer, like in Portugal and in Poland, or for specific medical products and their indication, like in Italy.

Claims databases were also mentioned in the interviews as possible data sources. Those databases were closely connected with the insurance systems, and the data was mainly inserted for financial reasons and not for HTA or medical reasons. As these registries are very dependent on the national insurance schemes, and their individual

traits, the content can vary largely from country to country, which means that they are difficult to compare for an outsider. Since the aim of the databases is not medical or for HTA, information on effectiveness of the medicines is not usually present. Instead information on current use, patient numbers and treatment length can be available which are also important for an assessment. These are of course important variables for evaluation. In some cases, the data can be used as proxy for the effectiveness of the treatments.

When it comes to access to data from the database categories described above, it looks different in each country. There are some similarities between agencies such as AIFA, AOTMiT, INFARMED, NICE and TLV that all mention that they have access to disease-specific registries. However, the set-up of this access is very different between the three agencies. INFARMED mentions access to a few disease-specific registries set up by the agency itself, the ministry of health or others, but this only covers a few illnesses. TLV also aims to use data from disease-specific registries. These have existed in Sweden for a long time, and are often set up by clinicians who have had full control of what parameters are registered. This can sometimes lead to issues, since TLV has need for other data points in order to follow up or compare medical products. INFARMED stresses in the interview the need to avoid additional administrative work for health care professionals occurring for current disease-specific registries. Both INFARMED and TLV highlights that they work in the direction of using national data, based on automated extraction of data from patient records. The Hungarian Agency, NIPN, also informed us about an initiative in this direction called the EESZT¹⁵ initiative. Thanks to a law change in the country it has been possible to link outcomes recorded in the real world practice such as reimbursement and claims data.

AIFA has created their own registry to manage patient access to innovative and high cost treatments. The term registry is described as “a drug and an indication”. The work on the registry started already in 2005 and has since then been a learning process step by step in order to scale up the number of products. Initially only data for the most innovative and expensive medical products with high level of uncertainty of effectiveness were added to the registry. There are five laws regulating the registry. The registry consists of a national clinical form that is developed in the agency and a web platform that is used to allow each centre of the national health system in the country to access the national clinical form and add data. The clinical doctors and pharmacists in each centre, are obliged to fill in all the required information in order to obtain reimbursement of the product. The products are followed up at agreed timelines, for example 6 or 24 months.

“After 24 months of the release of one AIFA Registry in the clinical practice, it’s mandatory by law to extract the data from the database for that particular registry, analyse it and if the main findings are pointing to that direction, re-negotiate the molecule.” (AIFA)

There has been a shift in the main objective of the AIFA registries from a simpler role of monitoring prescriptions and use of the medical products in clinical practice, to a role of performing clinical impact analysis aimed for example at evaluating market entry agreements. AIFA representatives stated:

¹⁵ EESZT: electronic health care records system

“In 2017, taking advantage of the fact that the AIFA registries are also monitoring the treatment for a given drug for a given indication at the indication level, AIFA was able to better define innovative indications in drugs and use this definition in the registries to address funding of the molecule that we believe will make a huge impact in clinical practice...”
(AIFA)

In Poland, there is a similar approach with new registries for expensive treatments, where the doctors have to fill in information. National registers are being built and they are aiming at having one registry for all diseases, but it is complicated due to the demands to have a free market. For MEAs there is a challenge in the regulation since data can only be gathered during 24 months, but sometimes longer time is needed for gathering effectiveness data. There is work ongoing to update the regulation for the registries and MEAs.

NICE, in the UK, has electronic patient records in their main registries as their principal data source. These registries are usually disease specific for example the one for Cancer called SACT database. The agency sees a fragmented nature of data sources as an issue and they see intellectual property as an important factor in blocking the access to data.

“I think that in the first iteration of search for data sources we found some 400 different sources. That is because again we come back to the philosophy of a problems-based approach or evidence gap approach. It could be, especially if we add an international dimension to this, an infinite number of sources that would be useful once in a life-time in some cases, not frequently useful.” (NICE)

As opposed to the agencies above, the following agencies mention claims databases as their main data source: the Estonian Health Insurance Fund, RIZIV/INAMI in Belgium, the National Institute of Pharmacy and Nutrition (NIPN) in Hungary and the Zorginstituut Nederland (National Health Care Institute, ZIN) in the Netherlands. Due to difficulties in accessing the data, it was mentioned by one agency that the data is underused, and it could be used much broader to answer HTA questions. Two agencies mention that they have the possibility to go into the database themselves and extract information at a granular level, agreed beforehand in their ethical approval. This makes it possible for the agency to make their own analysis and to get data access faster, but this is person dependent at one of the agencies at least, so it is not yet done in a systematic way. One agency has access to all data, but since the data is mainly inserted in free text it makes it difficult to analyse:

“... the problem is that many fields in the digital Health Information System are basically free-text fields and the doctors are not so keen on filling in specific fields of the formula. They put everything in the free-text field, i.e. they describe the patient only in the descriptive way, so it's very hard, not to say impossible, to extract the specific data [...] We do use data from our prescription centre as well as our treatments bills to check whether the budget impact prognosis seem feasible and/or to analyze what is the current standard of practice. [...] Currently, we're not using any data to evaluate efficacy of those drugs.” (Estonian Health Insurance Fund)

SMC in Scotland states that the data collection is company-led, so the agency is not setting up any data collection programs. The agency identifies uncertainties in their assessment reports, and it is subsequently the responsibility of the company to submit data required to lower uncertainties. It's too complicated for the agency to access patient data, so mostly other types of studies are used.

“We produce an ultra-orphan assessment report, but we don't issue a decision. The report highlights the strengths and also the limitations of the evidence base, i.e. the uncertainties and is designed to inform a period of company-led evidence generation. SMC needs to maintain independence, for this reason we don't direct the company to collect specific data - we highlight the uncertainties and step back, leaving the company to decide how best to address them.” (SMC)

Below SMC highlights the need for IT infrastructure setup and methods for making the data processable.

“If we had the necessary IT-infrastructure in place, and we had clean RWD, taking account of all the confounding factors et cetera, there would be the opportunity to use NHS datasets now, but we're not there yet.” (SMC)

Several agencies highlighted the need for international data in the view of rare diseases, and one already has the demand for international data in their process related to these medical products:

“...the registries should be international and as much as possible, not managed by the industry even if paid for by the industry. I think the industry should pay for that because it is their responsibility to provide more effectiveness data for their products” (RIZIV-INAMI)

“So, the ultra-orphan pathway is a three year pathway introduced by the Scottish Government, during which the medicine is available and further data are generated. Evidence generation is not limited to Scotland - we're a small country with a population of 5 million, as far as extremely rare conditions are concerned we're inevitably not going to have many patients. Therefore evidence generated across the UK, Europe and world-wide, via patient registries and other data sources all contributes to re-assessment after three years. The company is required to update their original submission with this information and we take it back through our assessment process.” (SMC)

INFARMED expresses that European collaboration on data is very useful in this area, because for some diseases there are not enough patients to ensure statistical robustness. They highlight the potential lack of a European coordinated approach, and the risk of duplicating work if registries are set up by different agencies simultaneously. They think that it would be useful to have a single EU entity leading this area to avoid duplication of registries. With one register the information needed for EMA for conditional authorisations and also for HTA re-assessments could be used. This is essential for orphan medical products. The agency highlights that it is useful to share methodology and the fields that are needed for these evaluations.

Access to data is a challenge for all agencies. No agency has a permanent flow of data that would allow assessment or follow-up of medical products in a structured way, neither as data itself, as statistics or as federated data. This is confirmed in the questionnaire where lack of data sources is the largest reason why RWD is not used in reimbursement decisions. Even though some progress has been made in most countries, this is not sufficient to meet the needs for data. If the legal issues of collection of patient data have been overcome there are other hindrances, like the data not being collected in a processable form. Italy has a legal demand on collection of data and subsequent evaluation. However, the registration procedure puts an additional administrative burden on health care professionals. Here we see that there is a need for a number of factors to be present in order to provide for a system that allows continuous collection of data that is processable. IT-systems, legal support, mandate for the HTA agencies to take part of data, collaboration on the needs of the various agencies involved and how they can engage with each other, are the most evident. This view is in line with the observation made in the 2019 OECD Report *Using Routinely Collected Data to Inform Pharmaceutical Policies Analytical Report*¹⁶ in which lack of data is described as a key barrier to use of RWD. Lack of resources and competences for analysis are other factors mentioned by the OECD.

Development of methods for the use of RWD. In-house work, collaboration with universities or external parties

There is a fragmented picture of methods development projects and collaboration with external parties such as universities. Several of the agencies say that they are too small, that they lack resources, vision or personnel. They rely on collaborations or learnings from other HTA agencies, such as NICE. Other agencies have either an ad hoc or an established work with external parties for developing methods for RWD use. A few agencies perform development work in-house.

There are three agencies with an established collaboration with universities, where ZIN mentions collaboration with the Erasmus University Rotterdam, Tilburg University and Utrecht University, TLV collaborates with among others Gothenburg, Stockholm and Uppsala Universities and NICE mentions that a lot of the methodology is developed outside of the agency in the broader scientific community. If NICE discovers a field where there is more support needed around using data, they can commission academia to produce technical support documents.

“Typically, they [academia] review the current state of play and produce guidance on best practices for a specific topic. That could be a technical topic, such as how to deal with analysis involving treatment switching, extrapolation of endpoints, how to treat single arm studies, various issues in modelling or the data synthesis. Through that mechanism we commission work from the academia.” (NICE)

NICE also highlights that if we are to rely on RWD, the matter of trust and quality and completeness of data needs to be addressed. Transparency is crucial to understand and

¹⁶ OECD, 2019. *Using Routinely Collected Data to Inform Pharmaceutical Policies Analytical Report, 2019* <https://www.oecd.org/health/health-systems/Using-Routinely-Collected-Data-to-Inform-Pharmaceutical-Policies-Analytical-Report-2019.pdf>

generate confidence in data. They see a need for generating frameworks around what needs to be published on the studies and how the data is subsequently analysed.

Both TLV and NICE have a clear mandate to perform these activities. TLV has received several governmental assignments on the theme, and NICE has a working plan where important development areas are identified.

ZIN mentions in the interview that they consult statisticians at different universities relatively often and are thinking of hiring their own statisticians for these kinds of questions. The Dutch agency highlights that the largest problem they see is the bias related to registries. There are problems with defining if the registry is really representative of the whole population.

INFARMED, has an established work with the National Oncology Registry, which makes analyses of data for the agency. Development of methods or analysis of data is not yet done in-house. The agency says that they do not yet have the expertise to do it themselves, but they aim for it since it would facilitate timelines.

AIFA in Italy states that the development of methods for using RWD is done in-house within their own registries. They have tried different approaches such as statistical adjustment of the data in the comparison, mainly using propensity score matching techniques or other techniques. Since there is a large number of patients in their registries, they use random extraction from the registries with the same background features as the patients reported in the pivotal clinical trials, in order to analyse the differences in outcome in the pivotal trials, with respect to what has been observed in the clinical practice. AIFA also has a project where they collect data from different administrative databases such as hospital and regional databases. They put all of them together and by using big data analysis techniques, like machine learning for example, they can extrapolate clinical evidence.

AOTMiT also has in-house development of methods, for example on machine learning. They have a collaboration within the EU-financed COMPASS where analyses are made from RWD to predict future changes in prostate cancer and lung cancer treatment effectiveness.

The rest of the agencies mention ad hoc collaborations with external partners when applicable. NIPN mentions the need for discussions on validation or interpretation of data, and also perform this when appropriate through personal channels at universities and other national authorities. It risks making the RWD analysis very dependent on the individual official.

Only one agency, in Estonia, mentions that they do not see any need to develop methods. They say that they are a little bit sceptical how well they can use the data and how comparative it is with the clinical trials, which are well conducted and followed up, and in very specific patients. So, they don't think that they are going to be the forerunners in this field.

RIZIV-INAMI in Belgium says that the mission of their agency is to be a payer, not a research centre, as opposed to another HTA agency in their country. Therefore, they do not have research expertise in-house.

“The research expertise is quite limited in INAMI, it’s not their mission. I think this could be more developed because it’s so important for HTA and our claims data could be very useful but is so much underutilized. But certainly, we’re not a research body.” (RIZIV-INAMI)

Also Scottish SMC note that competences can be scarce and that collaborations can remedy that situation. They are starting to look at solutions for this with partners:

“We’ve recently started to discuss a joint post which combines statistics support for SMC assessment with a research role to explore use of RWD in HTA. We know that we don’t have the necessary statistics expertise and resource in-house so we need to set up collaborations with relevant partners” (SMC)

In summary, there seems to be different levels of possibilities and ambitions for methods development, both in-house and in collaboration with external parties. A few agencies have established external collaborations and one has an established internal development process. Several agencies have conversations at an individual level with universities and other agencies. This makes the development work person-dependent and vulnerable. An important factor appears to be the vision and mandate of the agency.

Participation in European or international projects

All agencies except for the Estonian Health Insurance Fund and SMC have collaborations with European initiatives for the purpose of methods development. Both agencies mention lack of resources as their main reason for not participating hands on, but both say that they are open to learn from the ongoing initiatives.

The other agencies all participate in EUnetHTA. Some agencies participate in one more collaboration beside EUnetHTA: RIZIV-INAMI also participate in the BeNeLuxAIr, NIPN in the GetReal initiative, AOTMiT in COMPASS and AIFA in HTA10. ZIN participates in BeNeLuxAIr and the GetReal initiative.

TLV, ZIN and NICE take part in the Horizon 2020 project which is behind this HTx report. TLV takes active part in EUnetHTA Work Package 5 B, which works on Post-Launch Evidence Generation (PLEG), around usage of RWD. They also take part in the Horizon2020 project IMPACT HTA. Through FINOSE, that aims to perform joint evaluations of medical products at the three participating authorities¹⁷, TLV also initiates and takes part in methods development discussions.

Only one agency, NICE, participates in several initiatives for methods development, such as the EUnetHTA REQueST tool developed in Work Package 5B, EDHEN, IMPACT HTA and the IMI GetReal Initiative. The agency defines their research priorities and the projects they engage in need to fall under those agreed research priorities. One of the research priorities is the use of RWD and methods. In terms of the projects and broader learning, they have seen a great value in co-developing methods and solutions, and that

¹⁷ Alongside TLV also Norwegian NoMA and Finnish Fimea are part of FINOSE

is the approach they took in the GetReal-project for instance. GetReal has a broad participation with stakeholders bringing different perspectives looking at the question: what are the key challenges in bringing new drugs to the market? They looked at samples, case studies of these drugs, endpoints in those assessments and where non-randomised data could become useful in addressing those.

“We have had various developments around using RWD. For instance network meta-analysis is something we looked at. Essentially, I think there is a case being made now that we’re reaching a consensus on how to define regulatory quality data.” (NICE)

NICE identifies a need for broader collaboration around regulatory quality data.

“I think that this is something that needs to be done both by payers and HTA bodies in collaboration with the regulators, that is the EMA and national regulators.” (NICE)

There are a number of fields identified by NICE that would require further methods development. They were detailed in some extent in the interview and points to the importance of a broader perspective than just Europe:

“Then there are various discrete opportunities for methods development, for instance best practices in dealing with single arm trial data. There are elements relating to ensuring transparency of data – how data is generated. How it is synthesized is also really important. Quality and transparency are just cornerstones of what needs to be focused on but there are various projects, clearly, looking at this. Both in Europe and in the US. So, I think whilst it is useful to look at things in the European perspective, we shouldn’t lose sight of developments for instance in the US. The FDA does have a bearing on the data that eventually come to Europe as well.” (NICE)

There is a broad variance in participation in European projects on RWD. The more active an agency is, the more articulate it seems to be on what development needs are extant, and where it wants to do work on these. Also, agencies that do not collaborate and in that way miss to create and participate in networks, seem to prioritise RWD development less. These agencies seem to be the ones that have low or no mandate to work in RWD.

Platforms for information exchange

Since dissemination of acquired knowledge is a condition for implementation and development, for example in the use of RWD in reimbursement decisions and other in HTx activities, we wanted to explore this theme with our interviewees and learn from all of their proposals. Competence has also been highlighted in the interviews and the authors have concluded that it must be seen as one of the main policy factors, see Figure 4 above in the Methodological Framework section.

When discussing this matter with the agencies, it was highlighted that we need to ensure that products developed in earlier initiatives are reused, such as for example within previous IMI projects or in GetReal, such as a recommendation on data structures and how a European data pool should be created.

Another aspect that was brought up, was if the front runners and the early adaptors in RWD usage possibly can cooperate more, to learn from each other and not having to re-invent the wheel. Related to that, the agencies in the Netherlands and in Hungary highlighted the possible challenges in using the methods for RWD, if the agencies were not yet ready for them and if the setting were not totally adapted.

A practical advice was to try to create less complex stepwise recommendations which are easier to achieve or to implement even if an agency does not have direct access to patient level data. NIPN from Hungary expressed the following:

“I think you might consider a sort of a tiered approach, so if you’re dealing with a number of EU-countries, then you will have some countries that are way ahead using RWD and some others who are trying to pick up and doing their best. I think it might be useful to consider if there are steps that you can do as a country just picking up on or being interested in RWD, simple recommendations which are easier to implement even if you don’t have direct access to patient level data building up registries.”
(NIPN)

Several agencies propose that we use already existing networks to share expertise such as within EUnetHTA post launch evidence generation projects (INFARMED) or the EMA-MOCA-payer collaboration (RIZIV-INAMI).

“I see a solution in the dialogues the EMA is organizing pre launch and post launch. There I see a role for ESIP/MEDEV and what used to be MOCA. There you have an organization and logistics anyway for this kind of dialogues within the EMA and I think that HTA agencies and payers can step in.” (RIZIV-INAMI)

“Passive” information sharing such as published literature and databases were discussed together with conferences as potential information platforms, but one interviewee said that perhaps hands-on projects such as the EUnetHTA WP 5B projects on post-launch evidence generation (PLEG) would be more efficient.

One agency (AIFA) highlights the importance of a common approach in the collection of data. We understand this to mean some sort of data harmonization, so that there is a common view on what data stand for and a common practice on when to collect them. They also seem to have a view for a further collaboration as to what medical products could be reimbursed for a specific indication. If this would become reality, for instance for ultra orphan indications as SMC indicates (and already use other countries’ data for), there need to be a clear understanding of what data is relevant and how it is collected.

“Without a common basis by which data is collected in clinical practice, it’s difficult to take a step to joint integration and analysis of data. In order to analyse this data at European level, probably a common basis on the collection the data in the Real world practice could be also useful in order to explore at European level the impact of different reimbursement strategies in several European countries. And also, in order to explore a public rule in the reimbursement of the same medicine in the same indication across several countries.” (AIFA)

AOTMiT would find it of value to discuss RWD use and development of methods at a general level internationally, but it is of importance to start with the fundamentals first, such as agreeing on terminology through SNOMED. It is a challenge, even nationally to merge data with different terminologies. Platforms for sharing could be via webpages.

The main points that were proposed were the importance in reusing methods from earlier collaboration initiatives, using already existing networks to share expertise such as EUnetHTA and MOCA - EMA, and the need for creating less complex stepwise recommendations for partners without full access to data. The importance of sharing a basic approach in the collection of data was also mentioned.

ANALYSIS

This section has been written to discuss the results of this study in relation to our theoretical framework in order to be able to classify our findings and give them some context. This framework was inspired by the answers given in the interviews. Hopefully the framework will give a better understanding of the various aspects highlighted in the interviews and in the questionnaire. A general discussion of the answers will follow in relation to our five theoretical frameworks:

- *HTA agencies views on RWE in decision making*
- *Schematic model of the main questions that could be answered through RWD*
- *Data access and processing*
- *Change models*
- *Policy factors for RWD use in reimbursement decisions*

HTA Agencies' Views on RWE in Decision Making

Facey et al., in their article published in October 2020, described the HTA agencies view on settings where RWE could be used in decision making in order to resolve uncertainties in determination of value. The settings were: in initial HTA, in MEAs and in re-assessments.

According to the replies in the questionnaire, where 24 agencies participated, nine agencies responded positively, ¹⁸ on the use of RWD in MEAs. For re-assessments the corresponding numbers were nine positive, four negative and 10 with conditions. Many agencies said yes with conditions. It is hard to know at a general level how often the conditions would be fulfilled so it is not easy to know to what extent the RWD would be used in detail, but at least about 50 percent would say that RWD could be used. Unfortunately, no question was asked on the use of RWD in initial assessments in the questionnaire.

According to the interviews, most of the factors in the column to the right in the figure below, were described to be areas of usage for RWD. The interviews also informed us that more agencies than anticipated indicated that they would use RWD in the initial HTA. Since time is needed to gather effectiveness data, it was anticipated that a majority would use RWD in the re-assessment stage, but several agencies mentioned lack of data as their main reason for not doing re-assessments.

¹⁸ Some questions were not answered by all authorities that responded overall to the questionnaire. That is why in some cases the number of answers do not add up to 24.

Table 2. HTA agencies' views on RWE in decision making, Facey et al., 2020, adapted by HTx WP 4

Resolution of uncertainties in determination of value	Setting	Potential uses of RWE in decision making
	Initial HTA	<ul style="list-style-type: none"> • Describe current standard of care • Create external comparator to contextualise efficacy • Populate cost effectiveness and budget impact models
	Managed entry agreement	<ul style="list-style-type: none"> • Evaluate outcomes in clinical practice • Resolve uncertainties related to determination of value in the initial assessment
	Re-assessment	<ul style="list-style-type: none"> • Complement the clinical and economic evidence base that was available in the initial assessment • monitor utilisation and evaluate budget impact in clinical practice

Schematic Model of the Main Questions that could be Answered through RWD

As expressed previously, RWD could be used to answer different types of questions, and the main questions are on how the pharmaceutical is used or what the effectiveness is of the medical product in clinical practice. Within those two questions there are subcategories as depicted below.



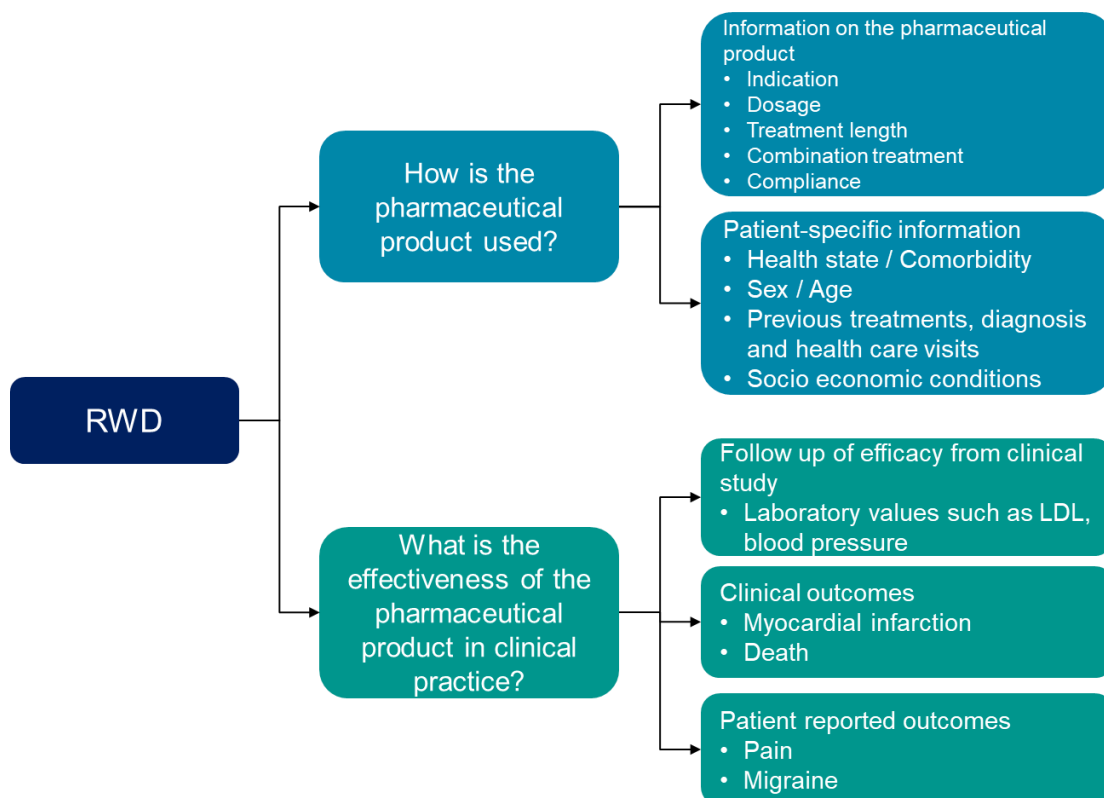


Figure 16 - Schematic model of the main questions that could be answered through RWD

In order to be able to classify which questions the agencies aim to or manage to answer, this should have been examined methodologically during the study, but this was not done since the theoretical framework was developed after the questions were created. Due to the importance and relevance of this theory frame, we will try to discuss this at a general level anyhow, since we have been able to see trends in the answers in the interviews. This can be subject to further studies.

Our impression is that the majority of the agencies are in the blue upper area since claims data seem to be the main data source, and data on effectiveness is very limited for most agencies, and mainly only for certain diseases. All the subcategories of questions in the blue area could not be answered through claims data though such as the important question on for what indication the medical product was used for, as mentioned by several agencies.

Even if clean effectiveness variables are not available for most of the agencies, it was highlighted that in some cases claims data can be used as proxy for effectiveness and the question on time for death can often be answered by claims data.

To better understand the attitudes and willingness to use RWD for reimbursement decisions, three questions were asked on this theme in the questionnaire. It was clear that a majority of the respondents see a need for a wider systematic use of RWD in decisions than what is their current practice. There is also a willingness among both assessors and decision-makers to accept RWD for decision-making. When we asked in which circumstances it could be more likely to accept RWD for assessments or decision

making, situations were described as when there was uncertainty over resource utilisation in clinical practice, or in effectiveness.

We would not accept it as the sole source of evidence / it would be supplementary to RCT evidence. If no RCT evidence is available, then data from single arm studies is accepted but the high level of uncertainty is a concern.

However, there seem to be few agencies that have developed a vision on how this will be done in a systematic way.

Data Access and Processing

In the Theoretical Framework a discussion on how the issues around data access and processing can be structured was presented. For the benefit of the reader the model is presented again in Figure 17.

A fundamental aspect of development of the use of RWD for decision making is the access to relevant data. Through the activities described in the interviews it becomes evident that there are few agencies that are not trying to improve the situation of access to data. This seems also to be the case in the broader group of the agencies that have answered the questionnaire.

There are a number of legal and ethical issues surrounding the gathering and use of data from clinical practice. Patient integrity needs to be preserved and measured against the needs of authorities to understand the effects of their decisions. The legal framework can be established before any work is done or as the development continues. As an example, Estonia has legislation that will allow the gathering of patient data but have other problems when using the data. Italy has established legislation that support the AIFA registries. It is our perception based on the interview that legislation has come after the activities have been piloted for a time.

A second issue is infrastructure. There is a need for infrastructure both to gather, store, transfer and analyse data. Preferably the collection of data can be made from patient registries without imposing additional tasks on health care professionals. This is discussed in both the interviews with AIFA and the Estonian Health Insurance Fund. AIFA has until now chosen not to consider this extra burden as a hindrance and imposes on doctors to make additional notations in the AIFA registries, even if they are looking at solutions for this issue. In Estonia, there is an ongoing discussion departing from the fact that the patient records, that can be accessed, are not structured but mostly consists of free text strings.

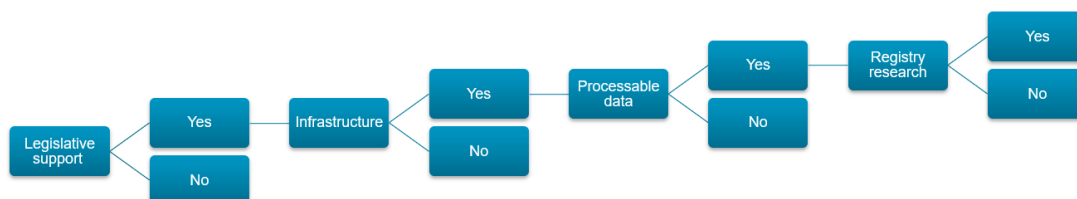


Figure 17 - Data Access and Processing

The need for data to be processable is also a challenge. This is partly linked to how it is gathered. In disease specific registries there might be important variables missing, for instance. It is in this context that statistical methods developed to overcome issues in registry data can be interesting. In TLV's two reports on RWD use there are a few pilots looking at methods from other disciplines, like economics, to see if they can be used to overcome the risk that we are comparing apples with oranges, and to ensure that evidence from the clinical practice can be solid despite lack of certain variables.

Finally, there is a need for competence in registry research. Some agencies, like INFARMED have solved this by relying on the competence accessible with the registry holders. Few seem to aim to develop this competence in the daily line of business. It remains a field for pilot groups and designated experts.

We have identified that only a few agencies or health care systems have come quite far in achieving all the above described criteria. Those are the agencies with the most developed data use such as AIFA, TLV and ZIN. It should be noted that it is not totally known to what extent the data is used, if only in a test environment or to some extent in the real decision making. Our understanding is that also NICE has fulfilled many of those criteria, but at the same time they have indicated that they do not access the data themselves, they only ask the companies to submit data.

Change Models

The authors of this report are keen to understand how HTA agencies are working with RWD and how the new-won knowledge can be implemented in the procedures of the HTA agencies. We are also interested in if it is possible to discern consensus making mechanisms from this work. We found that a deliverable from the same Work Package 4 in HTx could be useful for this discussion and it was briefly presented in the section Theoretical Framework¹⁹.

The category Adaptive Space described in the review of change models, is the one that comes closest to mind when looking at the work of the various agencies. Many are obviously isolating their work from the everyday business. That way RWD use can be developed without disturbing the handling of dossiers and slow down the work done in the core business. Also, the method will allow to involve stakeholders, like registry holders and patients, or acquire knowledge from outside the organisation, like from academia, before introducing the new practice in the daily work. This can also be considered as a *policy sandbox*.

Although no agency, from what we can judge from the interviews, is in a clear-cut case of adaptive space, many solutions seem to be variants of this way of working. NICE performs a lot of work in EU-projects, thus preparing methods before taking them home, INFARMED are working together with specific registries and are thus not involving the whole agency, and perform a large part of the work at the registries, or by the registries. TLV has set up a special team to solve the government assignments that have been the basis of the work, and it is only in the latest report that there is one example of work being done in the line; a re-assessment being done with RWD, for haemophilia products.

¹⁹ Review of change model methods for multi-lateral multi-stakeholder initiatives. 10 July 2020, Next Generation Health Technology Assessment (Htx) etc. Deliverable 4.1.1.

Also, the work presented in TLV's reports has been carried out in collaboration with academia, registry holders, patients (to some extent) and health care practitioners.

The other three change models described in the review are not methods that one can easily ascribe to the work of a specific agency in their totality. Possibly there are traits of all three of them at a number of the agencies. Midstream modulation is the method to have an expert on a field not usually represented in the work, to add knowledge instantly as the work proceeds. Developmental evaluation is a method where professional evaluation is performed as the project is carried out to quickly be able to assess what the result is. This method is, as we noted in the theoretical framework suitable to adapt innovation projects to a rapidly changing environment. Knowledge brokering is when there is a designated expert who knows both the new method and the conditions in the environment that will need to change. In the examples given this person is an intermediary between scientists and policy makers.

Looking at AIFA's model of working with registries it seems to be less isolated from the daily work, but rather be a way of constantly improving that work at the back-drop of the need to follow-up results of MEAs. It seems reasonable to believe that continuous evaluation has been a part of that working method. TLV has a number of dedicated experts working on RWD and they will surely be seen both as mid-stream modulators and knowledge brokers in a later phase when RWD will be used in a more continuous way. Also, the work at AOTMiT in Poland seems to be constructed around experts on interpretation of RWD.

We have seen at a number of occasions that there might be attitudes at management or policy level that form a hindrance to the development of methods for the use of RWD. The methods described briefly above can be ways of overcoming this dilemma. There is thus a need to create consensus in the authorities themselves. This is only partly handled by EU-projects that form adaptive spaces or policy sandboxes in their own right, but does not promote a certain method or use in any more tangible way. We will look further on these projects in the Section on EU-projects and consensus building.

Policy Factors for RWD Use in Reimbursement Decisions

During the course of the interviews, and looking at the questionnaire answers as a comparison the team started to note that some traits seem to be more present in the authorities that are very active in developing the use of RWD, as compared to in the one's that are more passive. From this observation we have developed a simple model of policy factors that we believe form the possibilities to use RWD. This was explained in detail in that part of the Theoretical Framework section.

The first step in the staircase of policy factors is stable institutions. By no means are we saying that the interviewed institutions are not stable. What we are looking at here is more to the side of how knowledge on RWD and procedures around treating data have been developed. It can be said that knowledge can be reified, turned into objects. Guidelines are such objects, just to give one example. Here, a set of knowledge is "frozen" into a document that builds on a large amount of experience and knowledge. Also formalised collaborations can be such reified knowledge and form part of what builds an institution. In this context collaboration with other authorities become a key issue, but also collaboration with disease-specific registries can become formalised and follow guidelines. Looking at our interviewees, we find that a few authorities give

examples of such stability in work practices and relations. AIFA has for instance built its system of registries on a practice that has developed internally over time. It certainly seems to have become a very stable institutional arrangement, without which it would struggle to even exist. TLV's partner authority The National Board of Health and Welfare is host to a set of key national registries. These registries and how they are accessed is very clearly regulated and there are strict procedures to follow to get data in the form of statistics. This might be an example of where the stability becomes a rigidity and difficult to change, but there are also ways to collaborate to achieve desired changes. Authorities that have no or low interest of using RWD will of course not have any reified knowledge supporting such use. We can only speculate that this is a hindrance in some countries. We have also seen in the Hungarian authority NIPN that individuals can create ways to work with data despite the lack of guidelines and similar. This is ground-breaking work and can become the basis for future reification of knowledge. Also, infrastructure for connections between authorities and registry holders can be a part of this step. Here we can again see that authorities that lack this infrastructure has a more complicated reality to work in. It can be the limitation of registries to only some diseases, or the lack of ways to transfer data between the authorities.

This leads us to the next level in the staircase, attitude and leadership. As the work on RWD is new practice for many agencies there needs to be substantial leadership and a positive attitude to achieve results. In the questionnaire, the agencies have ranked policy as one of the major reasons for not developing the use of RWD. In the authorities that accomplish results in this area, like NICE or AIFA there seem to be a very positive and open attitude to the use of RWD among the interviewees, even if the limitations in the use also is expressed in these interviews. The opposite attitude, that RCT is the only usable source of evidence, will stop any sort of development activities, independent of where in the organisational set up it occurs. A clear vision is necessary to formulate a workable mandate for activities. These can come from the inside, from needs in the daily running of business, or from an external party or a governing body. This can of course also be shaped in a dialogue. TLV has worked on a series of government assignments to develop the use of data from clinical practice. This has partly been formed from deliverables from earlier assignments and in dialogue between the Ministry of Health and the management at TLV. AIFA appears to have started their work on RWD from a genuine need to develop a system to do follow-up on very expensive medical products.

Another policy factor that has been evident in the analysis of the interviews is the importance of networks. It is through networks that ideas and inspiration can travel. They are important for the acquisition of knowledge and for the appropriation of knowledge through the interaction with colleagues with similar issues to solve. In networks, contact with academia can also be facilitated and that can also promote exchange of ideas and knowledge about recent developments. There is a broad variance in participation in European projects on RWD. Agencies that do not collaborate and in that way misses to create and participate in networks, seem to prioritise RWD development less. These agencies seem to be the one's that have low or no mandate to work in RWD. It is unclear what influences what, the famous hen and the egg question, but there seems to be a link. This observation should be treated cautiously, since it is a limited collection of authorities that have been interviewed, but it is a hypothesis that cannot be discarded.

As the respondents from the questionnaire were selected from the wide membership of EUneHTA, these agencies per definition are part of a network. In the interview an attempt was made to widen the circle and the Estonian Health Fund was invited to an interview. Is the relatively reserved attitude to RWD an effect of not participating so much in European networks, or is it a co-incidence? Also, NICE, first of all, but also AIFA, INFARMED, TLV, and ZIN have very broad participation in various European projects. There is cause to think about the inclusion criteria in consortia that get access to grants from the EU and if these circles risk to be(come) excluding. If you have participated in one successful project you are likely to get involved in a follow-up. The material is too small to draw reliable conclusions from on this matter, but more activity in European networks seem to go hand in hand with active RWD development, to judge from our limited material.

That competence is a key factor is perhaps too evident to mention, but there are some observations that can be made on this topic. Some agencies have clearly prioritised finding staff that will have knowledge on registry studies: AIFA, NICE, RIZIV-INAMI and TLV are all in this category. This is also interesting for the authorities that have made only first steps toward a more systematic use of RWD, where the activities are very dependent on individuals having both interest and knowledge that allows for competent action in front of the need of data from clinical practice. This is also an indication that this model in the form of a stairways is an image with its limitations. Interested and competent collaborators can achieve important progress. However, competence in an institutional way is developed if the new practice can be incorporated as a standard way of working. That will allow more staff to practice and train and will build institutional knowledge that will not be dependent on a few officials.

The last part of our stairway is legislative support. At a basic level this concerns the collection of data and integrity issues in the first instance. There must be legislative support for this. But this support can go further. The AIFA registries have support in law not only for their existence but also for the data extraction, the analysis and re-evaluation of the conditions of the MEAs after a certain time period. In this can also the status of mandated data handling authority be encompassed. In Sweden only a small number of agencies are mandated to handle statistics and data necessary to form statistics. TLV has asked for such a mandate in their reports to the government reporting the RWD-assignments. To have the status of a “data agency” could be valuable legislation also for agencies in other countries working with RWD.

EU-Projects and Consensus Building

The expression consensus building mechanisms surely calls up connotations to methods relevant to policy making and science. This chapter does not aim to make a review of that kind of consensus making models. Instead, we stipulate that for the purpose of facilitating the use of RWD, some EU-financed projects ongoing or finished are relevant consensus making models to explore and describe. We will also not provide an exhaustive list of these projects.

As described in previous sections there are a number of internal factors that will decide how an agency acts in this field, and also some change models have been described, that makes it clear that there is a need for consensus building also inside an agency and with its primary stakeholders. In this section we will look at what has been done so far to

achieve consensus among the agencies, registry holders, other stakeholders and ultimately governments, on how to use RWD through EU-projects.

EUnetHTA

In terms of HTA collaboration EUnetHTA is the project with most participants (some 70 agencies as Project participants), the longest time period covered and the largest scope among the EU-projects that we have identified. Having started as an EU-project in 2006 it is now on its fourth version as an EU-project and will end by mid-2021. For the latest Joint Action 3 the motto is “Turning pilots into standard practice”. The project has produced a large number of useful tools, the most important possibly the HTA Core Model®. That is a methodological framework for production and sharing of HTA information. Alongside this there is a large number of standard operating procedures, guidelines, databases and recently a tool for registries, The Registry Evaluation and Quality Standards Tool (REQueST). This aims at helping HTA authorities and other stakeholders to evaluate and improve registries for HTA use and is hoping to promote good practice and evidence quality for all sorts of registries.

In EUnetHTA, Work Package 5 B has the responsibility for Post-Launch Evidence Generation work, which is to a large extent directed towards the generation of data and evidence from real world settings. A relatively small number of different pilot studies have been made in the course of the project where agencies participating have been looking at joint evidence gap reports for both pharmaceutical and med tech products. From this, joint datasets have been developed and followed-up by analysis in the national settings. Until now it has not been possible to pool data to one agency from several others. The final conclusions of this exercise are still being prepared.

The EUnetHTA approach to consensus building has been agreeing while writing or doing. The pilot joint assessments of pharma and non-pharma products have permitted the participating agencies to test guidelines, SOPs and other tools previously developed, against their national practices. This has become a learning practice where a loop of joint efforts to solve a problem, has led to a result, documentation of the practice, reflection and then a new trial. In the pilots on RWD this has been less accentuated since this is new in JA3 and it has not been possible to make as many iterations as wished for.

GetReal Initiative

The GetReal Initiative²⁰ that is still ongoing is as its preceeding GetReal Project²¹ part of the IMI programme²². The Innovative Medicines Initiative, IMI, is at its second re-iteration. IMI2 has a budget of up till approximately 3.3 Billion euros and is funded to 50 per cent by the EU's Horizon 2020 programme and the outstanding 50 per cent coming from EFPIA and its members in kind. The IMI webpage states that there are some 160 projects that have been or are funded by IMI. This organisation of the overall programme is the basis for a collaboration between private and public stakeholders in every project. In the GetReal initiative, 16 partners participate, most of them pharmaceutical companies, but also a few research organisations/universities and the HTA organisations NICE and ZIN. The project aims to promote the adoption of tools, methodologies and best practices

²⁰ <https://www.getreal-initiative.eu/>

²¹ <https://www.imi-getreal.eu/>

²² <https://www.imi.europa.eu/>

developed in the initial GetReal Project and increase the quality of Real World evidence generation in medicines development and regulatory/HTA processes across Europe. The tools developed aim both at better understanding of the use of real world data like the RWE Navigator²³, which also provides guidance on study designs, or the GetReal Trial Tool²⁴ which offers step by step guidance to evaluate the options and implications of introducing Real World elements in clinical trial design.

In the GetReal Initiative, as in many IMI-projects, the collaboration with more stakeholders offers a different kind of logic as compared to EUnetHTA. Industry is a part of every project and often also some patient groups are involved. This is perhaps the reason why the focus on RWD is different. There is an interest in including RWE elements already in clinical trials, which would imply that the interest in evidence gaps that become clear later in the life cycle of a pharmaceutical product is less accentuated. As the GetReal initiative builds onto the results of the previous project and involves most of the participants from the project there is a will to promote an iterative process of learning and knowledge sharing. The Project chose to work on case studies linked to specific illnesses. The Initiative is more focused on the development of the learnings and the dissemination of knowledge of the output of the two projects.

Better Data for Better Outcomes, BD4BO, DO-IT

Another project in the IMI-programme that is of relevance for RWD-use is the coordination and support action Data for better Outcomes, policy Innovation and healthcare system Transformation (DO->IT). DO->IT was a part of Big Data for Better Outcomes. The overall goal of the Big Data for Better Outcomes (BD4BO) programme was to facilitate the use of 'big data' to promote the development of "value-based, outcomes-focused healthcare systems in Europe". The coordination action DO->IT resulted in a report on the data integrity issues and the use of informed consent forms and handled a number of other legal issues in the overall project. Also, several dissemination activities like webinars and conferences were conducted through DO->IT.

Again, this is a collaboration between both authorities and pharmaceutical companies. The project has mostly allowed for a single edition of products, which makes the iterative nature of learning less evident in this context. The learning process has been centred around the drafts' edition and discussion, which are designed to promote and distil consensus.

European Health Data and Evidence Network (EHDEN)

Work on data and the possibility of transferring data needs to be prepared by a certain amount of standardisation. The European Medical Information Project (EMIF; ended June 2018), also a part of the IMI programme, developed a method to standardise health data to a data model: the Observational Medical Outcomes Partnership (OMOP) Common Data Model. This standardization effort is carried on by the IMI project European Health Data and Evidence Network (EHDEN) which was launched in 2018, with the aim to standardise health data using the OMOP Data Model. The project is due to run until 2023 and with some 22 partners and close collaboration with the European

²³ <https://rwe-navigator.eu/>

²⁴ <https://www.imi-getreal.eu/News/ID/94/PragMagic-updated-to-GetReal-Trial-Tool-an-innovative-tool-for-navigating-RWE-options-in-clinical-trials>

Medicines Agency, EMA, it is designed to support other IMI2 projects, such as Big Data For Better Outcomes (BD4BO).

EHDEN aims to harmonise clinical data and develop a 21st century ecosystem for real world health research in Europe. The main objectives of the EHDEN consortium are according to the projects webpage to “implement a federated health data network in Europe; enhance the supply and demand side to form a health data eco-system in compliance with robust privacy and ethics governance; and enable the development of new and augmented health services through available and expanded technologies, in the interest of improving health outcomes.” The project also wants to test if the Data Model mentioned above can be used to construct a “federated network of data sources” that will eventually help decision-makers in HTA, payer and regulatory environments with evidence from a broader field of sources.

As EDHEN is an ongoing project it is hard to see what output will eventually be useful for HTA and payer organisations coming. There is an ongoing outreach from the projects with webinars and similar training activities. This can also be seen as consensus making efforts. With fewer HTA agencies involved in the project than in first of all EUnetHTA, it will have some issues in making a learning leading to consensus making outside of these participating agencies. This links to the discussion on networks mentioned in the analysis of the interviews.

Looking at these EU-projects as our proxy for consensus building mechanism we can see that there are some instances where the involvement of HTA agencies or payers is more developed and where also an iterative process will further a learning process. The loops of learning as defined in literature, for instance Argyris²⁵, presents an iterative process of problem solving, reflection and learning and renewed problem solving. This is of course not the only way of achieving consensus, but it is likely that there will be a challenge for projects with less tangible deliverables to make outside stakeholders accept their findings and agree on the solutions. Also, agencies that do not participate in this kind of projects are missing the opportunities to build networks, to learn and to influence. This risks to make projects weaker than they needed to be, in missing potential issues in the agencies and not catering to all needs, and also it risks to promote a fractioned level of knowledge on RWD in the EU where some agencies develop fast and others are left to their own devices.

²⁵ Argyris, C. (1976). Single-Loop and Double-Loop Models in Research on Decision Making. *Administrative Science Quarterly*, 21(3), 363-375. doi:10.2307/2391848

DISCUSSION

Our review of HTA agencies has shown that there is substantial work being carried out in a limited number of agencies, whilst most are still not actively working on methods for the use of RWD or access to data. The agencies that are developing their use of RWD are solving the issues involved in various ways. Some concentrate on access to data while others are keener to work on methods that will allow them to analyse the data. We have seen examples where solutions have allowed substantial steps forward, allowing for the use of RWD in the practice of the agencies. It should be noted that every agency works in its own environment of stakeholder demands, legislative restraints and need to provide evidence for decision-making. That means that there is no one-size-fits-all solution possible.

The purpose of this study was to find on-going work on RWD in the EU and by identifying it avoid duplication of work. There might be important work done in agencies that have not answered the questionnaire, and that is a limitation that will always haunt a study of this limited scope and time. It can also not be excluded that the very fact that the team has had nine intensive discussions of about an hour each with agencies might have triggered a new awareness of the issues and possibilities for internal discussions at the agencies. In normal studies that is seen as something negative, but in the context of HTx it can be seen as a possible positive spin-off. The time and design of this study does not allow for a very deep description of the various projects and development measures identified, but we hope that it can inspire to more publicly available description of this work and interaction between agencies.

The study has enabled us to identify a number of factors that is hampering the development of the use of RWD in the participating agencies. A special question on this was a part of the questionnaire. We have noted that there is a number of policy issues that can support or hinder the use of RWD and this was the starting point of the model on policy factors described in the Theoretical Framework Section. It is our conviction that the most important policy factor, at this stage in the EU, is attitude and vision. The agencies that have succeeded in this field, have all had a clear vision and support from at least agency management. In other cases the developments have been very dependent on individual officials. Infrastructure and data access are evidently very important factors, as well as management of data and in the end legislation, but all of that cannot happen without the right level of curiosity and management support.

A possible reason for lack of management support is that some systems do not demonstrate that immature data and evidence is a real problem in the current decision structure. One example is when budget impact is the main decision criteria in a system. Active management support is evident in the cases described where progress has been demonstrated in the interviews.

In the development of support for RWD use it must be taken into consideration that the agencies have different needs according to their systems and their current situation on for instance data access. This has become clear during the interviews and is a factor that makes the description of the various projects challenging. A deeper understanding of each country's health care system is needed in order to do valid comparisons and draw conclusions.

When studying the more successful projects in the agencies it becomes clear that some sort of legal support is an important factor. This might not be there from the start, but as the projects become an integrated part of the daily business the need for legal support becomes more evident and supports successful implementation. This legal support is unlikely to become reality unless the officials of the HTA authorities are active in suggesting it to their governments, explaining the needs and the benefits of legislation.

The lack of access to data remains one of the main factors behind a slow uptake of use of RWD. This has led some agencies to stop doing re-assessments. In fact, more agencies seem to be validating information on the current use of the drug and its comparators, and the traits of the patient population in the initial application for reimbursement, than those who perform re-assessments.

Closely linked to the lack of access is lack of relevant variables, which comes out in the questionnaire on the reasons for not using RWD. The lack of relevant variables can partly be overcome with statistical methods, which are developed in some agencies and EU-projects. However, lack of capacity to interpret data is also given as a reason for not using RWD. Clearly, there are links between the lack of data and the lack of competencies, and solutions to one of the two issues would benefit the other. In the OECD report, mentioned in the introduction, these issues are also seen as key barriers to better use of RWD.

There was an ambition from the HTx team to understand what methods are developed in the various agencies and what the possible hindrances to developing methods can be. Part of this is described in the above. It should, however, be mentioned that the details of methods development have been very difficult to explore through the interviews. The focus in many agencies are on the access to data and to discuss its possible use. The development of statistical methods has been limited and since it was deemed too technical, has not been discussed in detail in the interviews. Also, some of the more advanced agencies have avoided the questions by saying that it is very dependent on the setting. This has also stopped further exploration.

In the interviews the issue of who is going to pay for the use of studies based on data from clinical practice has been raised from a couple of agencies. There are of course costs associated with gathering of data, quality checks, analysis and so on. The extreme position in the discussions has been that the pharmaceutical companies should pay for this. In a TLV project on payment models for ATMP the possibility of including costs for follow-up studies in the health economic models has been discussed. Although the costs need to be distributed, it should be emphasised that they should be seen in contrast to the costs associated to the impact of decisions on reimbursement made on weak or mistaken evidence, and lost health due to delayed access to treatments.

The fragmented landscape of use of RWD is surely a challenge for those who want to support the development from a political level, like the EU and some member states' administrations. The EU-projects that are working with RWD are often limited in the number of participants. EUnetHTA with its many members, count considerably fewer when it comes to the work on RWD, or Post-Launch Evidence Generation, as is the EUnetHTA terminology. This means that many EU-projects are engaging the agencies that are already advanced in the field. It can also be debated if the tools produced in these projects to any larger degree help solve the issues in the national agencies that

have not yet worked so much on RWD. The tools can only be used when the agency has reached a certain level in the use of RWD in decisions. If an agency is convinced that RCTs is the golden standard, a tool for assessing registries is not really advancing the work, and risks to be left “on the shelf”. It can be argued that there is a need for examples of RWD use and advise on easier and less complex steps to take. There are many aspects in the access to data field that should be addressed, like technical solutions and IT, legal preparedness, and data quality and how data is updated. This should be taken into consideration also by the HTx project itself.

The European Commission recognises that the use of data in the EU is not as high as it could be and have taken an initiative named European Health Data Space. This is aimed “to promote health-data exchange and support research on new preventive strategies, as well as on treatments, medicines, medical devices and outcomes.”²⁶ Legislative proposals are likely to come in a relatively near future.

In the questionnaire, 22 of 24 agencies state that they have made negative reimbursement decisions due to high uncertainties in clinical efficacy. This leads us to reflect on the potential negative impact of not using RWD. Here, we are limited since these negative effects were not explicitly asked for in the interviews, but some aspects deserve to be mentioned in this discussion. The lack of methods and access to data is likely to lead to less transparency in the evaluations of medical products for reimbursement and a slower introduction to the market of innovative products. It can also probably lead to some decisions being less clear than they could otherwise be. In combination with the lessened appetite for re-assessments, this could lead to unnecessarily high prices, negative reimbursement decisions, in-efficient use of drugs over the life-cycle and in the end lost health for patients.

This should be viewed at the backdrop of the clearly expressed willingness among the agencies to accept RWD for decision-making and the fact that a majority of the agencies see a need of more systematic use of RWD than in current practice. There is also a great willingness to learn from other agencies and understand how they are working with RWD. That promises a more accelerated development in the near future.

²⁶ Mission letter to Stella Kyriakides Commissioner-designate for Health, 10 September 2019.

CONCLUSIONS

In the work described above we have been able to demonstrate that there is a considerable interest in working on RWD at the HTA agencies. A handful of agencies are leading the way in enabling access to data and developing the methods to analyse them. Others are hampered by the lack of access to data. In fact, no HTA agency has expressed that they have the data access that they need. However, this might not be the most important obstacle, that can be found in lack of vision and leadership in the field. Some agencies are very dependent on individual officials for their RWD work. Legal support can be very decisive but can often be put in place after the real changes have been piloted.

The leadership issues of RWD are evident in the material. There is a need for vision and mission in order to start working with RWD. Without leadership it is not possible to start overcoming hurdles like no access to data, poor quality and so on. These hurdles will need to be tackled through actions that fit every agency's need, but to wait and see will not bring solutions.

There is a considerable will to learn from other agencies in the field and also from external sources. Given where most agencies are in their developing work, it can be discussed if RWD projects in the EU-setting are helping but a few agencies. The European Health Data Space initiative is interesting to follow in this context.

Methods development seems to be a limited activity. Just a few agencies have established collaboration with external partners to explore possible methods development. Machine learning has been mentioned, but mostly standard statistical methods seem to be used. In this part there is certainly room for further research and for coordination of the work being done by a handful of agencies.

Almost all organisations answering the questionnaire have indicated that they have made negative reimbursement decisions due to high uncertainties in the clinical efficacy. The high rate implies that there's a need to investigate more what consequences this could have on patient access and how access to complementary data such as RWD could reduce the risks, since about 50 percent (10 agencies) meant that the possibility to collect data on effect and safety could have changed the decision and seven agencies said yes with a condition.

Faster learning processes using RWD around disease areas with several new treatment options, each studied in separate RCT-environments, have great potential to improve health outcomes. It should also be noted that the need for follow-up through RWD will increase and is probably of pivotal importance when it comes to facilitating the introduction of payments models for ATMP and connected combination treatments.

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Appendix 1

Questionnaire questions

Real world data

The following questions aim to identify HTA agencies that are considering wider use of real world data (RWD), or are encouraging, gathering or leading the development of methods for using RWD for decisions linked to reimbursement or the use of pharmaceutical products, medical procedures and devices. Although the focus in the overall survey is with the complex/complicated health technologies, we believe that we need to collect information on general aspects of RWD use and as well on RWD use specific for complicated assessments. Questions are general if not clearly indicated that they are about complex therapies. In order to assess the (future) use of RWD for these technologies, we also included questions about general perceptions and use of RWD. This will enable us to identify credible methods for using real-world evidence and understand the barriers to using this type of evidence. The definition that we use for RWD is: everything except for randomised controlled trials, as developed by Makady et al. (2017).

After a first evaluation of a new health technology, do you think that the reimbursement decisions based on your evaluation have been affected by the possibility to follow up on the use and treatment effect in clinical practice? Please briefly specify.

☐ Yes

☐ No

If so, who is responsible for evidence generation? Tick the boxes of relevant answers.

- ☐ The manufacturer
 - ☐ The agency
 - ☐ Academia
 - ☐ Other, please specify...
-

Do you think that negative reimbursement decisions have been made due to high uncertainties in clinical efficacy?

- ☐ Yes
- ☐ No

If yes, could the possibility of collecting RWD concerning treatment effect or safety, have changed the reimbursement decision?

- ☐ Yes
- ☐ No

- Only if...
-

Rank the following issues of reasons for not using RWD from top (most important reason) down (least important or no reason at all).

1. Existing policy structures / information governance (e.g. rules complicating or prohibiting use of RWD)
2. Data sources lacking
3. Long time to access data
4. Lacking relevant variables in registries
5. Financial issues
6. Lack of statisticians or other relevant analysts
7. No possibility to or difficulty with verifying/interpreting data
8. No possibility/experience to link various data sources
9. Lack methods to use RWD

Does your agency review previous decisions (reassessments)?

- Yes
 - No
 - Only if...
-

If yes, do you use RWD in your reassessment?

- Yes, reassessments are in response to new (RW) evidence
- Yes, if a reassessment is being done, RWE is considered
- No

If no, would the possibility of using RWD make it more likely for you to perform reassessments?

- Yes
 - No
 - Only if...
-

In general, do you think that the use of RWD would affect the outcome of reimbursement decisions in your country?

- Yes
 - No
 - Only if...
-

If so, what type of decisions could be affected? Multiple answers are possible.

- Reimbursement decisions for new products
- Reimbursement decisions in reassessments
- Withdrawal of reimbursement

- Price adjustments in later stages of the product's life cycle
- Managed entry agreements affecting reimbursement decisions

Do you use RWD for risk sharing (for example, managed entry agreements or outcome based rebate schemes)? If so, please specify.

- Yes

-
- No
 - Only if...
-

If no, do you see a need for using RWD in risk sharing? Please briefly specify.

- Yes
- No

Are you currently having any projects for developing and assessing methods for using RWD for decisions, in-house or in collaboration with external parties (for example an H2020, EUnetHTA or IMI project)? Please state which one(s).

- Yes...

-
- No

Does your agency see a need for a wider systematic use of RWD in decisions than what is your current practice?

- Yes
 - No
 - Only if...
-
-

If you answered yes, could you specify why?

If you answered no, could you specify why?

Is there a willingness to accept RWD for decision making among assessors and/or decision makers?

- Yes, among both assessors and decision makers
- Yes, only among assessors
- Yes, only among decision makers
- No
- I don't know this

If yes, in which context?

If no, are there other reasons than the reasons in question 31 above? (Attitudes? Politics?)

Are you interested in understanding how other agencies use RWD for decisions? Please briefly specify what it is that you're interested in, or why you are not interested.

☐ Yes...

☐ No

Do you consider RWD generated in other countries during assessment or decision making?

- ☐ Yes, even if I DO have access to data from my own country
- ☐ Yes, though only if I DON'T have access to data from my own country
- ☐ No

If yes, how do you evaluate the transferability of RWD?

If you are not using RWD generated in other countries, what are the biggest barriers for doing so?

Do you consider real world evidence (RWE) generated in other countries, if you do not have access to primary RWD?

- ☐ Yes, even if I DO have access to data from my own country
- ☐ Yes, though only if I DON'T have access to data from my own country
- ☐ No

If yes, how do you evaluate the transferability of RWE?

If you are not using RWE generated in other countries, what are the biggest barriers for doing so?

Can you think of any other circumstances where you are (or would be) more likely to accept the use of RWD for assessments or decision making?

Appendix 2

Participating HTA agencies in the questionnaire

Austrian Social Insurance, Austria

Ministry of Health Croatia, Croatia

Swiss federal office of Public Health, Switzerland

RIZIV INAMI, Belgium

FIMEA, Finland

Scottish Medicines Consortium, Scotland

Zorginstituut Nederland (National Health Care Institute), the Netherlands

National Center of Public Health and Analyses, Bulgaria

National Institute of Pharmacy and Nutrition (NIPN), Hungary

Danish Medicines Council, Denmark

Scottish Health Technologies Group, Scotland

OSTEBA Basque office for Health Technology Assessment, Baskia

UNIBA-FoF State Institute for Drug Control (SUKL), the Czech Republic

National Centre for Pharmacoeconomics, Ireland

TLV, Sweden

Norwegian Medicines Agency, Norway

Directorate for Pharmaceutical Affairs, Ministry for Health Malta

NICE, UK

Gemeinsamer Bundesausschuss (G-BA), Germany

National School of Public Health, Management and Professional Development
Bucharest, Romania

Agencja Oceny Technologii Medycznych Taryfikacji (AOTMiT), Poland

Appendix 3

Interview Guide for the semi-structured Interviews

1. Can you tell us a little more about your decision-making process and where RWD would come/comes into that? How about follow-up of decisions? What has worked well for you nationally in using RWD? How did you reach there?
2. What data sources can you access and what data sources would you like to explore more/develop? Are there any issues with the one's currently used?
3. Do you nationally develop methods to ensure that RWD can be used in your HTA process, that the data can be used for comparisons for example, so that you don't compare apples and oranges? Do you collaborate with other authorities? Universities or clinics? Registries? Are you encouraging or supporting any such work in other institutions? Could the methods be used for decisions linked to reimbursements?
4. What possibilities and risks/uncertainties do you see with the methods you participate in developing?
5. What strategies or methods do you apply if a good data source is missing vital data fields?
6. Do you see possibilities developing the use of RWD through European projects? What is your strategy there? Which projects do you participate in and in what role? Has your participation in the European projects affected your daily work?
7. How would you like to see an increased information sharing between HTA authorities in the EU or wider take form?

Appendix 4

HTA agencies participating in the interviews.

RIZIV INAMI, Belgium

The Estonian health Insurance Fund, Estonia

National Institute of Pharmacy and Nutrition (NIPN), Hungary

AIFA, Italy

Zorginstituut Nederland, National Health Care Institute (ZIN), the Netherlands

INFARMED, Portugal

Scottish Medicines Consortium (SMC), Scotland

NICE, UK

Agencja Oceny Technologii Medycznych i Taryfikacji (AOTMiT), Poland

National School of Public Health, Management and Professional Development
Bucharest, Romania – This interview was not used since it was deemed not relevant