2019

HTAi Global Policy Forum

Real-world evidence in the context of health technology assessment processes – from theory to action

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1 Introduction

This paper is to inform the discussion at the HTAi Global Policy Forum (GPF) Meeting in Barcelona, January 2019. The main aim of the HTAi GPF meeting is to discuss what the leadership roles of HTA and all its relevant stakeholders are in shaping the future availability and use of real-world evidence (RWE) in the context of health technology assessment (HTA) processes to inform decision-making. In the HTA glossary[1] RWE is defined as "evidence derived from the analysis of real world data" (RWD).[2] RWD is defined as "observational or administrative data that provides information on the routine delivery of health care and the health status of the target population."[3]

The topic was selected by HTAi GPF member representatives and HTAi Board members on the basis that the 21st century is bringing new sources and methodological ways of capturing the effects of health technologies in the real world. However, the use of RWE in HTA is not a new topic; much has already been said and written about it, and it is acknowledged that it is now time for action.[4]

Already in 2007, the ISPOR Task Force on RWD mentioned that "health decision-makers involved with coverage and payment policies are increasingly developing policies that seek information on 'real-world' outcomes".[5] Since then RWD and RWE are accelerating at an unprecedented rate of development, size, and scale. This presents challenges but also opportunities for stakeholders involved in the production and use of HTA.

The topic has also been highlighted during former HTAi Global and Regional Policy Forums. During the 2014 HTAi GPF, the implications of new adaptive approaches to licensing, using an "evolving" evidence base (e.g. via patient registries), were explored.[6] At the 2015 HTAi GPF meeting the topic of discussion was improving the effectiveness and efficiency of evidence production in HTA, including the opportunities provided by collaborative real-world evaluation of technologies. It was stated that "HTA needs to…actively align stakeholder expectations about realistic evidence expectations…. Collaborations between technology developers and health systems….should be encouraged to develop evidence that will inform decision making. New analytical techniques emerging for real-world data should be harnessed….for HTA."[7] During the 2016 HTAi GPF, better use of RWD was highlighted as a theme for changing the HTA paradigm; i.e. an issue where "innovation in HTA is needed".[8] The 2017 HTAi Asia Policy Forum on "Universal health care in Asia: HTA and real-world data overcoming barriers"

1 Available via: htaglossary.net (definitions will soon be included in the glossary).

2 Note: RWD are primarily analyzed through observational study designs. This RWE is characterized by the actual use of the technology in practice and by findings that are generalizable to the target population for the technology.

3 Note: Sources may include research data, patient-generated data or professional-generated data. These data may be collected in administrative datasets, case notes, surveys, product and disease registries, social media, electronic health records, claims and billing datasets, or mobile health applications. Reference: Makady, A., de Boer, A., Hillege, H. et al. What Is Real-World Data? A Review of Definitions Based on Literature and Stakeholder Interviews' Value in Health, 2017; 20 (7): 858-865

4 The Academy of Medical Sciences. Next steps for using real world evidence. Summary report of a FORUM follow-up roundtable held on 24 January 2018. Available via: https://acmedsci.ac.uk/file-download/7021031

5 Garrison, L., Neuman, P., Erickson, P., et al. Using Real-World Data for Coverage and Payment Decisions: The ISPOR Real-World Data Task Force Report. Value in Health, 2007; 10 (5): 326-335.

6 Husereau, D., Henshall, C., Jivraj, J. Adaptive Approaches to Licensing, Health Technology Assessment, and Introduction of Drugs and Devices. International Journal of Technology Assessment in Health Care, 2014; 30(3): 241-248.

7 Facey, K., Henshall, C., Sampietro-Colom, L. et al. Improving the Effectiveness and Efficiency of Evidence Production for Health Technology Assessment. International Journal of Technology Assessment in Health Care, 2015; 31(4): 201-206.

8 Husereau, D., Henshall, C., Sampietro-Colom, L. et al. Changing Health Technology Assessment Paradigms? International Journal of Technology Assessment in Health Care, 2016; 32(4): 191-199.

showed that access to RWD is important for achieving universal health care. However, several challenges remain, including a disconnection between what RWD HTA bodies and industry have knowledge of, and have access to as well as limited trust between stakeholders regarding the use of RWD for HTA purposes.[9]

In this paper the focus lies on important issues around the generation and analysis of RWD, and specifically the use of RWE. These issues may impact the way HTA is organized and produced, as well as the relation between traditional, and potentially new, stakeholders (e.g. those that collect and analyze RWD). There are, however, different views on how this process towards use of RWE in HTA should be approached and how to address the key challenges. In addition, there is a need to ensure that HTA processes continue to be robust, relevant and meaningful for different settings and the stakeholders involved, including **patients, health professionals, academia, industry, HTA-agencies, regulators, policy makers and payers.**

In order to inform the 2019 GPF, this paper was developed based on scientific and grey literature identified by the author through an unstructured search in Google Scholar based on recent key publications, reviewing websites/documents of relevant networks (e.g. HTAi, International Network of Agencies for Health Technology Assessment (INAHTA), European Network for Health Technology Assessment (EUnetHTA), International Society for Pharmacoeconomics and Outcomes Research (ISPOR)), regulatory agencies (e.g. European Medicines Agency (EMA), US Food and Drug Administration (FDA)) and HTA organizations using RWE in HTA,[10] as well as input from the HTAi Policy Forum Committee, Policy Forum members, HTAi Board members and the wider HTA community.[11]

The paper starts with introducing the topic, and describing the key challenges identified by GPF members and HTAi Board members that need to be addressed when generating RWD and using RWE in the context of HTA. Thereafter, relevant information to address these challenges is provided, as well as a description of the potential uses of RWE in the context of HTA and how such use could benefit various stakeholders. Finally, the intended outcomes of the 2019 GPF are mentioned along with several questions. The questions are aimed to direct the discussion at the 2019 GPF in Barcelona at the strategic level in order to address the key challenges identified and to move forward by defining actions. The annex provides a – non-exhaustive - overview of existing initiatives and policy-oriented documents regarding the topic, including links to access the related document(s). In addition, suggestions for a more in-depth reading of relevant and brief policy papers (if wished) are given.

[9] Mundy, L., Trowman, R., Kearney, K. Universal Healthcare in Asia: HTA and Real-World Data Overcoming Barriers. DIA Newsletter, January 2017. Available via: https://globalforum.diaglobal.org/issue/january-2018/universal-healthcare-in-asia-hta-and-real-world-data-overcoming-barriers/

[10] See Annex for an overview of publications and websites consulted.

[11] Through an online consultation of HTAi members, asking to provide feedback on the draft paper.

2 Challenges of using RWE in the context of HTA

It is increasingly argued that in addition to randomized trials, indirect and unintended outcome measures from more pragmatic settings and registries (taking into account patient heterogeneity and real life experiences) should also be considered whenever appropriate to answer the relevant HTA question. Increasing the amount of such RWE asks for new methodologies for capturing RWD along the life cycle through differing data sources (e.g. claims databases, registries, electronic medical records, wearables, social media platforms, genomics, biomarkers) and study designs (e.g. health surveys, pragmatic clinical trials).[12] Connecting real-time data (e.g. via smart applications, wearables) with modern technologies (e.g. big data architectures, block chain, artificial intelligence) that are both rapidly evolving, is central to the current digital transformation. The transformation is raising high expectations for the health sector, both on the short and medium term.[13] These developments, especially better use of RWD, will impact the HTA paradigm as already stated in the Introduction.

However, there is **no common understanding** amongst the different stakeholders **on how to define RWD and RWE** and this can result in confusion about how RWE might be used.[14] In the Annex, we provide an overview of the definitions of RWD and RWE used by several initiatives around the globe. As described in the white paper of the Duke-Margolis Center for Health Policy (2017) the "term RWE is often used when stakeholders are actually describing the development or use of RWD for a variety of purposes. However, it is acknowledged that data and evidence are not the same; RWD is necessary but not sufficient for generating RWE. There is a clear need to separate these concepts from one another *and* to clarify the full range of RWE itself."[15][16] Most often RWE is defined as: any data used for decision making that was collected outside of a RCT. [17][18] This is also reflected in the definitions of RWD and RWE provided in the HTA glossary (see Introduction section), and these definitions are used throughout this paper.

The abundance of RWD and RWE ultimately will not only affect **how** HTA is done, it will also have substantial implications for those **who** do HTA; and will this require new skills or professional profiles? Furthermore, there is discussion about **when** RWE should be

[12] Goettsch, W., Makady, A. IMI GetReal. WP1: Deliverable D1.3. Glossary of definitions of common terms. October 2016. Available via: http://www.imi-getreal.eu/Portals/1/Documents/01%20deliverables/D1.3%20-%20Revised%20GetReal%20glossary%20-%20FINAL%20updated%20version_25Oct16_webversion.pdf

[13] Van den Bergen, K., Oortwijn, W., ten Have, A. et al. The future of the medical technology market. Addressing challenges and utilizing opportunities. Rotterdam: Ecorys, 2018. Available via: https://www.rijksoverheid.nl/documenten/rapporten/2018/09/21/the-future-of-the-medical-technology-market-engels

[14] Makady, A. Real-world evidence for health technology assessment for pharmaceuticals: opportunities and challenges. PhD thesis, May 2018, p. 28. Original source: Makady, A., de Boer, A., Hillege, H., Klungel, O., Goettsch, W. (on behalf of GetReal Workpackage 1). What is Real-World Data (RWD)? A review of definitions based on literature and stakeholders interviews. Value in Health, 2017; Aug 20 (7): 858-865.

[15] Duke Margolis Center for Health Policy, 2017. White paper. A framework for regulatory use of real-world evidence. Available via: https://healthpolicy.duke.edu/sites/default/files/atoms/files/rwe_white_paper_2017.09.06.pdf

[16] Daniel, G., Frank, K., Romine, M et al. Duke Margolis Center for Health Policy, 2018. Summary of public comment. A framework for regulatory use of real-world evidence. Available via: https://healthpolicy.duke.edu/sites/default/files/atoms/files/final_rwe_comment_synthesis_20180522.pdf

[17] Miani, C., Robin, E., Horvath, V. et al. Health and Healthcare: Assessing the real world data policy landscape in Europe. Cambridge: RAND Europe, 2014. Available via: https://www.rand.org/content/dam/rand/pubs/research_reports/RR500/RR544/RAND_RR544.pdf

[18] Garrison, L., Neuman, P., Erickson, P., et al. Using Real-World Data for Coverage and Payment Decisions: The ISPOR Real-World Data Task Force Report. Value in Health, 2007; 10 (5); 326-335.

used in HTA and what consequences that would have for **HTA bodies, patients, health professionals, academia, industry, regulators, policy makers and payers**?[19] And for **what** purpose? Should RWD (as part of all available data) be used to get better insight into the value of different treatment pathways in practice at the developmental phase, the time of market launch, and/or post-market launch? As such, how do we better understand the usefulness and challenges throughout the entire lifecycle, and how do we encourage the optimal use of RWE in the context of HTA? The key challenges related to the use of RWE in HTA that were identified by the HTAi GPF and HTAi Board members through an online consultation include:

- For which information gaps / HTA questions might RWE be acceptable as fit for purpose?
- When to use RWE across the lifecycle?
- Quality of data from real world sources
- Data infrastructure and access to data
- Transferability issues

These challenges are also reflected by other stakeholders and initiatives (presented in the Annex) and further described below from the HTA perspective, using relevant literature and documents.

- **For which information gaps / HTA questions might RWE be acceptable as fit for purpose?**

The key questions that are related to this issue include: For what purpose will the HTA community use RWE? How can RWE be used to help inform the coverage decision-making and when to do an update on a prior HTA review? Also, what is the acceptability of RWE by decision-makers and payers (i.e., accommodating evidence needs)?

Most often RWE is used for multiple purposes, including drug development such as the natural history and epidemiology of a disease, to provide data on treatment pathways and comparator interventions in clinical practice, regulatory approval decisions, monitoring pharmacovigilance, and increasingly for HTA, especially cost-effectiveness[20] analysis and re-assessments[21], payer coverage decisions, and outcome-based contracting.[22][23]

[19] Hebborn, A. Reflections on the topic during the HTAi GPF scoping meeting in Vancouver, presentation, June 2018.

[20] Gillespie, J., Erdol, S., Strachan, L. et al. OP07 Real World Evidence: How can it improve Health Technology Assessment? Oral Presentations. HTAi 2018 Annual Meeting. Abstracts Book, p. 18. Available via: https://htai.org/wp-content/uploads/2018/08/AM18_Abstract-Book.pdf

[21] Jaksa, A., Pontynen, A., Wang, X. et al. OP05 Use of Real World Evidence in HTA Decision-Making from 7 Agencies. Oral Presentations. HTAi 2018 Annual Meeting. Abstracts Book, p. 16-17. Available via: https://htai.org/wp-content/uploads/2018/08/AM18_Abstract-Book.pdf

[22] Hampson, G., Towse, A., Dreitlein, T. et al. Real World Evidence for Coverage Decisions: Opportunities and Challenges A Report from the 2017 ICER Membership Policy Summit. ICER, OHE: March 2018. Available via: https://icer-review.org/wp-content/uploads/2018/03/ICER-Real-World-Evidence-White-Paper-03282018.pdf

[23] Murphy, G., de Léséleuc, L., Kaunelis, D., et al. Use of real-world evidence in single-drug assessments. Ottawa: CADTH; 2018. (Environmental scan; no. 74). Available via: https://www.cadth.ca/use-real-world-evidence-single-drug-technology-assessment-processes-health-technology-assessment-and

As stated in the 2017 white paper of the Green Park Initiative, RWE can be used for answering different questions, including comparative effectiveness, total costs of care, or patient-centered outcomes research. This means that in certain contexts, RWE may be more useful and relevant than a RCT. However, RWE can also provide useful information to complement evidence from RCTs or other existing research findings.[24]

There is, however, a **lack of agreement** between different involved parties regarding **what data are needed, at which point in time, and for what purpose**.[25] For example, in the US the lack of consensus among stakeholders about appropriate approaches and methods for using RWD, and RWE to support trials has slowed adoption for regulatory submissions.[26] Deloitte (2018) reported that health care stakeholder receptivity to RWE generated by industry and lack of an internal understanding of where such analyses can be applied are key barriers for using RWE. From a survey among 20 leading biopharmaceutical companies they found that 75% of the respondents felt a lack of receptivity by payers and providers; 70% reported internal stakeholders' lack of understanding, and 60% lack access to necessary external data.[27] Furthermore, a lack of trust and collaboration between key stakeholders has resulted in industry being uncertain as to what data is required in the context of HTA.[28]

Effective collaboration between industry, payers and other relevant key stakeholders in the development and use of RWE for coverage and formulary decisions was discussed at the Institute for Clinical and Economic Review (ICER) Policy Summit in December 2017. Based on this discussion, a framework was developed to guide the optimal development and use of RWE for coverage decisions. The framework consist of several steps to be taken when developing and using RWE, the **necessary evidence standards** for each step regarding the question that it is intended to support, and the context in which the decision needs to be made (see Figure 1 below).

[24] Green Park Collaborative. RWE Decoder Framework. A Practical Tool for Assessing Relevance and Rigor of Real World Evidence. February 2017. Available via: http://www.cmtpnet.org/docs/resources/RWE_Decoder_Framework.pdf

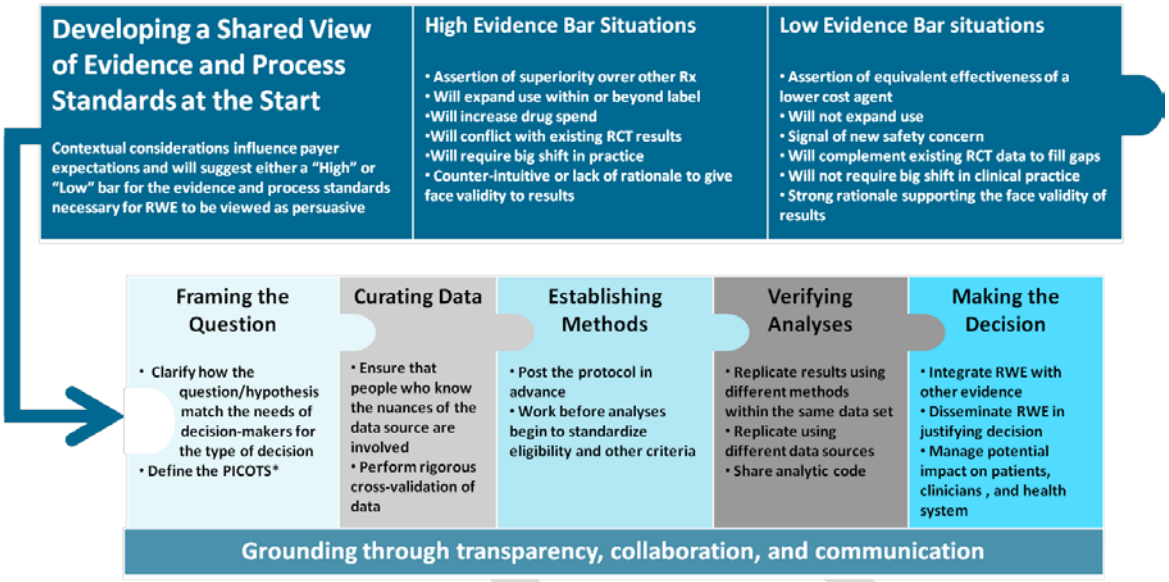
[25] Annemans, L. The use of real world data throughout an innovative medicine's lifecycle. Available via: https://www.riziv.fgov.be/nl/themas/kost-terugbetaling/door-ziekenfonds/geneesmiddel-gezondheidsproduct/terugbetalen/innovatieve-geneesmiddelen/Paginas/innovative-medicins-lifecycle.aspx

[26] Clinical Trials Transformation Initiative. Project Real World Evidence. Overview. Available via: https://www.ctti-clinicaltrials.org/projects/real-world-evidence

[27] Davis, B., Morgan, J., Shah, S. The future of real-world evidence. Biopharma companies focus on end-to-end, AI-driven, internally developed solutions, June 28, 2018. Available via: https://www2.deloitte.com/insights/us/en/industry/life-sciences/2018-real-world-evidence-benchmarking.html.

[28] HTAi Policy Forum Series Newsletter. Universal health care in the Asia Region: overcoming the barriers using HTA and Real World Data. December 2017. Available via: https://htai.org/wp-content/uploads/2018/05/HTAi_Asia-Policy-Forum_newsletter_20171208b.pdf

Figure 1. Conceptual framework to guide optimal development and use of real world evidence for coverage and formulary decisions



PICOTS: Patients, Intervention, Comparators, Outcomes, Time horizon, Setting

Source: Based on Pearson, Dreitlein, Towse et al, 2018; p. 15[29]

- **When to use RWE across the lifecycle?**

As stated above, there is **no clear consensus among stakeholders about when to use RWE**. RWE tends to be discussed within themes that are focused on product development, early adoption and innovation, especially targeting pharmaceuticals. However, some stakeholders believe that there is considerable potential for RWE to rationalize use of healthcare interventions and drive disinvestment decisions.

From a recent report on the use of RWE in single drug assessments (2018), it becomes clear that regulatory agencies Health Canada, the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA), all use RWE to supplement RCT data, both during pre-marketing authorization as well as for post-marketing authorization purposes. The authors did not find relevant information for the regulatory agencies in Australia (Therapeutic Goods Administration) and New Zealand (Medsafe).[30]

Since 2008, the FDA is using Sentinel (a national database) for the monitoring of safety of medical products.[31] The 21st Century Cures Act (2016) and the Prescription Drug User Fee Act VII (2017) include provisions for the FDA to develop a regulatory framework for the use of RWE in decision-making. In 2017, the FDA published a guidance document

[29] Pearson, S., Dreitlein, B., Towse, A. et al. Understanding the context, selecting the standards: A framework to guide the optimal use and real world evidence for coverage decisions. ICER, OHE, March 2018. Available via: https://icer-review.org/material/rwe-white-paper-companion/

[30] Murphy, G., de Léséleuc, L., Kaunelis, D., et al. Use of real-world evidence in single-drug assessments. Ottawa: CADTH; 2018. (Environmental scan; no. 74). Available via: https://www.cadth.ca/use-real-world-evidence-single-drug-technology-assessment-processes-health-technology-assessment-and

[31] For more information see Annex and the website: https://www.sentinelinitiative.org/

regarding the use of RWE in supporting regulatory decisions involving medical devices in August 2017.[32] Also, the FDA intends to release guidance on RWE for drugs and biologics.[33]

Both the FDA and the EMA have accelerated or conditional approval mechanisms in place for certain pharmaceuticals. This means that pharmaceuticals can receive marketing approval based on Phase II studies or surrogate outcomes, and that subsequent evidence concerning the efficacy and safety needs to be collected along its use.[34] In addition, EMA is offering adaptive pathways in patient populations with high medical need. Adaptive pathways allow for early patient access to medicines combined with RWD generation on benefits and harms.[35]

The EMA identified several challenges of using RWE for regulatory purposes, including data quality, limited data access and lack of sustainability of RWD sources. [36] EMA also uses RWE for post-marketing authorization purposes; i.e., to determine post-authorization safety and post-authorization efficacy/effectiveness.[37] With regard to the use of RWE post-launch, EMA also mentioned several challenges. These include the definition of relevant outcome measures and the extrapolation of data from non European registry databases.[38]

The EMA collaborates with the EUnetHTA Joint Action 3 (EUnetHTA JA3)[39] regarding providing parallel scientific advice during early dialogues in the field of pharmaceuticals and medical devices (pilot to be launched).[40] In addition, EUnetHTA JA3 is focusing on the quality of post-launch RWD for HTA purposes, and focuses specifically on the use of registries. Under the coordination of the French National Agency for Health (HAS), HTA bodies and other relevant stakeholders collaborate in order to agree on the requirements regarding post-launch RWD to be generated[41] (see Figure 2 below).

[32] U.S. Department of Health and Human Services, Food and Drug Administration. Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices. Guidance for Industry and Food and Drug Administration Staff. 31 August, 2017. Available via: https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm513027.pdf

[33] U.S. Food and Drug Administration. News. Implementing the 21st Century Cures Act: A 2018 Update from FDA and NHI. Testimony of Scott Gottlieb, Commissioner of Food and Drugs, FDA, 25 July 2018. Available via: https://www.fda.gov/NewsEvents/Testimony/ucm614607.htm

[34] Murphy, G., de Léséleuc, L., Kaunelis, D., et al. Use of real-world evidence in single-drug assessments. Ottawa: CADTH; 2018. (Environmental scan; no. 74). Available via: https://www.cadth.ca/use-real-world-evidence-single-drug-technology-assessment-processes-health-technology-assessment-and

[35] For more information on adaptive pathways: https://www.ema.europa.eu/en/human-regulatory/research-development/adaptive-pathways

[36] Plueschke, K., McGettigan, P., Pacurariu, A., et al. EU-funded initiatives for real world evidence: descriptive analysis of their characteristics and relevance for regulatory decision-making. BMJ Open 2018; 8 (6): e021864. doi:10.1136/bmjopen-2018-021864

[37] Moseley, J. Regulatory perspective on Real World Evidence in scientific advice. Presentation 17 April 2018. Available via: https://www.ema.europa.eu/documents/presentation/presentation-regulatory-perspective-real-world-evidence-rwe-scientific-advice-emas-pcwp-hcpwp-joint_en.pdf

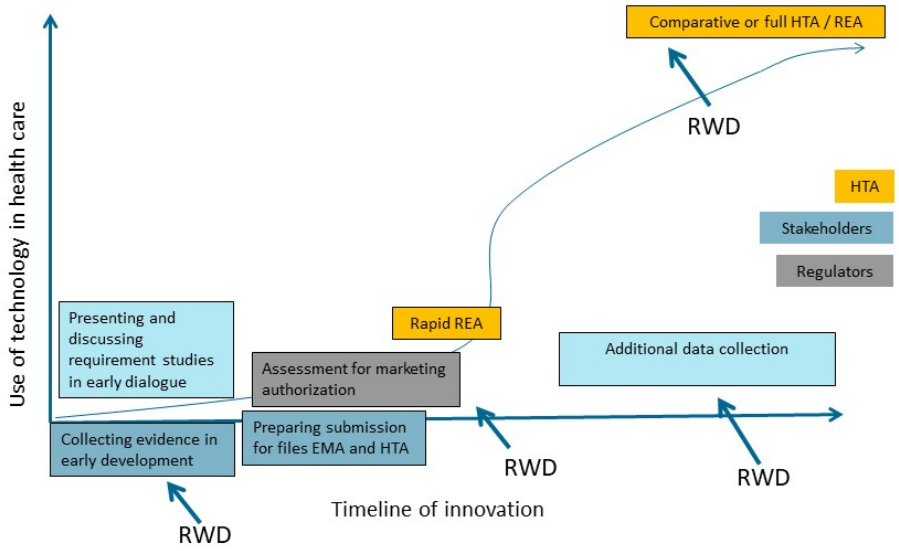
[38] Plueschke, K., McGettigan, P., Pacurariu, A., et al. EU-funded initiatives for real world evidence: descriptive analysis of their characteristics and relevance for regulatory decision-making. BMJ Open 2018; 8 (6): e021864. doi:10.1136/bmjopen-2018-021864

[39] The aim of EUnetHTA JA3 (2016-2020) is to define and implement a sustainable model for the scientific and technical cooperation on HTA in Europe. For more information: https://www.eunethta.eu

[40] For more information: https://www.eunethta.eu/services/early-dialogues/

[41] Guzina, I., Meyer, F., Belorgey, C. OP06 Collaboration on Real World Data Generation: Current EUnetHTA Results. Oral Presentations. HTAi 2018 Annual Meeting. Abstracts Book, p. 17. Available via: https://htai.org/wp-content/uploads/2018/08/AM18_Abstract-Book.pdf

Figure 2. RWD in the lifecycle of health technologies



REA = relative effectiveness assessment

Source: Based on Ermisch, 2017[42]

With regard to the use of RWE by HTA bodies, the report by Murphy, de Léséleuc, Kaunelis et al (2018) summarizes the available evidence from existing literature and a survey among several agencies.[43] As with the regulatory agencies, HTA bodies[44] use RWE to confirm or supplement the findings from RCTs on the treatment effects of pharmaceuticals. In specific cases RWE could be used to demonstrate treatment effects (e.g. when RCTs are not feasible or unethical, and when there is significant unmet need). However, HTA bodies prefer RCT data and in case of using RWD they require an explicit justification of its use as well as a discussion of potential biases and its consequences on treatment effect estimates.

In Latin America (LATAM), RWE is also used in the context of HTA, and mainly for monitoring safety and effectiveness. From a study conducted in 2018, it can be concluded that there are huge differences between countries and that RWE is not

[42] Ermisch, M. Some thoughts on additional data collection through different sources. Presentation EUnetHTA Forum, Amsterdam, 14 September 2017 (Slide 7). Available via: https://www.eunethta.eu/wp-content/uploads/2018/01/6_s4_forum_-_combined_-_final.pdf

[43] Murphy, G., de Léséleuc, L., Kaunelis, D., et al. Use of real-world evidence in single-drug assessments. Ottawa: CADTH; 2018. (Environmental scan; no. 74). Available via: https://www.cadth.ca/use-real-world-evidence-single-drug-technology-assessment-processes-health-technology-assessment-and

[44] In the research the following HTA bodies were included: CADTH, NICE, SMC, TLV, IQWiG, INESS, HAS, NOMA, PBAC, PHARMAC, PPB, and ZIN.

consistently captured at the national level.[45] In the Asian region, countries have conservative approaches to RWD access. This is mainly due to privacy, legal, ethical and custodial concerns around public health database linkage.[46]

- **Quality of data from real world sources**

The **variable quality of data, as well as incomplete data** are key issues to be addressed when using RWE.[47] For example, whether and how to use RWE that exists for comparator interventions when only clinical trial data is available for the emerging intervention. Another challenge is to identify sound methodologies for collecting RWD (standardization of RWD) to support the assessment of efficacy and effectiveness.[48] This is due to differences in clinical practices between and within countries/regions, leading to wide heterogeneity in RWD.[49] This situation compromises the quality and usability of RWD and RWE, and also limits **interoperability** between different datasets. Therefore, it has been noted that **minimum requirements for data input and collection may be needed** to ensure high-quality data and interoperability, where possible using existing standards or guidance that are applied in clinical practice.[50] During the meeting in June 2018 to scope the topic HTAi PF members questioned whether HTA and health authorities should take on the role of certifying specific data sources as adequate quality for using as RWE. It should be recognized, however, that currently RWD cannot achieve the same internal validity as that of RCTs. For instance, there is evidence from literature that RWD may wrongly estimate comparative effectiveness.[51] Furthermore, the existence of cultural views against the use of RWE in terms of adhering to evidence hierarchies in which RWE is seen as of lower quality is also mentioned as a barrier. [52]

Capacity and specific capabilities are needed to ensure routine collection of RWD and use of high-quality RWE. This may require supporting health professionals and other stakeholders that collect data with data entry and standards as well as ensuring sufficient capabilities in data collection and data science. However, it is more likely that it will

[45] Justo, N., Espinoza, M., Ratto, B. et al. RWE in healthcare decision-making: Global trends and case studies from Latin America. Stockholm: ICON, 2018. Available via: https://www.researchgate.net/profile/Diego_Rosselli/publication/325343320_Real_World_Evidence_in_healthcare_decision_making_Global_trends_and_case_studies_from_Latin_America/links/5b06b9094585157f8709f055/Real-World-Evidence-in-healthcare-decision-making-Global-trends-and-case-studies-from-Latin-America.pdf?origin=publication_list

[46] HTAi Policy Forum Series Newsletter. Universal health care in the Asia Region: overcoming the barriers using HTA and Real World Data. December 2017. Available via: https://htai.org/wp-content/uploads/2018/05/HTAi_Asia-Policy-Forum_newsletter_20171208b.pdf

[47] Annemans, L. The use of real world data throughout an innovative medicine's lifecycle. Available via: https://www.riziv.fgov.be/nl/themas/kost-terugbetaling/door-ziekenfonds/geneesmiddel-gezondheidsproduct/terugbetalen/innovatieve-geneesmiddelen/Paginas/innovative-medicins-lifecycle.aspx

[48] European Medicines Agency. Final report on the adaptive pathways pilot. EMA/276376/2016 28 July, 2016. Available via: https://www.ema.europa.eu/documents/report/final-report-adaptive-pathways-pilot_en.pdf

[49] Annemans, L. The use of real world data throughout an innovative medicine's lifecycle. Available via: https://www.riziv.fgov.be/nl/themas/kost-terugbetaling/door-ziekenfonds/geneesmiddel-gezondheidsproduct/terugbetalen/innovatieve-geneesmiddelen/Paginas/innovative-medicins-lifecycle.aspx

[50] The Academy for Sciences. Forum. Next steps for using real world evidence. Summary report of a FORUM roundtable held on 28 January 2018. Available via: https://acmedsci.ac.uk/more/news/next-steps-for-using-real-world-evidence

[51] Annemans, L. The use of real world data throughout an innovative medicine's lifecycle. Available via: https://www.riziv.fgov.be/nl/themas/kost-terugbetaling/door-ziekenfonds/geneesmiddel-gezondheidsproduct/terugbetalen/innovatieve-geneesmiddelen/Paginas/innovative-medicins-lifecycle.aspx

[52] Murphy, G., de Léséleuc, L., Kaunelis, D., et al. Use of real-world evidence in single-drug assessments. Ottawa: CADTH; 2018. (Environmental scan; no. 74). Available via: https://www.cadth.ca/use-real-world-evidence-single-drug-technology-assessment-processes-health-technology-assessment-and

require a new workforce with capabilities to turn RWD into useful information (RWE) for HTA purposes. Engagement with relevant stakeholders, including patients, clinicians, regulators and commissioners to foster an understanding of the value of RWD is also crucial.[53]

Another quality aspect concerns **transparency of RWD**. The joint ISPOR-ISPE Special Task Force recently published two papers (2017) that address several key aspects of transparency in a) overall study planning and procedural practices and b) implementation of studies to facilitate study reproducibility. These papers aim to provide guidance that will ultimately lead to increased confidence in using RWE for healthcare decision-making.[54] They provide specific recommendations for studies that provide data on treatment effectiveness with explicit a priori hypotheses (so-called Hypothesis Evaluating Treatment Effectiveness - HETE studies), including registering the study protocol and design before conducting the study, publishing the study results and any deviations from the protocol and analysis plan in the public domain, enabling replication of the study, performing the study on a different data source and population than the one used to generate the hypotheses to be tested, unless it is not feasible, addressing potential methodological criticisms of the study in the public domain and including key stakeholders (patients, caregivers, clinicians, clinical administrators, HTA, payers, regulators, industry) in designing, conducting, and disseminating these studies.[55]

Furthermore, **data integrity** is a quality issue, and this refers to maintaining and assuring the accuracy and consistency of data collected.[56] As stated by the Green Park Collaborative (2017) it is important that sources present clear parameters of integrity. These include data source and intention, fidelity (e.g. a female is coded as a female), completeness (i.e., absence of missing data), plausibility (i.e., the data is believable), and cohort construction and linkage.[57]

Most often it is mentioned that RWE are only part of a solution and that a perspective could be that different sources of data, RWD and RCTs are used simultaneously to provide the best estimations of effectiveness and cost-effectiveness of health technologies in daily practice (i.e. hybrid approach). However, how can we ensure that fit-for-purpose methods for RWE are going to be developed and implemented in HTA practice?

[53] The Academy for Sciences. Forum. Next steps for using real world evidence. Summary report of a FORUM roundtable held on 28 January 2018. Available via: https://acmedsci.ac.uk/more/news/next-steps-for-using-real-world-evidence

[54] Berger M., Sox, H., Wilke, R. et al. Good practices for Real-World Data Studies of Treatment and/or Comparative Effectiveness: Recommendations from the Joint ISPOR/ISPE Special Task Force on Real-World Evidence in Health Care Decision Making. Value in Health, 2017 (20): 1009-1022.

[55] Berger M., Sox, H., Wilke, R. et al. Good practices for Real-World Data Studies of Treatment and/or Comparative Effectiveness: Recommendations from the Joint ISPOR/ISPE Special Task Force on Real-World Evidence in Health Care Decision Making. Value in Health, 2017 (20): 1005-1008.

[56] Annemans, L. The use of real world data throughout an innovative medicine's lifecycle. Available via: https://www.riziv.fgov.be/nl/themas/kost-terugbetaling/door-ziekenfonds/geneesmiddel-gezondheidsproduct/terugbetalen/innovatieve-geneesmiddelen/Paginas/innovative-medicins-lifecycle.aspx

[57] Green Park Collaborative. RWE Decoder Framework. A Practical Tool for Assessing Relevance and Rigor of Real World Evidence. February 2017. Available via: http://www.cmtpnet.org/docs/resources/RWE_Decoder_Framework.pdf

- **Data infrastructure and access to data**

The challenges regarding data infrastructure and access to RWD are, for example, described by Annemans (2017).[58] He indicates that differences in structure, setup and content of different databases can lead to significant challenges in the sharing of RWD across countries and/or regions. There are also considerable challenges with regard to the **lack of governance**. Most often there are no or poor standards for collaboration, there is a lack of incentives for data sharing, and there are issues with regard to privacy and data security that may severely hamper access to data. These challenges are acknowledged by the EMA. The EMA stated for example that in order to meet regulatory needs, any future European framework must be sustainable using a governance structure which respects data privacy obligations and involves all stakeholders.[59]

Even though excellent RWD sources exist, **access to the data** may be difficult or even impossible due to rules and restrictions regarding data sharing. In some circumstances, access is possible but this may come at a high price. The infrastructure for generating RWD studies can be costly and complex, it can also require substantial change to routine clinical practice and associated clinical pathways, including the establishment of supporting infrastructure such as IT systems. Such costs and complexity can deter industry investment.[60] This is also a challenge for regulators. For example, the Sentinel system provides the U.S. FDA with an ultimate level of access and control but this requires significant financial resources. For Europe it is a challenge regarding how to achieve this level of re-assurance when the European regulatory system cannot exert the same level of control. [61]

- **Transferability issues**

RWD often relates to specific contexts (e.g. local health system) and the question is whether there are frameworks for RWD collection across jurisdictions. Although usual care (or standard of care) is included as a comparator in a trial, its application in the study (for example, dose, frequency, route of administration, monitoring) may differ from usual care in the country of interest. Moreover, the population characteristics for the same type of disease may differ between countries, and this will have different implications for the treatment and its effectiveness. This may raise concerns about the **transferability of study results** (e.g. on the use of diabetic drugs in a population from the US. The diabetes population in the US includes relatively more patients with obesity, and these patients need a higher dose of diabetic drugs. The results of such a study cannot be easily transferable to countries where the number of diabetic patients with

[58] Annemans, L. The use of real world data throughout an innovative medicine's lifecycle. Available via: https://www.riziv.fgov.be/nl/themas/kost-terugbetaling/door-ziekenfonds/geneesmiddel-gezondheidsproduct/terugbetalen/innovatieve-geneesmiddelen/Paginas/innovative-medicins-lifecycle.aspx

[59] European Medicines Agency. STAMP Commission Expert Group. Real World Evidence. RWD focused activities – electronic health records. HMA-EMA Joint Big Data Taskforce. Presentation 8 June 2018. Available via: https://ec.europa.eu/health/sites/health/files/files/committee/stamp/stamp_9_41_2_en.pdf

[60] The Academy for Sciences. Forum. Next steps for using real world evidence. Summary report of a FORUM roundtable held on 28 January 2018. Available via: https://acmedsci.ac.uk/more/news/next-steps-for-using-real-world-evidence

[61] European Medicines Agency. STAMP Commission Expert Group. Real World Evidence. RWD focused activities – electronic health records. HMA-EMA Joint Big Data Taskforce. Presentation 8 June 2018. Available via: https://ec.europa.eu/health/sites/health/files/files/committee/stamp/stamp_9_41_2_en.pdf

obesity is less substantial). In some cases the clinical background and skill level of health professionals involved (e.g. clinicians) may also be important.[62]

An interesting example regarding **standardization of RWE** is the Big Data for Better Outcomes (BD4BO) programme that is part of IMI2. The overall aim of this programme is to facilitate the use of 'big data' in the development of more value-based and outcomes-focused healthcare systems in Europe. One of the ways the programme is supporting this objective is through the standardization of outcomes in different disease areas. This enables the pooling of outcome data across a wider population. Individual disease-specific projects are focused on developing a minimum set of outcomes, incorporating perspectives of important key stakeholders.[63] Other examples regarding common standards for data input and data organization include the European Reference Networks and EMA's initiative on patient registries.[64]

This section presented the key challenges that were identified by HTAi GPF members and HTAi Board Members. These challenges need to be addressed to fully utilize the potential of RWE in the context of HTA. The potential of RWE in the context of HTA is summarized in the next section.

62 Innovative Medicines Initiative Joint Undertaking GetReal. RWE Navigator. Effectiveness challenges – Intervention/Comparator. Available via: https://rwe-navigator.eu/homepage/review-supporting-material/effectiveness-challenges/intervention/

63 Innovative Medicines Initiative 2 Joint Undertaking (IMI2). Big Data for Better Outcomes. A practical toolkit for the identification, selection, and measurement of outcomes including in real-world settings. Available via: http://bd4bo.eu/index.php/toolkit

64 Annemans, L. The use of real world data throughout an innovative medicine's lifecycle. Available via: https://www.riziv.fgov.be/nl/themas/kost-terugbetaling/door-ziekenfonds/geneesmiddel-gezondheidsproduct/terugbetalen/innovatieve-geneesmiddelen/Paginas/innovative-medicins-lifecycle.aspx

3 The potential value of RWE in the context of HTA

There is no clear consensus on the added value of RWE in the context of HTA due to the challenges described in the former section. The Academy of Sciences state in their 2018 summary report of a roundtable regarding the use of RWE that "since 2015 progress in the use of RWE beyond pharmacovigilance has been incremental rather than transformational". [65] However, relevant stakeholders including regulators, HTA bodies and research organizations are committed to exploring its potential.

The potential value[66] of RWE along the life cycle of technology development can be summarized as follows (based on Annemans, 2017):[67]

During the **development phase of a new health technology**, RWD can enable more effective and efficient research and development processes as it can help:

- to better characterize diseases, patient populations, and help to understand patient needs (e.g. RWD can provide information on the number of patients with a given disease who are insufficiently controlled or whose treatment is inadequate, and it can provide information on patient characteristics);
- to better identify and recruit participants for research (e.g. databases using electronic medical records enable the identification of patients who meet the inclusion criteria of a study);
- to make the design of RCTs more "pragmatic" (e.g. claims databases can provide information on follow up visits and examinations in daily practice and this information can be used in the trial).

During the **market access phase**, RWD allow a better understanding of:

- the patient management strategy, and modalities of the current standard of care, for comparison with the new treatment;
- real outcomes related to the standard of care, such as the number of complications, adverse events, disease progression, resource use and costs.

In case of (very) rare diseases, where conventional RCTs are often not possible, RWE can fill evidentiary gaps which are not specifically addressed with conventional RCTs. This may also apply to cases where it is unethical to conduct RCTs, in case of conditions that would be fatal without an intervention in the short term, and in cases of significant unmet need. In these situations, RWD can reduce time and cost of evidence development, and potentially result in earlier access to innovation. Furthermore, in the absence of head-to-head RCTs, RWD may be used to inform indirect treatment

[65] The Academy for Sciences. Forum. Next steps for using real world evidence. Summary report of a FORUM roundtable held on 28 January 2018. Available via: https://acmedsci.ac.uk/more/news/next-steps-for-using-real-world-evidence

[66] Pharmafocus. Riding the wave: the FDA and real world evidence. Interview with Jacqueline Corrigan-Curay, Director of CDER's Office of Medical Policy at the FDA.18 January 2018. Available via: http://www.pharmafile.com/news/516308/riding-wave-fda-and-real-world-evidence

[67] Annemans, L. The use of real world data throughout an innovative medicine's lifecycle. Available via: https://www.riziv.fgov.be/nl/themas/kost-terugbetaling/door-ziekenfonds/geneesmiddel-gezondheidsproduct/terugbetalen/innovatieve-geneesmiddelen/Paginas/innovative-medicins-lifecycle.aspx

comparison. Finally, RWD can supplement RCT data if data on specific subpopulations or long-term follow-up is lacking.[68]

Finally, during the **post launch phase**, RWD allow:

- the provision of data on the use of treatments in practice (e.g. in which patients, according to which treatment modalities (dosage, duration etc.), the adherence and other outcomes (tolerance, safety, and effectiveness));
- the assessment of outcomes in practice, which may serve as input in outcomes-based managed entry agreements and price setting. RWD would enable stakeholders to determine a point of verification, which allows assessing whether the predicted benefits of a health technology can be confirmed.
- the development of clinical decision support systems;
- re-assessment of health technology.

As described earlier, it is acknowledged that the attitude in HTA should be which data do stakeholders need and when do stakeholders need it in order to answer the relevant question? It is therefore important to state that the availability of RWD before, in parallel to, and after RCTs broadens the options to collect relevant data and has different purposes. The combination of both types of data (RCT and RWD) can help to better estimate the impact of (new) health technologies. However, in the CADTH report on the use of RWE in single drug HTAs (2018) it is stated that "stakeholders generally agree on many uses of RWD that may contribute valuable information for regulatory and reimbursement decision-making, the use of RWE to answer questions or relative effectiveness of interventions is controversial and some question the possible impact of increased reliance on these data. At the regulatory level, acceptance of a 'lower standard' of evidence and accelerated approvals may allow unsafe or ineffective products to reach the market".[69]

[68] Murphy, G., de Léséleuc, L., Kaunelis, D., et al. Use of real-world evidence in single-drug assessments. Ottawa: CADTH; 2018. (Environmental scan; no. 74). Available via: https://www.cadth.ca/use-real-world-evidence-single-drug-technology-assessment-processes-health-technology-assessment-and

[69] Murphy, G., de Léséleuc, L., Kaunelis, D., et al. Use of real-world evidence in single-drug assessments. Ottawa: CADTH; 2018. (Environmental scan; no. 74). Available via: https://www.cadth.ca/use-real-world-evidence-single-drug-technology-assessment-processes-health-technology-assessment-and

4 Key issues for the 2019 Global Policy Forum

There are indications that new sources for gathering and analyzing RWD will probably make the HTA process more efficient and effective for informing decision-making across the health technology lifecycle and in different contexts. There is also considerable potential in terms of strengthening relations with regulatory agencies, and partnerships with health systems, patient advocacy groups, start-ups and other RWD-based organizations. There are, however, still key challenges to be addressed. The key challenges highlighted most by HTAi GPF members and HTAi Board members are:

- For which information gaps / HTA questions might RWE be acceptable as fit for purpose?
- When to use RWE across the lifecycle?
- Quality of data from real world sources
- Data infrastructure and access to data
- Transferability issues

Moreover, the characteristics of emerging, innovative health technologies (i.e. more personalized), the trend towards learning health systems,[70] along with the increased availability of sources for information gathering as well as the need for relevant stakeholder involvement, necessitates a change in the way HTA is going to be organized and conducted in the medium and long term.[71] Therefore, important questions from a HTA perspective are: Does the current HTA workforce have the capabilities and capacity to deal with the changing environment? Should the HTA process move from a linear to a circular model (i.e. interactive (re-)assessment)? Should HTA continue to act as the "gate-keeper" of health technologies that want to enter health systems, or does it need to take a convener role of decentralized performed assessments?

In order to address the current and medium-long term challenges that RWD/RWE pose to HTA, the **objective of the 2019 HTAi GPF meeting is twofold**:
1. identify actions that can contribute to overcoming the current challenges;
2. inspire the development of "road maps" for the medium term in which HTA bodies and industry work collaboratively with other relevant stakeholders in adjusting the HTA process to the new requirements demanded by innovative health technologies and new sources of information (RWD).

For the latter, it is important to take a visionary perspective and try to understand how stakeholders can address the challenges collaboratively; taking a future perspective of what HTA will look like in the future in order to be prepared.

[70] A learning health system is defined as a system in which "science, informatics, and culture are aligned for continuous improvement and innovation, with best practices seamlessly embedded in the delivery process and new knowledge captured as an integrated by-product of the delivery experience." Source: Institute of Medicine. The learning healthcare project website (2015). Available via: http://www.learninghealthcareproject.org/section/background/learning-healthcare-system

[71] Eichler, J., Bloechl-Daum, B., Broich, K. et al. Data rich, information poor: can we use electronic health records to create a learning health care system for pharmaceuticals? Clinical Pharmacology & Therapeutics, 2018; 4 September. doi: 10.1002/cpt.1226

Some **relevant questions** that could be addressed during the 2019 HTAi GPF meeting include:

- Quality, acceptability and transferability:
    - What would make RWD of the same or close to the quality of RCT considering the hierarchy of evidence?
    - How to build trust in a situation where there will be a lot of misguided information (e.g. sources of information very accessible to patients, risk of fake news)? What could be the contribution of HTA and industry?
    - Should HTA bodies become a certified body for quality of data sources?
    - What could be considered acceptable RWD? What conditions should data have for payers to accept HTA recommendations based on RWE?
    - What happens if RWE provides suboptimal, not uncertainty related, effects; i.e., less good than predicted?
    - When no local data exists, what would be the conditions for accepting RWD from other countries?
    - What are the requirements to trust RWE?
- Governance and accountability:
    - Which stakeholders are responsible for RWD collection and RWE generation?
    - Who should decide the type of RWE needed?
    - Who should bear the cost of RWD collection?
    - Who should control access to RWD?
    - Who should have access to RWD?
- Are there any lessons to be learned from experiences with coverage with evidence development (CED) and the use of pragmatic trials to inform decision-making using RWE?
- For which information gaps / HTA questions might RWE be acceptable as fit for purpose? (I.e. when and for what can RWE best used in the context of HTA?)
- In the light of current trends and envisioning the future, if the relevant stakeholders (HTA bodies, industry, patients, etc.) are going to design a HTA system from scratch, what would it look like? How would the HTA process need to change? How would industry need to change? (e.g. considering workforce, organization of the assessment process, time and point of assessment, interactions with traditional stakeholders and new potential incomers, etc.) - i.e. identifying elements for developing the “road map”.

Annex Overview of selected relevant initiatives and suggested reading (in bold)

Organization / Author	Title	Purpose/description	Definition of RWE used	Link to sources for more information
ABPI (2011)	Guidance. Demonstrating value with real world data. A practical guide	Guidance seeks to provide further clarity around the definitions, use and practical issues which arise when undertaking RW data projects	Any data outside the constraints of conventional RCTs to evaluate routine clinical practices. RWD will refer to data obtained by any non-interventional methodology that describes what is happening in normal clinical practice	http://www.abpi.org.uk/media/1591/2011-06-13-abpi-guidance-demonstrating-value-with-real-world-data.pdf
Annemans, L (2017)	The use of real world data throughout an innovative medicine's lifecycle	To discuss the usefulness of RWD throughout the lifecycle of innovative medicines, thereby providing realistic expectations about their possibilities and pointing to their limitations; To list the current issues in the collection, interpretation and implementation of RWD; and to propose principles of good practice and necessary actions to improve the use of RWD throughout the lifecycle of innovative medicines	Any data not collected in 'conventional randomized controlled trials (RCTs)'. It may include data from existing secondary sources (e.g. databases of national health services) and the collection of new data, both retrospectively and prospectively (RAND Europe, Health and Healthcare: Assessing the Real World Data Policy Landscape in Europe, 2014)	https://www.riziv.fgov.be/nl/themas/kost-terugbetaling/door-ziekenfonds/geneesmiddel-gezondheidsproduct/terugbetalen/innovatieve-geneesmiddelen/Paginas/innovative-medicins-lifecycle.aspx
CADTH (2018)	**Use of Real-World Evidence in Single Drug Technology Assessment Processes by Health Technology Assessment and Regulatory Organizations**	**Environmental Scan to identify, describe, and compare how regulatory frameworks and HTA processes in Canadian and international organizations incorporate RWE in single-technology assessment of drugs**	None. They listed definitions used internationally and concluded that there was no consistent definition of RWD or RWE.	https://www.cadth.ca/use-real-world-evidence-single-drug-technology-assessment-processes-health-technology-assessment-and **https://www.cadth.ca/sites/default/files/pdf/es0323-rwe-in-single-drug-appraisal.pdf**
Clinical Trials Transformation Initiative – CTTI (2018)	Real World Data and Evidence in the Evaluation of Medical Products	Describe how RWD sources such as electronic health records, payment claims, and registries can be used to support planning and execution of randomized controlled trials;	Real World Evidence (RWE) is the clinical evidence regarding the usage, and potential benefits and risks, of a medical project derived from analysis of RWD. Real World Data (RWD) is data relating to	https://www.ctti-clinicaltrials.org/projects/real-world-evidence;

Organization / Author	Title	Purpose/description	Definition of RWE used	Link to sources for more information
		Identify barriers and potential solutions to adoption of RWE generation; Identify concerns with RWD/RWE, describe how they can be addressed, and clarify when using RWD/RWE is impractical or unwise; Describe practical models and operational guidance for the use of RWD in randomized clinical trials to generate RWE in specific clinical trial operations activities	patient health status and/or the delivery of health care routinely collected from a variety of sources.	https://www.ctti-clinicaltrials.org/briefing-room/meetings/real-world-data-and-evidence-evaluation-medical-products-0
CMTP (2017)	Green Park Collaborative (GPC) – RWE Decoder	GPC convenes working groups to develop condition and technology-specific study design recommendations that focus on real-world effectiveness and value, meet the evidence expectations of payers, and are informed by the views of patients and clinicians	*Evidence.* Health services researchers produce many kinds of information that might be considered "evidence." This includes: (1) descriptive information on the burden of illness, provider performance, the rate of adverse events, costs, and utilization; (2) evidence about whether interventions "work," that is they effect outcomes of interest (positively or adversely), as well as for whom and in what contexts; and (3) how and why the intervention works, and how a model can be amended to work in new settings. The primary focus of the RWE Initiative is (2) and (3). Note: sometimes evidence isn't sufficiently rigorous to be sure that the intervention and the outcome are causally related but that causal relationships are implicit in "works" or "effect outcomes of interest." *Real World.* This implies that the evidence was generated during the delivery of healthcare in realistic settings. Typically, observational evidence, i.e. not randomized, but PCTs and stepped-wedge randomized cluster designs conducted in real practice may also be considered RWE	http://www.cmtpnet.org/docs/resources/RWE_Decoder_Framework.pdf
Deloitte Center for Health Solutions (2018)	2018 RWE benchmarking survey	Survey results on how leading biopharmaceutical companies are trying to optimize the use of RWE through investment, application, external partnerships, and technology	Clinical evidence about a product's usage, potential benefits, and risks derived from RWD.	http://learn.deloitte.com/rwe-survey-deloitte-insights

Organization / Author	Title	Purpose/description	Definition of RWE used	Link to sources for more information
			Data (=FDA definition). RWD refers to health care data gathered from a variety of sources, outside of randomized controlled clinical trials	
Duke-Margolis Center for Health Policy (2017)	Duke-Margolis RWE Collaborative / **A framework for regulatory use for real-world evidence (White paper)**	**To advance policy development related to the regulatory acceptability of RWE by engaging multiple stakeholders, with the express aim of informing and supporting the FDA as it works to meet RWE milestones as established in the 21st Century Cures Act and the sixth Prescription Drug User Fee Act (PDUFA VI)**	RWE is defined as evidence derived from RWD through the application of research methods. For regulatory applications, RWE can further be defined as clinical evidence regarding the use and potential benefits or risks of a medical product derived from analysis of RWD. RWD is defined as data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources	https://healthpolicy.duke.edu/real-world-evidence-collaborative https://healthpolicy.duke.edu/events/public-workshop-framework-regulatory-use-real-world-evidence https://healthpolicy.duke.edu/sites/default/files/atoms/files/rwe_white_paper_2017.09.06.pdf
EMA (Plueschke, McGettigan, Pacurariu et al, 2018)	EU-funded initiatives for real world evidence: descriptive analysis of their characteristics and relevance for regulatory decision-making	Review of European Union (EU)-funded initiatives linked to RWE to determine whether their outputs could be used for the generation of RWD able to support the European Medicines Agency (EMA)'s regulatory decision-making on medicines	IMI GetReal Glossary of Definitions of Common Terms (Goettsch, Makady, Available via: http://www.imi-getreal.eu/Portals/1/Documents/01%20deliverables/D1.3%20-%20Revised%20GetReal%20glossary%20-%20FINAL%20updated%20version_25Oct16_webversion.pdf)	https://bmjopen.bmj.com/content/bmjopen/8/6/e021864.full.pdf
EMA	EMA Adaptive Pathways Pilot project – a regulator-led forum to simulate adaptive pathways (Final report, 2016)	To explore the practical implications of the adaptive pathways concept with medicines under development. It reflects the experience gained in the pilot project (2014-2016), discusses the practical findings and outlines the next steps to further explore the concept; it reflects the different perspectives on the adaptive pathways concept that were collected through a questionnaire circulated via the European Commission Expert Group on Safe and Timely Access to Medicines for Patients (STAMP) to the Member States, EUnetHTA and network of	RWD as a complement to RCTs. in an adaptive pathways proposal, a coherent, prospective plan for RWE is designed to collect high-quality data to further refine the benefit/risk profile, the therapeutic value and the price of a medicine.	https://www.ema.europa.eu/documents/report/final-report-adaptive-pathways-pilot_en.pdf

Organization / Author	Title	Purpose/description	Definition of RWE used	Link to sources for more information
		Competent Authorities for Pricing and Reimbursement (nCAPR), and a company survey conducted within the ADAPT-SMART IMI project		
	Follow-up – parallel advice with HTA bodies (2017)	From 2017 onwards, EMA offers consultations in parallel with EUnetHTA to allow medicine developers to obtain feedback from regulators and HTA bodies on their evidence-generation plans to support decision-making on marketing authorization and reimbursement of new medicines at the same time. These consultations can take place before or after the product is made available on the market. The objective is to help generate optimal and robust evidence that satisfies the needs of both regulators and HTA bodies	RWD: data on health interventions collected outside highly-controlled RCTs. RWE is part of evidence generation package, complementary in nature	https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance/parallel-consultation-regulators-health-technology-assessment-bodies; https://www.ema.europa.eu/documents/presentation/presentation-regulatory-perspective-real-world-evidence-rwe-scientific-advice-emas-pcwp-hcpwp-joint_en.pdf
	HMA (Heads of Medicines) - EMA joint task force Big Data (2017)	To establish a roadmap and recommendations for use of big data in assessment of medicines	A subset of big data is real world evidence, which encompasses the use of sources such as electronic health records, registries, hospital records and health insurance data	https://www.ema.europa.eu/news/how-big-data-can-be-used-development-regulation-medicines; https://ec.europa.eu/health/sites/health/files/files/committee/stamp/stamp_9_41_2_en.pdf; https://www.ema.europa.eu/documents/other/hma/ema-joint-big-data-task-force_en.pdf
	EMA Patient Registries Initiative (2015)	To make better use of existing registries and facilitate the establishment of high-quality new registries if none provide an adequate source of post-authorization data for regulatory decision-making. To support the initiative, EMA set up a cross-committee task force on registries, comprising representatives from EMA scientific committees and working parties and experts from national competent authorities. It has established links with HTA bodies and payers and the European Commission	Not specifically defined. Definitions include registry, disease registry, product registries, and patient registry.	https://www.ema.europa.eu/en/human-regulatory/post-authorisation/patient-registries

Organization / Author	Title	Purpose/description	Definition of RWE used	Link to sources for more information
EUnetHTA JA3 (2016-2020)	WP5 Evidence Generation; A: Initial evidence generation: Early dialogues; B: Post-launch evidence generation (PLEG), with a special focus on registries	To help to generate, all along the technology lifecycle, optimal and robust evidence for different stakeholders, bringing benefits for patient access and public health	RWD are non-RCT data versus experimental data or EPR data, reference to Makady, A., de Boer, A., Hillege, H, et al. What Is Real-World Data (RWD)? A Review of Definitions Based on Literature and Stakeholder Interviews. Value in Health 2017; 20 (7): 858-865	https://www.eunethta.eu/ja3-archive/work-package-5-life-cycle-approach-to-improve-evidence-generation/; https://www.eunethta.eu/wp-content/uploads/2018/01/6_s4_forum_-_combined_-_final.pdf
FDA (2017)	Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices	Guidance to clarify how FDA evaluates RWD to determine whether they are sufficient for generating the types of RWE that can be used in FDA regulatory decision-making for medical devices	Clinical evidence regarding the usage, and potential benefits or risks, of a medical product derived from analysis of RWD. RWD is data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.	https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm513027.pdf
	FDA Sentinel (2008) and mini-Sentinel initiative (2011)	Sentinel is a network of distributed data approach which allows the FDA to rapidly and securely access information from large amounts of electronic healthcare data, such as EHRs, insurance claims data and registries. It is primarily intended for the monitoring of safety of medical products but has also been used in approval decisions; The “Mini-Sentinel” pilot program was FDA’s first step towards building a nationwide rapid-response electronic safety surveillance system for drugs and other medical products As of 2018, the Sentinel System has more than 223 million members within a network of 17 data partners and many more collaborating institutions.	RWD: data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources, can come from EHRs, claims and billing activities, product and disease registries, patient-related activities in out-patient or in-home use settings, and health-monitoring devices The data in the Sentinel system is largely claims and pharmacy data.	https://www.sentinelinitiative.org/ http://www.pharmafile.com/news/516308/riding-wave-fda-and-real-world-evidence
ICER (2018a)	Real World Evidence for Coverage Decisions: Opportunities and Challenges	To stimulate discussion at the 2017 ICER Policy Summit meeting; paper sets out the potential opportunities and important challenges and limitations that must be addressed in considering options for using RWE to inform insurer coverage decisions	Adapted from FDA (2017): RWE is the clinical evidence regarding the usage, and potential benefits or risks, of a medical product derived from analysis of RWD. RWD are data relating to patient health status and/or the delivery of health care collected either prospectively or retrospectively from observations of routine clinical practice	https://icer-review.org/wp-content/uploads/2018/03/ICER-Real-World-Evidence-White-Paper-03282018.pdf

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ICER (2018b)	**Understanding the Context, Selecting the Standards: A Framework to Guide the Optimal Development and Use of Real World Evidence for Coverage and Formulary Decisions**	**Presents a new conceptual framework to address three elements largely missing from these earlier efforts focused on defining "best practices" or "standards" for RWE: 1) how to understand the role that contextual factors play in determining how high the evidentiary standard, or "bar" will be in each situation; 2) how to tailor key process and methodological approaches to the height of that evidentiary bar; and 3) how to ensure that broader process principles that support transparency are integrated successfully throughout the course of any RWE initiative**	See ICER 2018a	https://icer-review.org/wp-content/uploads/2018/03/ICER-RWE-Framework-Companion-White-Paper-03282018.pdf
Innovative Medicines Initiative (IMI)	**Advancing Evidence Generation for New Drugs (2017)**	**IMI GetReal's Recommendations on Real-World Evidence. Aims of GetReal (2013-2017) were to explore how robust new methods of RWE collection and synthesis could be adopted earlier in pharmaceutical R&D and the healthcare decision making process**	It is stated that there is a need for common understanding, reaching consensus on the relevance of RWD, and harmonizing the requirements and improved methods and governance.	https://www.imi-getreal.eu/Portals/1/Documents/01%20deliverables/2017-03-29%20-%20WP1%20-%20Advancing%20Evidence%20Generation%20for%20New%20Drugs.pdf
	Goettsch, W., Makady, A. IMI GetReal. WP1: Deliverable D1.3. Glossary of definitions of common terms (2016)	Glossary of definitions of key terms, both for the purpose of GetReal, and also with the aim of providing clarity to external stakeholders around these terms.	*RWD*: An umbrella term for data regarding the effects of health interventions (e.g. safety, effectiveness, resource use, etc) that are not collected in the context of highly-controlled RCT's. Instead, RWD can either be primary research data collected in a manner which reflects how interventions would be used in routine clinical practice or secondary research data derived from routinely collected data. Data collected include, but are not limited to, clinical and economic outcomes, patient-reported outcomes (PRO) and health-related quality of life (HRQoL). RWD can be obtained from many sources including patient registries, electronic medical records, and claims databases. (See also "randomized controlled clinical trial", "real-world evidence" and "real-	http://www.imi-getreal.eu/Portals/1/Documents/01%20deliverables/D1.3%20-%20Revised%20GetReal%20glossary%20-%20FINAL%20updated%20version_25Oct16_webversion.pdf

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			world study")(Adapted from Garrisson, 2007 (ISPOR Taskforce) and IMI-GetReal Glossary Workgroup, 2016); *RWE:* is the evidence derived from the analysis and/or synthesis of RWD. (GetReal).	
IMI2 Joint Undertaking (2017-2018)	ADAPT SMART - Evidence generation throughout lifecycle	ADAPT SMART is a multistakeholder consortium that has performed a review of IMI and non-IMI projects resulting in a gap analysis. The gap analysis identified areas along the MAPPs (medicines adapted pathways to patients) where tools and methods for evidence generation essential for enabling a MAPPs approach were lacking or where more tools/methods development was needed.	*Not defined in the report, but it is considered to supplement data from RCTs as part of MAPPs*	https://www.infographic.adaptsmart.eu/sites/adaptsmart/files/AS%20Deliverable%20D1.04.pdf
	Big Data for Better Outcomes (BD4BO), includes IMI-Roadmap (Alzheimer's disease); Harmony (hematologic malignancies); bigdata@heart (cardiovascular), pioneer (prostate cancer) (2016-2024)	Define outcome based health care system; Exploit the opportunities offered by large data sets from variable sources to increase medical innovation and deliver better quality healthcare systems (= network of different health data sources); Support the evolution towards value-based and outcomes-focused sustainable healthcare delivery systems through engagement of key stakeholders	Use of data from a range of sources from 'real world settings in addition to clinical trials	http://bd4bo.eu
INAHTA (2018)	Panel session during HTAi 2018 - Promise or compromise? The value of RWE in HTA: INAHTA members experiences	Overview of activities by selected INAHTA members in the field of RWE and HTA: PBAC (Australia), HAS (France), IETS (Colombia), IHE (Canada), NECA (Korea).	Any data used for decision making that was collected outside of a RCT	Notes taken during panel session by scientific secretariat
Joint ISPOR/ISPE Special Task Force on RWE in Healthcare Decision-Making	Using Real-World Data for Coverage and Payment Decisions: The ISPOR Real-World Data Task Force Report (2007) / Good Practices for Real-World Data Studies of Treatment and/or Comparative Effectiveness:	The mission of the Task Force (2007) was to develop a framework to assist health-care decision makers in dealing with RWD and information in RW health-care decision-making, especially related to coverage and payment decisions, to make recommendations regarding good procedural practices that would enhance decision makers' confidence in evidence derived from RWD studies. In 2017, The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and the International Society for	Used RWD as term: *Data* conjures the idea of simple factual information, whereas evidence connotes the organization of the information to inform a conclusion or judgment. *Evidence* is generated according to a research plan and interpreted accordingly, whereas data is but one component of the research plan. Evidence is shaped, while data simply are raw materials and alone are non-informative	https://www.valueinhealthjournal.com/article/S1098-3015(10)60470-6/pdf?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS1098301510604706%3Fshowall%3Dtrue

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	Recommendations from the Joint ISPOR-ISPE Special Task Force on Real-World Evidence in Health Care Decision Making (2017)	Pharmacoepidemiology (ISPE) created a task force to make recommendations regarding good procedural practices that would enhance decision makers confidence in evidence derived from RWD studies		https://www.ispor.org/docs/default-source/publications/newsletter/rwe-data-treatment-comparative-effectiveness-guideline.pdf?sfvrsn=7f7bf1f9_0
MHRA, UK (2018)	Early Access to Medicine Scheme (EAMS)	To provide early patient access to medicines in an area of high unmet need where there is no licensed treatment available. A therapy typically spends six months in EAMS before marketing authorization during which there is the opportunity for gathering RWE to support future decision-making	Data from routine clinical practice including electronic health records (EHRs), pragmatic trials, registries, observational data, monitoring devices and other sources	https://www.gov.uk/guidance/apply-for-the-early-access-to-medicines-scheme-eams; https://acmedsci.ac.uk/file-download/7021031
MIT NEW Drug Development Paradigms Initiative (NEWDIGS) (2017)	WISDOM project	To explore how new kinds of evidence (integrated with that from traditional RCTs) could impact regulatory and reimbursement decision making. it provides a structured framework for the planning and production of integrated evidence (RCT + real world) across the life span of products	Evidence from RWD sources beyond traditional RCT, this includes sources from medical records to social media	https://newdigs.mit.edu/sites/default/files/documents/NEWDIGS%20WISDOM%20June%202017.pdf
Division of Phamacoepidemiology & Pharmacoeconomics Brigham & Women's Hospital and Harvard Medical School	REPEAT is a non-profit program committed to improving the transparency, reproducibility and validity of longitudinal healthcare database research	Measure the current state of reproducibility and robustness of healthcare database studies; highlight the areas that most need improvement; propose specific, empirically based recommendations to improve the conduct and quality of RWE	Utilizing electronic data that are generated by healthcare systems through insurance claims, through electronic health records… to understand how medical interventions, and medical products like medications and devices work in routine care	https://www.repeatinitiative.org/about.html; http://www.clinicalinformaticsnews.com/2018/09/06/rinse-and-repeat-accessing-transparency-in-database-research-and-real-world-evidence.aspx