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RWE in Europe Paper V

Policy challenges around Real World Evidence adoption
in Europe

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Abstract

This paper summarises discussions held at the fifth roundtable style meeting with a group of expert stakeholders with experience in specialist disease areas and commissioning of care plus prior experience in the field of real world evidence (RWE). The aim of these meetings was to gain an understanding of the use of RWE across Europe and to develop a road map of initiatives for the pharmaceutical industry in order to enhance their use of RWE. This fifth paper outlines the perceived challenges for the adoption of RWE in Europe, the potential role for the pharmaceutical industry to support the adoption of RWE, and how RWE can provide key data in HTA decision-making where other sources are less feasible.

Introduction

Randomised clinical trials (RCTs) are seen as the gold standard for drug approval data and evidence requirements. However, the limited representativeness of RCT populations, overly controlled study environments, increasing complexity, high budget impact, and small potential study populations for orphan drugs and treatments for rare diseases are creating a need for complementary evidence generation techniques for the evaluation of clinical and cost effectiveness of novel medicines. This was recently highlighted by Thomas Senderovitz, the Director General of the Danish Medicines Agency, who stated: "I'm not saying at all we have to kill the RCT but I do say that RCTs per se in the future will not be the only way we look at data. It will require a change in mindset. It will require an upgrading of our skill sets." (Kenny, 2018).

Real world evidence (RWE) is the analysis or synthesis of real world data (RWD) obtained from sources such as patient registries, electronic medical records, pharmacy prescription data, selected data from social media, and claims databases. RWE has shown promise as a valuable source of information and evidence when RCTs may not be feasible evidence sources for market access and reimbursement decisions. However, the presence of methodological difficulties in collecting RWE remains an obstacle for its uptake, including issues such as a lack of randomisation and representativeness, bias (for example confounding by indication), inflation of treatment effects and issues around data quality (Pietri & Masoura 2014). Therefore the uptake of RWE in Europe, particularly for market access and reimbursement decision-making, is limited. For example, RWE is accepted for questions related to epidemiology of diseases in Germany, but not as a data source for issues relating to the effectiveness and safety of new drugs, or to the patients' quality of life when using these drugs.

This paper is the fifth in a series discussing the use and potential of RWE in Europe. Previous papers have focused on the use of RWE for pricing and reimbursement across Europe, the use of RWE in chronic conditions, oncology and the rare disease arena, and the development of a three-year roadmap of initiatives for the enhanced use of RWE in decision-making, and the role for the pharmaceutical industry in the RWE roadmap (Gill et al., 2016, Gill et al., 2017a, Gill et al., 2017b; Gill et al., 2018).

The current paper describes discussions at the most recent meeting held in October 2018 in Madrid where the objectives were as follows:

- (1) Reflect on the work of the pharma industry to develop a policy approach for RWE, as well as their approach to improve the legitimacy of RWE in health technology assessments (HTA).
- (2) Provide clear guidance on key levers and help the pharma industry shape future initiatives in RWE in a way that is actionable and considerate of regulators, payers and customers' needs and agendas.

Methods

In line with the four previous papers, this paper is based on outcomes from a roundtable style discussion with a selection of contributors with significant experience in specialist disease areas and commissioning of care, as well as prior experience in the field of RWE. Attendees included those from the Czech Republic, Germany, Italy, Portugal, Spain, and the United Kingdom with representation from academia, health services, government bodies, patient organisations (PO) and payers.

During the day-long focus-group discussion, the eleven participants explored issues related to (a) challenges to the use of RWE and (b) the potential for collaboration across stakeholders to encourage adoption in RWE. The discussion was a structured debate guided by four questions:

- (1) *What do you believe are the key challenges to RWE adoption in Europe?*
- (2) *What do you believe are the key opportunities and initiatives?*
- (3) *What are the key challenges in gaining HTA acceptance for the adoption of RWE?*
- (4) *What are the key levers or solutions required to build that acceptance for RWE in HTA?*

The general focus was on two treatment areas (oncology and rare diseases), although discussion here covers both treatment areas simultaneously. Each session consisted of a topic introduction presentation by one of the delegates followed by a combination of group breakout sessions, with set questions to be addressed, and opportunity for plenary feedback.

As with the four previous outputs from this series, discussions were initiated and led by F. Hoffman-La Roche AG, but the novel approaches to RWE, initiatives around data generation, and collaborations discussed here, are applicable to all industry stakeholders aiming to enhance their use of RWE.

Session 1: Policy challenges and opportunities around RWE adoption in Europe

RWE adoption has high variability across Europe. Institutions in some countries may only accept 'locally' collected data, while others may not accept RWE in any instance. While RWE has the potential to be a supplementary source of key evidence of the efficacy and efficiency of treatments, its uptake may be hindered by key challenges at various levels. The discussion centred on what the perceived challenges are, and on the resulting needs or actions. It considered five separate challenge areas: Data sources, data infrastructure, data access and security, the mindset associated with data use in combination with the perceived credibility of RWE, and (the lack of) joint stakeholder collaboration.

To understand the policy challenges surrounding the use and adoption of RWE in Europe, the session focused on two questions:

- (1) *What do you believe are the key challenges to RWE adoption in Europe?*
- (2) *What do you believe are the key opportunities and initiatives?*

Key challenges

Data sources

Potential data sources for RWE include EHRs (electronic health records), patient registries, and other data registries (where a registry is a prospective collection of data on a clearly defined cohort of patients, e.g. with a specific disease, treated with a specific drug or tested positive for a specific molecular marker). Currently, data sources for RWD/E are varied and fragmented across Europe.

Registries and EHRs have different objectives. EHRs generally do not track patient outcome data in a standardised way, and act as a reference for the treating physician, while patient registries may provide partially or fully standardised outcome data. For registries to be an effective source of RWE, they would ideally need to be built from scratch and be well-designed for the purpose of collecting of useful data. However, while a well-designed registry might be more likely to track the data points needed in the use of RWE, the cost and resources associated with the set-up of a registry for a large range of (rare) diseases may be prohibitively high. Thus, as setting up multiple small disease-

based registries can be inefficient, EHRs may provide a cost-effective, interim source to identify patients with a specific disease (which can then be used for modelling exercises), taking into account the well-known limitations of this source of RWE.

Participants thought there was a general increase in the use of EHR across Europe, but its presence may not necessarily enhance the rather slow growth in acceptance of RWE. Participants also noted that during the next 5 to 10 years there will be challenges in using EHRs for research purposes, while developments in, for example, artificial intelligence technology may improve RWE/D use as digital records become more feasible.

The benefit of RWE collected outside of clinical, controlled settings may be hindered by the manner in which this data is collected: the measurement of outcomes may inherently not be 'real' if it is obtained as a result of requesting doctors to add a non-routine activity to their process. Outcome measurement, including Patient-Reported Outcome Measures (PROMs), need to be a standard part of review in order to create semi-structured data with credibility. Otherwise, the level of detail and accuracy provided by different doctors will vary substantially.

Data infrastructure

A major challenge to the use of RWE in Europe is facilitating the collection of consistent RWE across the EU Member States, while ensuring that RWE responds to specific requirements set by national HTA or reimbursement bodies. In order for data to be used for HTA and reimbursement decisions, interoperability of national data infrastructures and systems is key.

However, RWE sources like EHRs and registries vary in development and wide-spread use across the European countries, and may be available only in national languages. So while relevant data might be hosted within EHRs, they may not be useable because they cannot be accessed in a standard, structured format. The heterogeneity of health data across the EU, variable definitions and possibly varying typologies used to structure data, may provide a barrier to the cross-border use of EHR data.

The European Commission has made steps in this direction through a European Communication focused on securing the interoperability of health data systems across the region, the pooling of health data, and citizen empowerment through these tools.

Further solutions to this issue may include harmonised data formats, or other technological advances to ensure data is available across countries. In assessing the limitations of the current system(s), it is key to recognise the human factor in using systems: cultural and national influences may still cause different interpretations or data input. A response to this could be to set stringent definitions and include variation limits. In addition, an interim stage prior to consolidating infrastructure could be to view registries as a stepping stone to structured patient data.

Data access and security

Data access and security concerns may provide an additional threat to the use of registry and/or EHR data. In particular, data should be anonymised across individuals and geographies to the point where the patient is non-identifiable. Issues with anonymisation may be larger for small patient populations, particularly as no two patients are identical.

The European General Data Protection Regulation (GDPR) can be seen as a threat and an opportunity to this effort to establish sufficient data security: while the recently introduced Regulation can provide a platform for countries to implement an aligned national-level data legislation which takes RWE use into account, GDPR may also impose strict standards and additional implementation measures which make RWE use more difficult and, in certain cases, impossible.

Credibility of RWE

Above all, the credibility of RWE as a supplement to, not as a replacement of, randomised trials, needs to be asserted in order to encourage a change in mindset. The potential of RWE should be highlighted in areas where RCTs are currently less feasible – for example in certain populations (children, the elderly, particular drug interactions, or comorbidities) – to showcase how RWE can be a credible, complementary source of data. RWE can be used to document off-label use as a foundation for proposing a case for broader indications or usage, especially for generics and/or where there is lower feasibility for RCTs. Participants noted off-label paediatrics and the 'post-approval' stage as potential areas to drive RWE use and credibility.

The credibility and institutional mindset regarding RWE can be ameliorated by encouraging discussion on the delicate balance between safe, good, and useful data. Where good and useful data may not (yet) exist, RWE can bridge the gap.

Lack of joint stakeholder collaboration

Within the challenges for RWE defined above, there should be scope for stakeholders in the health sphere to collaborate on minimising these gaps.

A number of external policy shaping initiatives were discussed during the sessions (Figure 1). Some of the initiatives focusing on RWE adoption may have potential overlap in their remit. The Board discussed potential objectives of such collaboration: the design of methodologies for comparable data and the setting of minimum common denominators for evidence were both considered key. Unmet need was identified as the most impactful criterion, with the note that there is no common definition.

Key opportunities

Given the large group of stakeholders in this field, there may be indirect areas of engagement for industry, including advisory board participation, industry sounding boards, and interest-sharing dialogues. Figure 1 outlines major initiatives in the field in Europe, considers the main stakeholders these initiatives are aimed at, and provides actionable next steps for the pharma industry in engaging with these issues.

Figure 1: Key external policy shaping initiatives

	Shared objectives	Industry involvement and/or other stakeholders	Actionable next steps for industry
European Medicines Agency	Data collection and study methodologies to: <ul style="list-style-type: none"> - Develop a minimum common denominator for data - Agree a conceptual framework for data in different contexts - Create understanding that definitions may need to be approximate as standardisation is difficult - Identify where to make impact on decision-making at a local level 	Limited role for industry Medical societies and patient organisations Registry owners	<ul style="list-style-type: none"> - Gain commitment / declaration of intent from all parties to develop a coalition - Understand interest and incentives of stakeholder and align on points of engagement - Define the role of industry
European Reference Networks (ERNs)	Ensure data uniformity	No direct industry involvement permissible	<ul style="list-style-type: none"> - Identify terms of reference and route for industry involvement - Establish stronger connections with networks and members - Set up parallel information sounding boards
E-Health Network	Advance e-health to: <ul style="list-style-type: none"> - Improve transparency on other actions - Collaborate and avoid duplication - Develop agenda where EC does not have acting powers 	No direct industry involvement permissible	<ul style="list-style-type: none"> - Identify terms of reference and route for industry involvement - Establish stronger connections with and between networks and members - Set up parallel information sounding boards
Rare disease registry networks	Demonstrate value of RWD through pilot case studies	Clinicians, network administrators, academia, patient organisations	Develop and align study methodology and data requirements
ICPerMed	<ul style="list-style-type: none"> - Understand why private sector participation is not permissible - Define type of evidence required to assess the benefit of a drug - Address concerns surrounding 'personalised healthcare' as just a new private sector business model - Ensure clarity around the industry agenda 	Policymakers (regulators) Physicians Patients Other industry players	<ul style="list-style-type: none"> - Define and validate what is meant by "personalised healthcare" - Define appropriate methodology for RWE in different patient cohort sizes ("single patient", sub-populations, or public/population level) - Facilitate dialogue between stakeholders to agree on methodologies
ISPOR	<ul style="list-style-type: none"> - Build understanding of how to validate methodologies and improve routine use of RWD - Outline and agree on guidelines for patient consent 	ISPOR RWE taskforce Patient organisations	<ul style="list-style-type: none"> - Focus on specific taskforce methodologies - Define data sources and their validation - Produce and publish guidelines on methodologies - Outline different levels of consent for patients to agree data use
EFPIA	<ul style="list-style-type: none"> - Create new research initiatives - Foster policy collaborations - Gain validation and transferability of endpoints for decision makers - Contribute to the harmonisation of endpoints which will be most appropriate for RWE 	n/a	<ul style="list-style-type: none"> - Paediatric oncology is a potential focus area - Outline common methodologies to assess smaller populations - Define "innovative" and "unmet clinical needs" as they require different approaches - Define the data sets required for different conditions

Session 2: Increasing the use of RWE in HTA decision-making: a collaborative effort

A recent European survey, carried out by researchers at LSE (Kanavos et al. 2018, unpublished) analysed the current use of RWE in HTA across the region. RWE is currently viewed as moderately important by decision makers, and, despite the fact that HTA agencies are increasingly looking at single arm Phase II trial data in cancer and rare disease indications where a control arm is lacking and a historic control might be beneficial, in general its use in HTA still poses both methodological and empirical issues. The discussion in this session centred on defining these perceived challenges, and identifying potential solutions to allow the pharmaceutical industry to approach HTA authorities with RWE based data.

To understand the space for collaboration in promoting the use and adoption of RWE in Europe, the session focused on two guiding questions:

- (1) *What are the key challenges in gaining HTA acceptance for the adoption of RWE?*
- (2) *What are the key levers or solutions required to build that acceptance for RWE in HTA?*

Key challenges for RWE in HTA

RWE is not accepted by most European national agencies for benefit-assessment/reimbursement (HTA) discussions. In many countries, HTA guidelines remain strict: data generated for regulatory acceptance may not necessarily be useable in HTA processes with different data standards. For example, in the German HTA process, data based on single arm trials may not be accepted for approval. Often the use of retrospective or historical control data is restricted and clinically relevant outcome data (such as Progression-Free Survival in cancer) from RWE, is hard to gain acceptance for, particularly when comparing with RCTs. Data from RWE may provide a solution or complementary data for disease areas where establishing a control group may not be possible, or in cases with small, heterogeneous patient populations.

A lack of patient representative involvement or voice in HTA or reimbursement processes may also mean the value of RWE is less appreciated, and considered less legitimate compared to other data and outcomes.

Participants noted RWE has been accepted by the European Medicine Agency (EMA) in instances of early accelerated approval. However, the use of RWE/D within Europe is limited by the fact that national HTA and/or reimbursement decision-makers across Europe have different evaluation methodologies, with sub-national approval processes in place within some countries.

It is also recognised that institutional inertia may be an additional barrier, with minimal scope for new assessments, paradigms, or processes in established institutions. Institutions may feel RWE is used as an excuse to obtain approval for high cost drugs, and the classification of 'rare' diseases may be used to that end. Definitions surrounding rare and ultra-rare may influence whether data will be accepted. There is little dialogue between regulatory bodies and other stakeholders on what would be a feasible alternative or complementary data source to showcase benefit, as often HTA bodies do not accept other data sources, exacerbated by path dependency within institutions. This is not limited to decision-making organisations: a barrier to RWE evidence use may also lie in the interests of academics or researchers acting as (Principle) Investigators, who may insist on clinical trials because of publishing and academic credentials.

Solutions for RWE in HTA

Participants noted RCTs and systematic reviews and meta-analyses of RCTs are the gold standard for data and evidence use and should be completed where possible. However, the complementary role of RWE should lie in areas where RCTs are extremely difficult to generate or where evidence gaps exist. RWE could bridge a data availability gap where surrogate endpoints are defined through strong biomarkers. The success of RWE for orphan drugs, for example, can then be used to promote RWE in the future.

Participants were asked to identify a number of actionable steps that could be taken by the pharma industry to build the credibility of RWE.

For the use of RWE, participants suggested the following:

- The *identification of areas of unmet need*, with weak or unfeasible RCTs, and/or time pressure, where RWE/D can be used to supplement existing data and fill

evidence gaps. Success of RWE in instances like this, such as the case of orphan drugs, may provide an initial base, or proof of concept, for RWE in pharmaceutical decision-making.

- The *targeting of specific therapies* with 'single arm' approvals to find ways to use data that exists as a historic control, either pre- or post-approval.
- The use of *post-approval, off-label RWE* to document potential benefit or harm and to validate action, and thereby identify additional potential population or reduce the time required to access appropriate patients for additional trials.
- The use of *RWE data collection after RCTs* have been run are also a mechanism which can contribute to the validity of RCT findings and create credibility for RWE. RWE may capture a reality that no clinical study can, particularly for measuring quality of life and individual variation in response to treatment. Participants noted there is a cost implication for the collection of RWE, which may limit the extent of the use of this recommendation.
- The *use of RWD to document tested companion diagnostics* (validate biomarkers) and focus on next generation sequencing.
- The *design of a comparative study or model using RWE* to document clinical benefit where RCTs are not feasible or realistic. An RCT could be designed but completed using RWE to create two cohorts: one arm based on registry data and one arm on historical data to generate data for an early approved drug to support future economic discussions, negotiations and appraisals.

System-level recommendations included the following:

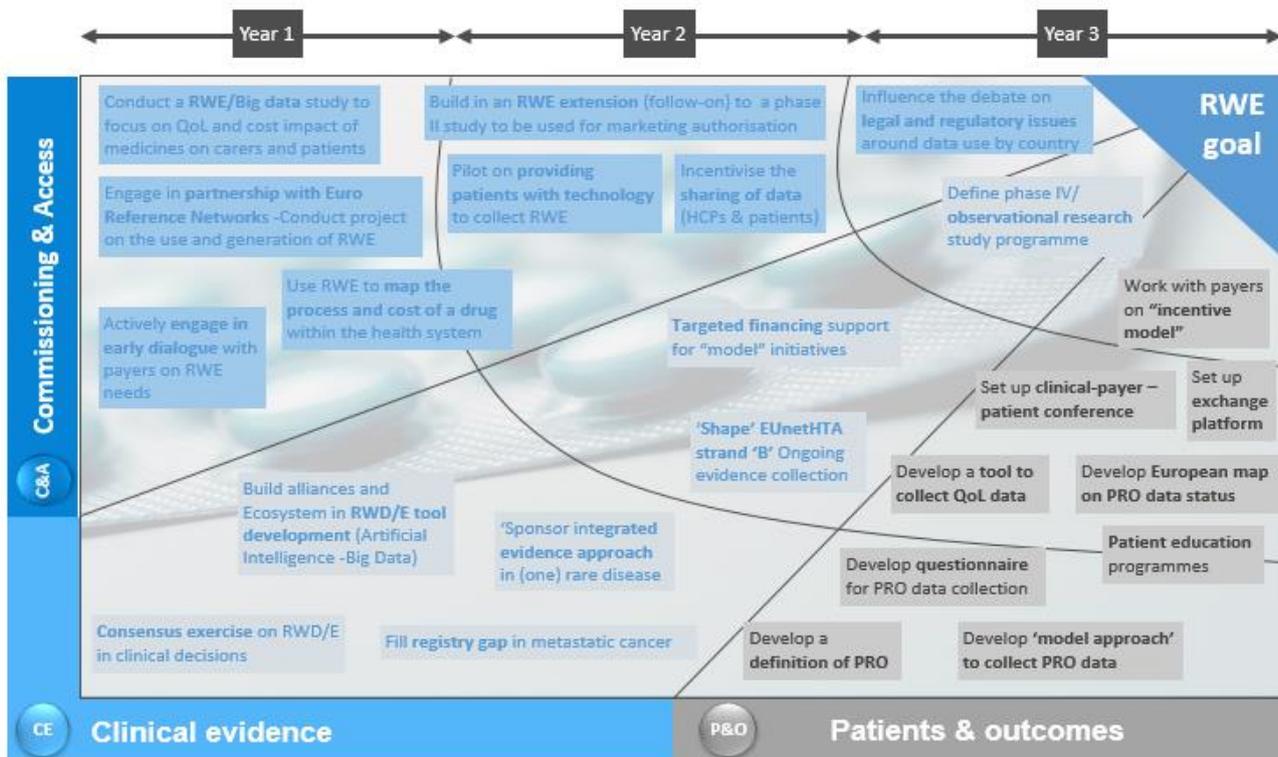
- The use of *evidence-based conditional approval can be encouraged* to reduce uncertainty (similar to the use of CED in the Netherlands, Sweden and the United Kingdom), particularly in the field of rare diseases and oncology.
- The *testing and design of stronger methodologies* for RWE generation through stakeholder collaboration may contribute to the credibility and likelihood of RWE.
- The dissemination of the message that *today's "orphan model" represents tomorrow's norm* (e.g. CAR-T), and there is a need to build evidence case studies and address concerns about sustainability.

- At country level, *encourage the creation of comparable criteria* for the use of RWE, aimed at upholding key data standards and avoiding the relaxation of criteria to strengthen faith in data.

The way forward

Based on the challenges and opportunities reviewed by the members of the group, three key steps were identified for the implementation of an RWE roadmap (Gill et al., 2017b). Figure 2 presents this RWE roadmap, which prioritises relevant initiatives for the pharmaceutical industry across three significant areas over a three-year period: Commissioning & Access, Clinical Evidence, and Patients & Outcomes (for more information on the roadmap, see Gill et al., 2017b).

Figure 2: RWE Roadmap



To ensure the implementation of the roadmap presented in Figure 2, three key areas were identified for the pharmaceutical industry for action. Firstly there is a need to focus the RWE proposition by:

- prioritising areas of focus;

- defining, articulating and validating methodologies which will be used to deliver RWE; and
- identifying credible data sources.

Then, open doors must be identified by:

- leveraging the value of European level endorsement;
- defining in which countries and with which authorities and partners an impact can be made; and
- identifying supporting stakeholders and ways to engage with less 'pharma-friendly' authorities.

Finally, a consistent approach needs to be delivered by:

- developing an action bias for engaging and sharing methodologies;
- building best practice case studies and sharing with stakeholders to educate and build confidence in RWE; and
- demonstrating the value of RWE in contributing to decision making.

Conclusion

This report documents discussions held at the fifth roundtable style meeting with stakeholders in RWE. This session built on previous work to develop a policy approach for RWE by providing guidance on key levers and potential future initiatives that are actionable and considerate of all stakeholders. The discussion was framed in the understanding that RCTs are a gold standard for evidence, but recognised the need to fill data gaps, particularly in instances where RCTs are not feasible or do not provide enough data.

On defining the scope of where RWE may be a salient source of data, participants considered challenges to RWE adoption, the role of the pharmaceutical industry in promoting RWE use, and how RWE may be used more in HTA processes across Europe. This paper identifies crucial hurdles for the uptake of RWE as relating to data sources, data infrastructure, data access and security, the mindset associated with data use in combination with the perceived credibility of RWE, and (the lack of) joint stakeholder collaboration. In addition, this paper reviews institutional inertia, the lack of stakeholder engagement in the process, and differing standards for data across Europe as crucial

explanatory factors to understanding the resistance towards RWE in HTA processes across Europe.

Participants highlighted the need for progress in terms of framework harmonisation across the EU, as well as highlighting the differences, and working on alignment of these differences, in HTA bodies across the region with the possibility of developing a 'master HTA process' to facilitate the incorporation of RWE data where needed.

This paper concludes that there are three ways the pharmaceutical industry can advance the RWE debate: (a) by focusing on the RWE proposition by defining credible data sources, creating acceptable methodologies for RWE, and prioritising the use of RWE, (b) by identifying open doors by leveraging European level endorsement, defining key areas or regions to pilot the use of RWE, and identifying supporting stakeholders, and (c) by securing a consistent approach by developing an action bias, building best practice case studies, and demonstrating the value of RWE in contributing to decision-making.

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