RWE in Europe Paper III:

A Roadmap for RWE

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Abstract

Real world evidence (RWE) has been touted as a remedy for current market access issues, facilitating quicker approvals and increased odds of reimbursement at a good price. It is therefore an attractive avenue for pursuit for manufacturers today. This paper, the third in a series looking at the use of RWE in Europe, outlines the discussions held between key opinion leaders in pricing and reimbursement across a number of European countries at a roundtable-style meeting. The aim of the meeting was to develop a 3-year roadmap, and resulting action plan, of initiatives for the enhanced use of RWE in decision-making in the pharmaceutical industry. Following a series of brainstorming sessions across the areas of commissioning and access, clinical evidence and patients and outcomes, contributors were asked to prioritise the importance of a refined set of initiatives identified in these brainstorming sessions to develop the three-year road map. Finally, four key points from the roadmap were identified for initial action: *actively engage in early dialogue with payers on RWE needs; consensus exercise on RWD/E in clinical decisions, develop a definition of patient reported/relevant outcomes* and *develop a model approach for the collection of patient reported/ relevant outcomes data.* These action points are seen as the most imperative steps for enhancing the role of RWE. If its use is to become more common addressing these steps, as quickly and efficiently as possible, will be vital for all stakeholders in the pharmaceutical arena.

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Background

The use of real world evidence (RWE), which is derived from analysis or synthesis of real world data (RWD) obtained from sources such as patient registries, electronic medical records and claims databases, is increasingly recognised as a valuable source of information for market access and reimbursement (Makady *et al.,* 2017). Whilst there are discrepancies between HTA bodies and their willingness to use RWE in any decision-making the EUnetHTA Joint Action 3 project focuses on evidence generation in Work Package 5 (Lifecycle approach to improve evidence generation). This work package aims to generate the right evidence along the technology life cycle and identify where further evidence generation or tools for data collection are required (EUnetHTA, 2016).

Increased supply of data is thought to be one of the four key drivers for future clinical research which include: a focus on research and resource waste, where quantity is more valued than quality, clinical research design needs are driven by payers, regulators and industry, rules are being put in place for the use of RWE in drug approvals, and trial costs are ever increasing; evidence generation from big data, which is becoming easier to electronically capture and analyse; routinely collected data (RCD, data not collected for the purposes of research), including data from electronic health records, registries and administrative data; and the integration of RCT (randomised controlled trial) technology and RCD which may improve validity and relevance, save resources and costs and increase speed allowing for longer term follow up. In short, in the near future both RWE and RCD will play a vital role in clinical evidence generation, quality of care research and benchmarking.

There are already European examples of such data collection and so called 'big data' used to guide decision making, for example, the Swedeheart Study, a national registry of coronary artery disease care and valvular interventions which has been found to improve quality of care, outcomes, cost effectiveness and save money (Jernberg *et al.,* 2010). Countries like Denmark and Norway are also paving the way in using personal registration numbers for linkage with multiple databases and databanks to aid the collection of big data.

As far as manufacturers are concerned, RWE has been touted as having the potential to solve problems inherent to getting a drug to market, despite issues around poor data quality and data security concerns. Using real world data may be a better means of proving the value of a new medicine to payers resulting in quicker approval, more valuable discussions and the development of flexible reimbursement agreements, meaning that patients can access novel drugs at a sustainable price in a timely manner. As a result, the demonstration to stakeholders of the real life value of novel drug outcomes is key to improved patient access and manufacturer success.

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This report, the third in a series discussing the use of Real World Evidence (RWE) in Europe, documents discussions with a number of stakeholders at a round-table style meeting and follows on from two previous meetings (and accompanying reports) held in 2016 and 2017. These discussion sessions were held following a 2015 "*Payer RWE voice of the customer project*" which gained insight into RWE needs and priorities across various EU countries. As a direct result a series of stakeholder meetings were set up, with the first being held in London in June 2016. During this initial meeting six contributors with significant experience in various clinical specialties and commissioning of care, as well as prior experience in the field of RWE, covered a number of topics related to the use of RWE in decision making across Europe. Discussion at this meeting confirmed that RWE is used to some extent in all European countries represented, generally in the areas of accelerated access and re-review. Stakeholders valued its contribution to decision-making in combination with traditional RCT data, particularly in the chronic condition arena, where time taken to gather outcomes evidence is increasing due to life extension, and in the orphan drugs field where, despite accelerated drug development for the small patient populations, delayed recruitment to RCT is becoming more of an issue (Gill *et al*., 2016).

The second meeting built on the results from the first discussion and focused on use of RWE in licensing, commissioning, clinical decision-making and patient and outcome related decision-making in different treatment areas – chronic disease, oncology and rare diseases. It is likely that these different treatment areas will have differing requirements for RWE going forward. For example, in the rare disease arena, RWE may have a role in licensing based decisions, but this is unlikely for chronic disease or oncology. Understanding these differences and varying levels of utility will enhance our abilities to develop well-organized, high quality systems for data generation, interpretation and use. Facilitating this will require a multi-stakeholder approach at the EU level, with collaboration between national and supranational organizations and other stakeholders including reimbursement agencies, manufactures and patient organizations (Gill *et al*., 2017).

The third meeting, the results of which are discussed in this report, focused on actionable results. It built on discussion points from the two previous meetings to develop a 3-year roadmap of initiatives for the enhanced use of RWE in decision-making. Whilst discussions were initiated and led by F. Hoffman-La Roche AG (referred to as "Roche" for the rest of this report) the roadmap, and resulting action-plan, described in this report are applicable to all industry stakeholders aiming to enhance their use of RWE.

In line with previous meetings, it involved a round-table style discussion with 15 participants from 12 European countries (Austria, Czech Republic, Denmark, France, Germany, Italy, Poland, Portugal, Spain, Sweden, Switzerland and the UK). Participants included those from academia, clinicians, health services,

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government bodies, patient organisations (PO), regulatory bodies and payers. 12 of the attendees at this meeting were present for at least one of the preceding two meetings described previously. The discussion, held in June 2017 in Rome, had a number of specific objectives:

(1.) Share expertise and best practice – draw on the collective speciality and expertise in the room to stimulate and challenge thinking to identify opportunities for Roche to develop RWE.

(2.) Build an RWE roadmap – generate ideas and initiatives that Roche can undertake over the next three years to use RWE in generating credible data in support of regulatory and/or HTA submissions.

(3.) Identify actionable next steps – prioritise RWE initiatives and define actionable next steps for Roche to undertake in the next 12 months.

To facilitate these objectives, the meeting centred around a series of expert presentations followed by a number of working sessions incorporating both breakout and feedback. Session one focused on *Opportunities for RWE* and saw participants work together to brainstorm a large list of opportunities for RWE use in Europe. Three specific areas were covered by different groups of participants – Commissioning and access; Clinical evidence; and Patients and outcomes. In the second session participants worked on refining the long list of 24 initiatives identified in session one and prioritizing these on a three-year implementation roadmap. The final session involved the identification of four key points for initial action on the roadmap and development of action plans for these individual points. Results from these discussion sessions are outlined below.

Section 1: Opportunities for RWE

During the first stage of the workshop, participants were asked to breakout into three groups to brainstorm a list of what they saw as potential opportunities for the use of RWE in Europe by Roche, and other pharmaceutical manufacturers, to add value in market access. These three groups concentrated on three specific areas: Commissioning and access; Clinical evidence; and Patients and outcomes. The RWE opportunities proposed by participants in each of the three areas will now be discussed.

Commissioning and Access

The use of RWE in commissioning decisions, which in this context relates to the process of financial decision-making (rather than reimbursement decisions that determine costs when the drug is used in the real world), may be limited by the rules of specific commissioning bodies. For example, in England, health technology assessments are generally carried out shortly before a drug is licensed, such that

there is no RWE available for incorporation into decision-making. Despite this, participants were able to identify a number of situations related to commissioning and medicine access where they thought there were opportunities for RWE.

RWE could be used as a tool to increase understanding of the use of drugs in practice, by collecting data on drug usage, which may guide treatment decisions and enhance access in certain patient groups. So called 'big data' could be used to identify the impact on society of a condition such as Alzheimer's or dementia in terms of indirect costs and direct quality of life (QoL) impact for both patients and their caregivers. RWE can also be used to identify broader social benefits and ascertain the impact that care can provide.

In order to increase the effectiveness of RWE a number of issues need to be addressed. Firstly, pursuing partner engagement with European reference networks (ERNs)[1] such as EuroCan, EuroBlood and Paediatric Network, could improve the collection and resulting use of RWD. Similarly, increasing the direct dialogue with payers, in terms of helping them recognise the evidence base and identifying the specific requirements needed to substantiate value could prove useful. It will be vital to ensure that, if Phase II data is used to gain marketing authorisation, any studies are designed to ensure that data collection continues in order to maximise available RWD. Providing data on the process of RWE, for example, how it works, what it costs, as well as specific resources for data collection, i.e. financial support and networks, alongside facilitating the development of a 'data sharing mind-set' amongst health care practitioners may increase the usefulness of RWE in terms of improving access. In future, engagement of a technology partner may support additional, patient-related data collection. There may also need to be some country-specific analysis and adaptation of current legal and regulatory issues around the use of patient and other data to ensure that all stakeholders are willing to continue data sharing.

Clinical Evidence

In terms of increased RWE use in a clinical setting, drivers include reimbursement/risk sharing, the collection of outcomes data and assisting clinicians with effective decision making in situations where RCTs will not be available. In line with the latter point it is important to note that most industry experts believe it unlikely that RWE will ever fully replace RCT such that there is a need for both types of data.

In order to enhance opportunities for RWE in the clinical setting there needs to be an increased effort to support registries financially and develop a consensus exercise in order to set definitions and standards for data collection in the clinical

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1   European Reference Networks (ERNs) are virtual networks involving healthcare providers across Europe. They aim to tackle complex or rare diseases and conditions that require highly specialised treatment and a concentration of knowledge and resources (European Commission, 2015).

domain. Furthermore, identifying and building relevant networks and alliances as well as accelerating the development and completion of model initiatives with targeted financial support, developing 'ecosystems' and alliances for the development of tools for the effective use of big data and artificial intelligence (AI), and shaping relevant EUnetHTA streams for ongoing data collection will maximise the effectiveness of RWE. Defining the Phase IV (observational research study programme), sponsoring an integrated evidence approach for rare disease and working towards filling registry gaps, for example in metastatic cancer, were also suggested as future targets to enhance the use of RWE in clinical settings.

Patients and Outcomes

In the final area of discussion RWE opportunities in terms of patients and outcomes centred on four areas – definition and collection; incentivisation; promotion of collaboration and increased transparency:

- In terms of **definition and collection** contributors thought that work should focus on developing a common definition of patient reported/relevant outcomes (PROs), supporting the development of methodology for the collection of such data, increasing awareness amongst stakeholders of the importance of the collection of PRO, supporting exchange platforms to motivate data collection and developing the tools and supportive technology required for the collection of QoL data and tracking of patient data collection skills.

- At the **incentivisation** level, contributors suggested offering data collection tools in a package alongside medicine supply. For example, charging €100k for a €60k drug and a tool specifically for the collection of RWE related to the drug. Pharma companies should be seen as the drivers for the collection and monitoring of PRO and guidebooks should be developed for all stakeholders.

- In order to **promote collaboration** the patient-clinician exchange needs to be enhanced, there also needs to be systems in place to ensure that patients are exposed to relevant information related to data collection and QoL in terms of enhanced patient education.

- Finally, for **increased transparency** a European cross-country border map should be developed which identifies those responsible for the collection of PRO and defines the current status of PRO data in each country as well as the roles and responsibilities of those involved in PRO collection.

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Section 2: Developing a Three-year Implementation Roadmap

Following the brainstorming sessions designed to develop a long list of potential RWE-related initiatives, a three-year implementation roadmap for the pharmaceutical industry was produced. Across the 3 areas of interest (Commissioning & Access – C&A, Clinical Evidence – CE and Patients & Outcomes – P&O) 24 refined initiatives were identified from the long lists developed during brainstorming. Participants were then asked to prioritise the importance of these initiatives for Roche over a three-year period (Figure 1).

Figure 1: Three-year prioritisation of 24 refined RWE initiatives identified by the expert panel
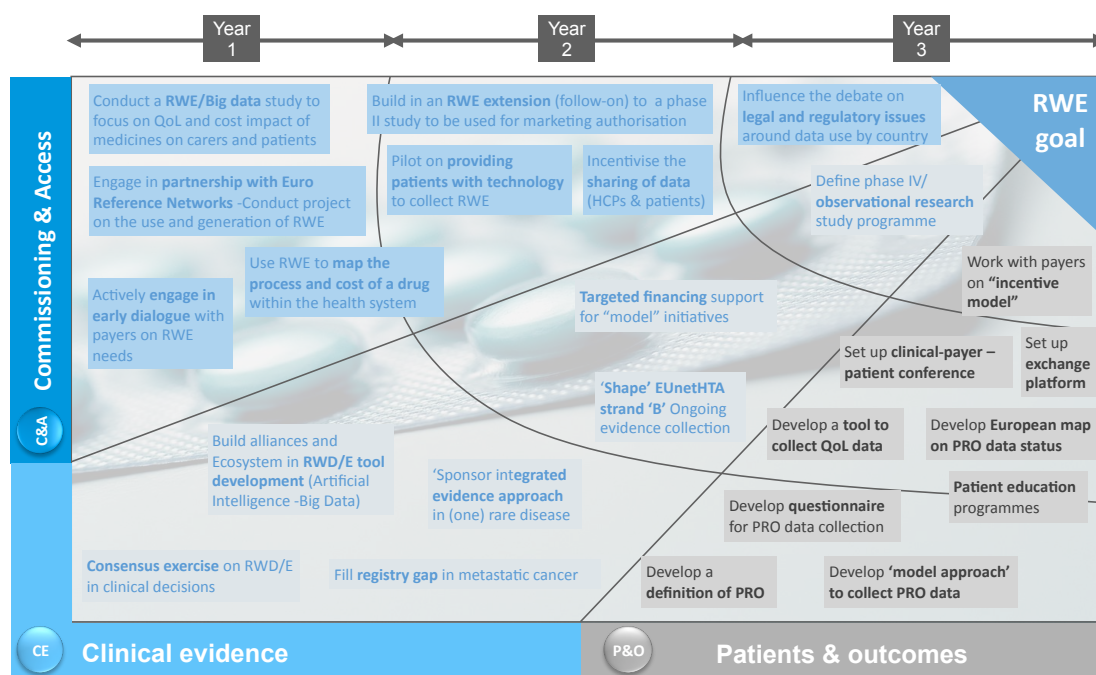

Generally, those initiatives placed in Year 1 were either thought to be the most urgent, or were seen as easier to complete than initiatives placed in Year 3. Similarly, those initiatives placed in Year 3 were seen to be less urgent, or required the completion of other initiatives before they could be tackled. For example, in the P&O section, experts thought it vital that a definition of PRO be completed before a European map on the status of PRO was developed.

Section 3: Action Planning

Following the development of the three-year implementation road map participants were asked to vote on what they thought were the top two areas for initial focus. Participants had two votes each. Their first vote was worth two counts whilst their second was worth one count. Initiatives with the most votes (Figure 2) were then pursued in the action planning stage.

Figure 2: 24 refined RWE initiatives highlighting those achieving most votes for action planning pursuit
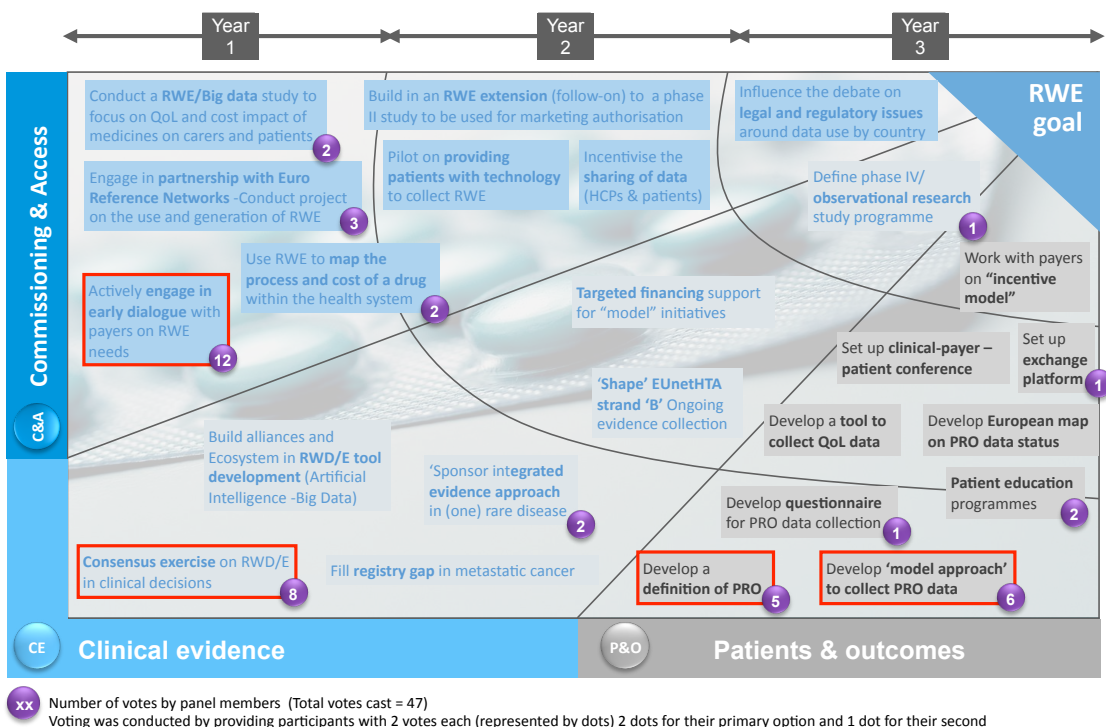
Four different initiatives received five or more votes (with remaining initiatives receiving zero, one, two or three votes). These top four initiatives were then discussed in further detail in order to ascertain the key stakeholders involved, the key milestones required and a specific action plan.

Actively engage in early dialogue with payers on RWE needs

The initial priority action point is to actively engage in an early dialogue with payers on RWE needs, with the aim being to develop better evidence packages to upskill payers. Within this action point are five additional actions. The first is to review the experience of the use of RWD/RWE in nations considered early decision makers such as the United Kingdom and France via both internal and external review. Following this review is the development of separate or joint processes (as applicable) with the EMA or EUnetHTA. The next step is to expand

early dialogue to other markets, where the focus will be on the comparator, on financing mechanisms and on sub-group data 'options'. Of lower priority is the targeted development of "Early Access" evidence packages for specific products and conducting education exercises for payers.

Key stakeholders in the development of this action plan include HTA agencies and internal Roche, or other pharmaceutical manufacturer, audiences in the initial, higher priority stages, leading to hospital management, payers, budget holders, Ministries of Health, administrative personnel, and academic and medical societies in the later stages. Key milestones include initial, early stage discussions on certain aspects of the pharmacoeconomic profile, such as direct and indirect costs, and subset population involvement; the development of Masters or PhD courses on the use of RWE in decision making; the development of a toolkit of methodologies for data integration; and finally the development of an RWE conference to showcase concrete examples of RWE use, with payers as the key audience.

Consensus exercise on RWD/E in clinical decisions

The second priority action point is to perform a consensus exercise on the use of RWE in clinical decision making with the aim of allowing pharmaceutical manufacturers to define a process by which to develop clinically relevant RWE. Of the six action points under this heading the first, and that seen to have the highest priority by stakeholders involved in this consultation process, is the requirement for an agreement on the definition of key data points used in RWE. For example, long-term safety, long-term benefit and PROs. Subsequently there will be a requirement to generate evidence in sub-populations that are not currently covered by existing trial populations and data, for example, those with co-morbidities who are often excluded from clinical trials. Defining the minimum standards for quality and methodology of data sets, such as functional state, morbidity and mortality, ensuring robust data standards and methods, and developing or enhancing chronic disease management systems in terms of clinical pathways and practice guidelines, are the subsequent steps needed to build the action plan. Once these standards and systems have been developed and defined the final step in the action plan is to capture data on resource use to inform both payers and policy makers.

Initial key stakeholders include clinicians, regulators, the research community and academic centres followed by payers, patients and patient advocates. There are a number of requirements in order to make sure the action plan succeeds. For instance, ensuring that IT systems and existing data interfaces are advanced enough, optimising existing patient registries and developing centres of excellence for collaboration and/or endorsement. Furthermore, understanding the current legislative frameworks – data ownership, requirements for data sharing and

confidentiality, conditions for data release and finally ethics requirements – will be required to ensure that any RWE is used in the correct manner. Key milestones include producing a consensus on what to expect, defining clear outcomes and pathways (for example, for biosimilars), signing off on required methodology and completing an end-to-end example process using RWE for a specific product.

Developing a definition of PRO

Developing a universal definition of patient reported and relevant outcomes may lay the foundations for empowering patients to engage more actively in the use of RWE, enabling them to increase their understanding of its importance, making them more likely to support the use of their data. Initial actions include researching the existing definitions, approaches and best practices with the help of key opinion leaders, academia, patients and their advocates and industry partners. This will ensure sufficient topic knowledge and ensure that any definitions are not focused on 're-designing the wheel'. The next step is a gap analysis and assessment to visualise issues with current definitions before the research question, priorities and research agenda are defined with the help of academia, regulatory and HTA bodies and patients. The final step will be aligning stakeholder perspectives and definitions via round tables and workshops with all stakeholders including clinicians, patients, payers, regulatory and HTA bodies and industry. Key milestones for this action point include the development of a survey report and publication on the existing definitions, approaches and best practice, a research agenda defining the key questions and a final, useable definition of PRO.

Develop a model approach for the collection of PRO data

Following the development of a definition of PRO, the final action point is to develop an approach that can be used to usefully collect PRO data. Initial steps here include mapping a process for data collection – i.e. identifying where data does and does not exist, assessing the quality of data required for any decision making and then defining a criteria for data quality and availability. Subsequent stages include setting objectives for data collection and defining a model process considering data laws and any compliance issues, and identifying any infrastructure/technology needs. These action points will be led by industry with multiple stakeholders including patients, clinicians and regulatory bodies. Data gathering requirements mirror those in the action point above. The development of surveys will allow the identification of current data possibilities, whilst the development of an expert network and round tables will enable the assessment of data quality and allow criteria development and model process definition. Specific milestones include a defined set of criteria objectives, a mapped and validated process and a model playbook.

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Conclusions

This report documents the discussions held at a roundtable-style meeting with a number of stakeholders. This is the third discussion session in this series with previous sessions developing our understanding of the role of RWE across the EU. The aim of this session was to assist Roche to develop a roadmap for action to enhance the use of real world evidence for improved market access for all pharmaceutical manufacturers.

Increased use of RWE is becoming more common and associated benefits more relevant, but there is no doubt that significant work needs to be done in the areas of data generation, interpretation and use to make its inclusion in commissioning and licensing based decision-making more mainstream. We have developed a series of proposed initiatives, each with a number of associated action points, which need to be pursued in order to further develop the use of RWE in decision-making. Focusing on avenues for early dialogue with payers in terms of their RWE needs, developing a consensus exercise on the use of RWE in clinical decisions, developing a definition of patient reported/relevant outcomes and developing a model approach for the collection of this data are seen as the most imperative steps for enhancing the role of RWE. If RWE use is to become more common then these steps should be addressed as quickly and efficiently as possible.

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