RWE in Europe Paper IV:

Engaging pharma in the RWE Roadmap

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Abstract

This paper summarises discussions held at the fourth round-table 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, the fourth and final paper in this series, outlines the future potential of the stakeholder group involved in the project to date.

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Background

Real world evidence (RWE), derived from the analysis or synthesis of real world data (RWD) from patient registries, electronic health records (EHR) or claims databases, is becoming more interesting to stakeholders in pharmaceutical development and regulation due to the increasing expense of randomised clinical trials, the current gold standard in terms of data collection. Issues with data availability and quality led Dr Robert Califf, former commissioner of the US Food and Drug Administration (FDA) to state that "*The current deficit in evidence has become particularly acute for the FDA, which in numerous areas lacks vital evidence needed to support definitive regulatory determinations of safety, efficacy, and appropriate indications for marketed medical products*" (Kaplan, 2016).

This gap in data availability and quality could be filled by RWE. There are three stages in pharmaceutical development where RWE can be useful – understanding medical need, having an input on medicines development and supporting market access. The healthcare environment is changing in relation to RWE and regulatory guidance is growing. Pharmaceutical companies need to utilise RWE and require reliable data sources in order to do this alongside sufficient compliance procedures, and utilisation of existing organisational and governance structures. However, pharmaceutical companies are now competing with organisations focused on building technological and digital capabilities related to RWE such as Flatiron Health (flatiron.com). In response, many patient organisations are beginning to focus on the RWE that they have access to and are willing to build capabilities and resources, engage patients, advocate for legislation change and explore new business models.

This report is the fourth in a series discussing the use of RWE in Europe. All four reports have outlined discussions held with a number of stakeholders, all of whom have significant experience in specialist disease areas and commissioning of care plus prior experience in the field of RWE, at four round-table style meetings held between June 2016 and October 2017. Previous meetings 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 finally the development of a three-year roadmap of initiatives for the enhanced use of RWE in decision-making (Gill *et al*., 2016, Gill *et al*., 2017a, Gill *et al*., 2017b).

This report describes discussions at the most recent meeting held in October 2017 in Zurich where the objectives were as follows:

(1) Gain insights into new approaches in RWE – develop a better understanding around novel approaches to gathering RWD, its analysis, application and potential impact on patient access.

(2) Share experiences and expertise in RWE initiatives – to provide input and feedback to novel initiatives around data generation and patient group engagement.

(3) Define the way forward for the group – identify ways to best utilise the capabilities of the stakeholder group to develop mutually beneficial and tangible outputs going forward.

Whilst discussions were initiated and led by F. Hoffman-La Roche AG (referred to as "Roche" for the rest of this report), 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.

The emerging role of RWE in the oncology setting

Current RWE use allows us to identify rare patient sub-groups, assess off-label efficacy, follow up on clinical outcomes and conduct pragmatic trials. However, it is not currently accepted for regulatory use by organisations such as the U.S Food and Drug administration (FDA). Data requirements for regulatory grade RWE mean that data has to be aggregated, high quality, complete and longitudinal with reproducibility and provenance. There must be specific endpoints and outcomes and patient-level data linkage. *A priori* there must have been identification of study objectives and analysis plans as well as careful cohort selection.

In order to develop methods for the collection of regulatory-grade RWE Flatiron Health (www.flatiron.com), an American company focused on dramatically improving treatment and accelerating research in the cancer arena, has partnered with the FDA with the aim of defining standards for regulatory grade RWE to enable it to be used for regulatory purposes.

In the oncology arena trials are both timely and expensive, whilst treatment protocols are dynamic. This means that by the time lengthy trials have been completed treatment options have developed further and those on trial have become irrelevant. RWD can often vary significantly from RCT data in that scans and changes in treatment are less periodic. Furthermore, oncologists are often highly time stretched and have a limit on the data variables they are able to capture. In order to develop regulatory grade RWE Flatiron has developed sets of data derived from outside the clinical trial setting, for example, EHR, claims/administration data, registries and patient generated data. Their databases, which encompass two million active patient records, 2500 clinicians and 256 cancer clinics, consist of structured (diagnosis, lab results, therapy information) and unstructured data (pathology results, patient notes). These data are collected and standardised using a technology platform that involves human data capture. Whilst this method of data extraction is labour intensive it is verifiable and accurate and can support the production of regulatory grade RWE, although there is room for a more automated system that can limit levels of human error, reduce any bias and improve the speed at which data can be made available.

One recent successful project saw a retrospective analysis of patient level EHR of those with a diagnosis of metastatic non-small cell lung cancer (mNSCLC) and the frequency of PD-L1 testing, which can impact immunotherapy treatment decisions, and treatment effectiveness. Using Flatiron data sets it was clear that testing rates for PD-L1 were low and that clinician education was important as information on optimal PD-L1 testing strategies guiding treatment decisions increases.

Improving the use and implementation of RWE in the EU

The stakeholder group was asked to discuss the practicalities of a Flatiron style system in the EU. Questions for the stimulation of discussion focused on the possibilities of using EHR based RWE, the best way of collecting RWE data for such projects, the biggest barriers and challenges associated with the collection and use of this data and methods for overcoming any potential challenges.

In order for similar studies in the EU to support improved access to medicines stakeholders thought that validated biomarkers would be required to ensure precision and that the consistency of data collection will need to improve. It will also need to be more focused on a specific product, rather than the collection of a large number of variables. Country specific preferences within the EU 28, as well as priorities, policies and practices will need to be taken into consideration to allow for innate differences. The meaning of outcomes, and their linkage to reimbursement will also need to be defined. Highlighting the potential value that RWE can bring, as well as addressing specific pathologies, may enhance its use.

Challenges identified include the limited transparency in the data collection process, as well as a lack of data collection related to outcomes. In order to enhance this both physicians and patients need to be schooled in the importance of data collection. Furthermore, IT solutions across countries are not always consistent which could lead to data loss. EHR, and other analogous data sets, may well exist, but it is likely that these vary dramatically between countries, cities and individual hospitals. Data protection standards may also vary significantly across countries which could make consistent use of RWE less practical.

Addressing these challenges will require consistent drive from all stakeholders. The first step will be identifying the problem that needs addressing, for example, is it related to licensing of a new medicine, or adaptive licensing? We then need to identify the right markets with strong, single, standardised EHRs in use. Using a panel of experts to advise on the specific data and variables that require collection and defining relevant outcomes from the outset, to allow for outcomes based reimbursement, will be required. Clarifying the data collection domain, in terms of research, safety or resource deployment will also be necessary, as well

as developing data hierarchy guidelines. Similarly, communicating the benefits of data collection and the outputs produced to all stakeholders, and using RWE to justify cost versus resource use will lead to increased use.

Early Engagement

Early engagement was one of the priority points for action in Year 1 of the roadmap (Figure 1) developed at the last roundtable in June 2017. Whilst developments in pharmaceuticals are obviously important for modern healthcare they also create challenges. This generates resulting challenges for all stakeholders including payers, pharma companies and patients themselves. Early engagement, between payers, and other stakeholders, related to RWE requirements could potentially mitigate any issues related to these novel challenges.

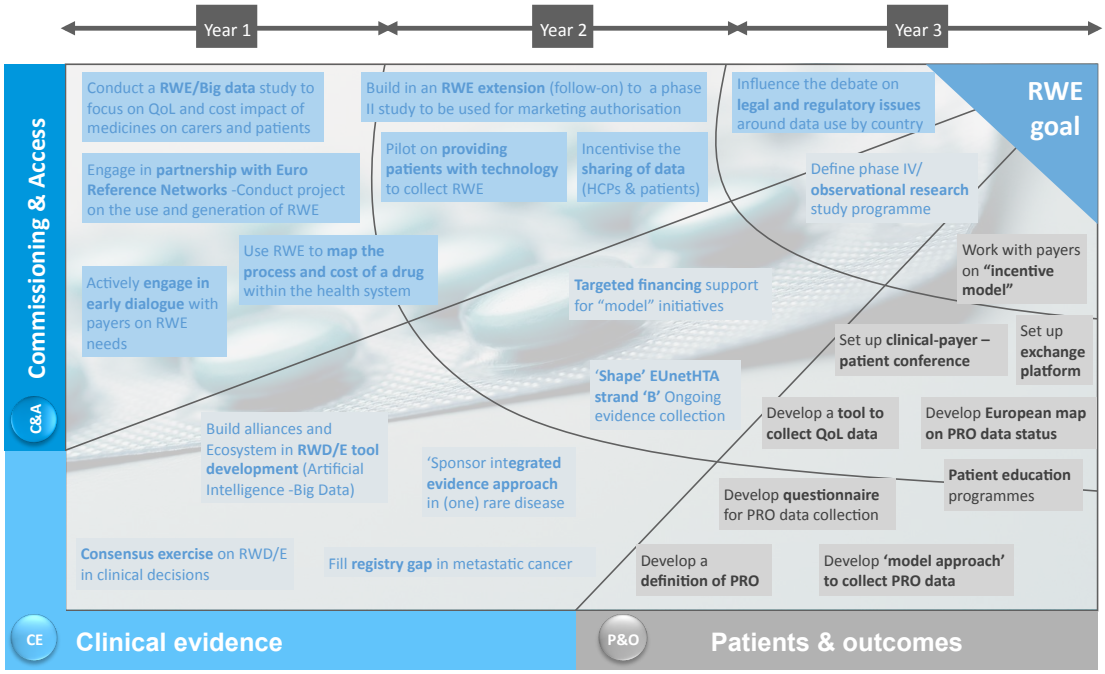
There are also a number of things that the pharmaceutical industry can do to build on the potential of RWE, pioneer developing the data and grow the community in order to advance the generation of RWE. Early engagement with patient organisations (PO) and proactively driving development of long term partnerships with POs to gain independent and representable RWE may also help alleviate issues related to the development of novel pharmaceuticals. We discuss the importance of patients, and patient organisation based RWE in the next section.

Realising the value of RWE across the product cycle

It is hoped that RWE generation will work towards enhanced treatment, earlier diagnosis, improved treatment quality, improved adherence and efficacy, enhanced treatment outcomes as well as improved overall survival and disease free survival. One of the key outcomes of our previous meeting, at which we developed a road map for RWE related progress (see Figure 1), was the requirement to produce a definition of PRO (patient relevant outcomes), and to develop a 'model approach' to collect this PRO data. Whilst there is often interest in patient reported outcomes, which can be implemented in early phase trials, patient relevant outcomes are often not addressed, despite the fact that some evidence shows that cancer patients who engage in their treatment and outcome levels gain 5 months survival advantage. Patient organisations are well placed to impart the importance of PRO, and RWE, collection to their patient groups and there is a significant space for relevant education around this area.

The patient is the one who knows the answers to many of the questions related to a medicine's impact and there is therefore a requirement to support and empower patients to take ownership of their data and increase their understanding of the implications of this data. Longitudinal data is highly valuable, and some emerging markets, such as Brazil, are working with technology partners to harness this value and generate data for long term commercialisation. Similarly, 'Patients Like Me', a website where patients share health data which can be used as RWE, is an example of how PO can monetise the data from the patients they represent and develop a business model providing patient relevant data to organisations for analysis purposes.

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



In order for this to be feasible an operating model and regulatory framework is required for PO to empower patients, facilitate long term collaboration and advance RWD use. As it stands collection and analysis of PRO are not available for all diseases but big data capabilities will allow us to capture much more data, reducing bias, one of the aspects of RWE thought to make it less valuable than traditional clinical trials. This advancement will require a clear understanding of the burden of disease and unmet clinical need; assessment of parameters relevant to patients – not just regulators; open dialogue with stakeholders; looking beyond simple completion of QoL assessments; building capabilities and developing resources; and ensuring patients understand and advocate their own rights.

There are examples of such collaborations. For example, in Roche there is an ongoing collaboration with the European Haemophilia Consortium to prospectively collect treatment-usage patient data in support of an innovative pricing strategy. They

are also forming 'molecule-enabling' projects with well-defined scope, expected benefits, governance and resource with the aim of further exploring the external environment and supporting PO in building RWE capability as well as optimising the internal environment and increasing the utilisation of PO derived RWE across the product lifecycle.

RWE generation by patient groups

In order to get an understanding of the current 'state of the nation' in terms of PO use and collection of RWE we asked two patient organisation representatives for their insights on systemic RWE generation in their organisations as well as the wider network.

A number of limitations and gaps in systemic RWE generation were highlighted during this process. Examples include competence, lack of capacity building, lack of advocate education, manpower issues, lack of financial support for both capacity building and data collection and inconsistencies in the methodologies used for RWE collection.

We asked the representatives to describe their organisation's maturity in terms of RWE generation for four areas – knowledge, capabilities, technology and patient buy-in. Both thought that knowledge around RWE is limited, but can vary across the EU with some countries being better than others. Capabilities were thought to be mainly poor with some progress being made. Technology was recognised as being available but not utilised effectively. In terms of patient buy-in strong patient organisations have significant expertise, but this can be limited to a number of active, mature patients.

In terms of patient organisations that are using best practice the European Federation of Allergy and Airways Diseases Patients' Associations (EFA), the Austrian Lung Union and the Swedish Prostate Cancer Organisation (PCF) were highlighted. Typical RWD endpoints used by PO include QoL, compliance with national guidelines, side-effects, overall survival, medicines adherence and access to medicines.

Next steps in RWE/conclusions

The final part of the session looked toward the future and asked stakeholders to think about methods for realising the roadmap within Europe finalised in the previous meeting (Gill et al 2017b) (see Figure 1).

First steps will involve mapping any ongoing global and national RWE projects in order to increase understanding of current projects. It is vital to capture learnings from any, already implemented, initiatives in this way, as well as sharing experiences of best practice and advice developed as a result, both internally and externally.

Within Roche, the roadmap initiatives must be evaluated and aligned with current commercial objectives and product needs before a three-year implementation plan can be drafted for RWE in Europe. The roadmap, which will be an ideal platform to launch new projects, is a valuable opportunity for internal collaboration within Roche and may go some way to overcoming 'silos' often present in pharma companies that can inhibit knowledge sharing and idea generation.

Subsequently, developing a business case for pursuing the prioritised initiatives such as filling registry gaps in metastatic cancer – for example there may be an opportunity for the pharmaceutical industry to collect significant amounts of data related to breast cancer management. Furthermore, developing a definition of patient reported/relevant outcomes and developing a model approach to collect such data will be a focus. There is then a requirement to develop an implementation plan and identify the resources required, secure financial support, engage resources, key stakeholders and partners and finally implement individual projects.

Over and above the specific road map there is also a place for pharma to develop standardised tools and data which can support various engagements in RWE. They can play a role in empowering and validating patient groups and organisations as well as clinicians – a key request from patients is for training, support and education in data collection. They can also assist with clearly defining outcomes for the disease area in focus, make data meaningful for all stakeholders and develop 'smart data' (digital information that is formatted so that it can be acted upon at the collection point before being transferred to an analytics platform for consolidation and analysis).

In terms of the future of this group of expert stakeholders, involved in the exploration of RWE across Europe since June 2016, there is the opportunity to improve and diversify their contribution by providing alternative avenues for research and support of local ideas and initiatives. They could play a role as a sounding board, provide valuable information and advice as well as feedback on the methodologies developed by pharma for the development of future RWE and its utilisation.

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