The use of Real World Evidence in the European context

An analysis of key expert opinion

Gill, J.L, Avouac, B., Duncombe, R., Hutton, J., Jahnz-Rozyk, K., Schramm, W., Spandonaro, F., Thomas, M. and Kanavos, P.G

Abstract

Randomised controlled trials (RCT), traditionally seen as the gold standard in drug approval requirement terms, are becoming more difficult due to, among other reasons, budget constraints, increasing complexities and the shrinking of patient populations. Real world evidence (RWE), data used for decision making that is not derived from traditional RCT, may in future play an increasing role in market access and reimbursement decisions. This paper analyses key pricing and reimbursement stakeholders' opinions of RWE across five European countries via a focus group-style discussion. Areas probed included regulatory implications and the role of RWE in the study countries, RWE processes and implementation on decision making, meaningful outcomes from RWE and priorities for future focus and industry support. Results showed that RWE was used to some extent in all countries, generally in accelerated access and re-review situations, with accepted endpoints including overall survival, morbidity, avoidable mortality and quality of life among others, but that there were a number of areas where improvement was necessary if RWE use was to become more common place.

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Introduction

Despite randomised clinical trials (RCTs) still being seen as the gold standard in terms of drug approval data requirements recently real world evidence (RWE) has shown particular promise in its potential to contribute to improved understanding. The limited generalizability of RCT, due to restrictive enrolment criteria, increasing complexity and overly controlled study environments as well as the shrinking of potential populations for Phase 3 trials for orphan drugs and treatments for rare diseases and budget constraints are some of the issues forcing policy-makers to look for alternative, or complimentary, methods for the evaluation of clinical and cost effectiveness of novel medicines to determine appropriate resource allocation.

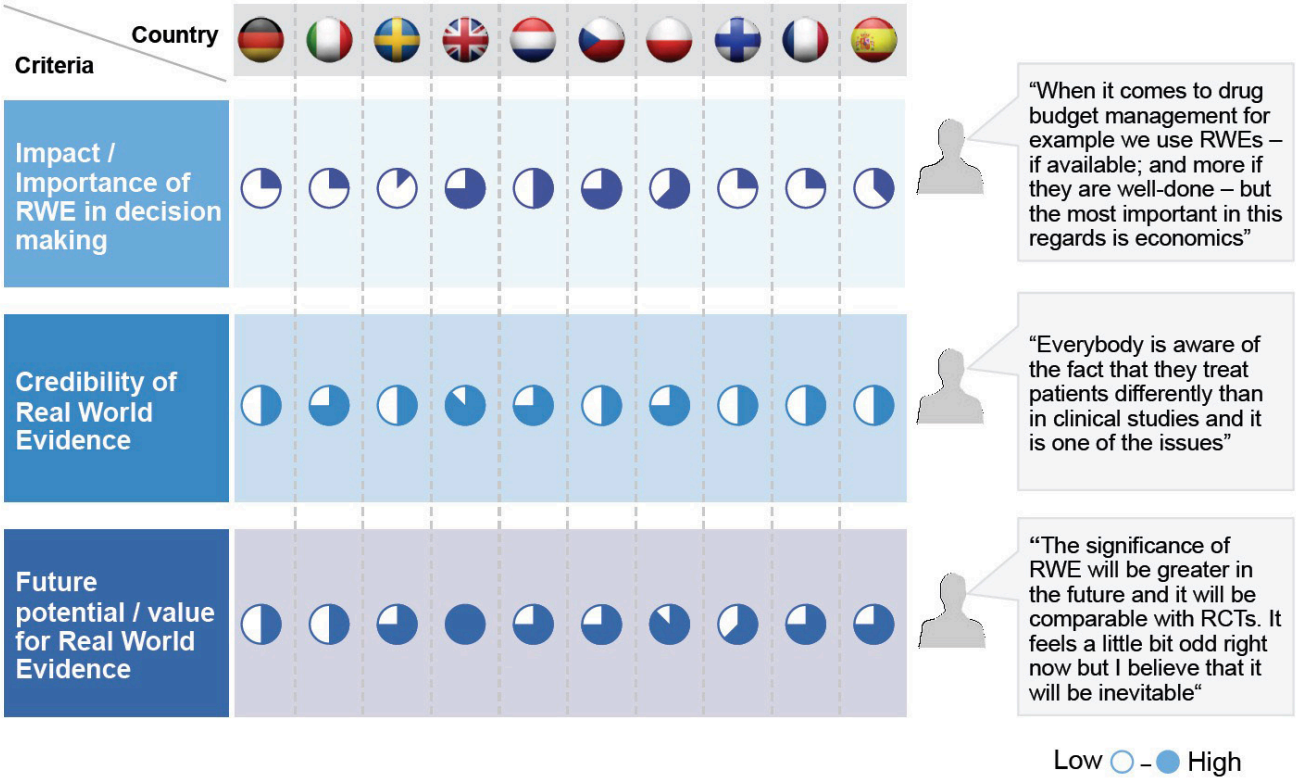
RWE was defined by the 2007 ISPOR Real-World Data Task Force as any "data used for decision-making that are not collected in conventional RCTs" (Garrison *et al.* 2007) and data sources can include prospective or retrospective RWE from patients, caregivers or healthcare workers collected via practical controlled trials, registries, administrative data, health surveys and electronic health records. It can play a role in both pre- and post-marketing authorisation approval. In the pre-approval setting RWE can enhance the effectiveness of RCTs via the identification of patients from specific subpopulations (i.e. background epidemiology) which could potentially lead to shorter and more effective trial periods. It also has a role in the evaluation of unmet clinical need, defining care pathways and in data collection for use in HTA (Bonnelye & Miniuks 2015) where the focus would largely be on obtaining data about the competitors already in routine use. In the post-approval setting RWE has a role in analysing patient outcomes in real world settings to generate further insight on safety and effectiveness of innovative products, as well as increasing understanding of real-life treatment pathways, treatment sequences, length of required treatment and the resources required plus specific disease processes.

There seems to be consensus that the use of RWE is valuable for the provision of clinical practice evidence on treatment pathways, resource use, long-term natural history and true effectiveness – results from RCTs have been criticised for being hard to generalise to clinical practice. It also allows for broader comparisons, with comparators other than those in registration trials, and the collection of longer term data – vital for the analysis of drugs used to treat chronic, long term conditions – as well as allowing a wider range of endpoints than the traditional RCT.

Despite these apparent positives there are a number of methodological challenges faced by those using RWE such as a lack of randomisation, bias and issues around data quality (Pietri & Masoura 2014). One study has shown RCT data is still used in most health technology appraisals (HTA) – 90% of CADTH appraisals, 80% of PBAC appraisals, 64% of NICE appraisals and all IQWiG appraisals in 2015 used RCT-based evidence with only three positive appraisals based solely on non-RCT evidence (Griffiths & Vadlamudi 2016).

Notwithstanding these issues RWE is increasingly recognised as a valuable source of evidence for both market access and reimbursement decisions. In 2015 a "*Payer RWE voice of the customer project*" gained insight into RWE needs and priorities across ten European markets. **Figure 1** shows the value and importance placed on RWE in each of these ten countries.

Figure 1: Opinions of RWE use across ten European countries



The current study is a follow up to the voice of the customer project carried out in 2015. The aim here is to further analyse the opinions of key experts in pricing, reimbursement and RWE from a number of European countries to get a more in depth understanding of the current use of RWE in their respective countries as well as the future potential for RWE across Europe.

Method

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 were invited to participate in a discussion group to garner opinion on the use of RWE in Europe. Via a day-long focus-group discussion on the 27th of June, 2016 in London, six experts, from five European countries, addressed a number of specific topics across four sessions. Attendees included those from the United Kingdom, Germany, France, Italy and Poland with representation from academia, health services, government bodies and payers.

Topics covered in the focus group included: (a) Regulatory implications and the role of RWE; (b) RWE processes and implementation in decision making; (c) Meaningful outcomes from RWE; and (d) Priorities for focus and opportunities for industry cooperation and partnership.

Sessions involved a combination of questions, scenarios and case-studies. Sessions one and four consisted of standard questioning/discussion processes; session two consisted of reflection on two settings where RWE is used – accelerated access and reassessment/review – where the focus of the discussion was on challenges and opportunities for stakeholders; and session three involved the identification of criteria for meaningful outcomes by exploring three case study scenarios based around accelerated access, lack of long term data and appropriate endpoints.

Results

Results from each of the four sessions will now be discussed in turn.

Session 1: Regulatory implications and the role of RWE

The primary questions in this session centred around the use of RWE in individual countries and its incorporation into the local regulatory environment. Participants were asked questions around how RWE forms part of the local regulatory system in their countries and what the main challenges and opportunities were for RWE.

In the United Kingdom RWE is seen as supplementary to phase 2 and phase 3 data, as well as in cases of ongoing evidence collection, for example in situations where regulators are willing to use available evidence to make initial decisions but require more evidence as time progresses. Generally RWE is not seen as a substitute for randomised controlled trials (RCT), unless there is a clear reason why the use of RCT is not feasible.

However, the paradigm is seen to be changing – conditions like cancer are becoming more 'chronic' as opposed to acute, and the time taken to gather evidence on final outcomes (such as overall survival) is lengthening as a result of life extension. Similarly as drugs are developed for orphan conditions, with small patient groups, the rate of recruitment to traditional RCT might lead to excessive delays in meeting conventional licensing criteria. If licences are granted without conventional RCT data RWE is likely to play a larger role in those therapy areas, as the only means of collecting data to validate the original.

There is also evidence of a growing gap between the data needs of the regulator and commissioners. NICE is likely to have different requirements for the commissioning of a 'safe' medicine compared to the requirements for the initial approval of a medicine via the EMA or MHRA. RWE tends to play a larger role in the post-regulatory setting in order to support economic arguments. Whilst registry data is relatively complete (compared with countries such as Germany, see below) the question still remains–who is seen to be responsible for the collection of RWE, pharma companies or the regulators? Evidence shows that despite the funding of many cancer drugs not considered cost-effective by NICE over a period of around five years via the Cancer Drugs Fund in England there is limited resulting data on the effectiveness, both clinically and economically, of these medicines. Recent changes in the evaluation processes for cancer drugs should lead to a more efficient system of ensuring that effective drugs are utilised as quickly as possible and at an appropriate price.

In France, as in other European countries, RWE is not used in regulatory (licensing) decision-making as the EMA decision is based on a risk-benefit ratio however it does serve to support post-marketing evaluations, particularly in innovative drugs where a five year re-evaluation of pricing and reimbursement may well include RWE to bridge any data gaps. When used the credibility and quality of RWE is considered and comparator data is preferred. It also has a role in ATU in France – Temporary Use Authorisations which are used for patients/diseases where there are no current treatment options available–whereby innovative medicines that have not yet been approved by the EMA can be used based only on Phase 2 assumptions of benefit. In such situations payers expect industry to propose and design RWE solutions addressing the efficacy, effectiveness and value versus new drugs/comparators as well as validating intermediate endpoints with clinical outcomes.

In Germany RCT data is the only drug-specific evidence available prior to market authorization and hence serves as the primary driver behind initial pricing, reimbursement and market access decision making. IQWiG assesses the additional benefits of a new medication relative to the standard of care. RWE can be used to define this standard of care, to quantify resource use and to assess the quality of healthcare delivery. German stakeholders still see key hurdles in

both the generation and usage of RWE in terms of the quality of the data and the privacy of such data. The interest in RWE has increased since 2015 legislation encouraged health care research and subsequent real life data collection.

In Poland the specific disease area tends to determine how evidence is valued, although certain levels of efficacy and efficiency will be required. The current reimbursement process is long and complex and focuses on economic commissioning, price negotiating and managed entry agreements. Recently, in order to provide a new methodological framework, new HTA guidelines were published. The most important change is that RWE is now considered to be equally important to classical experimental evidence. Whilst the growing importance of RWE is visible in Poland the pace of such growth will depend on the degree of recognition of RWE by decision makers as well as the availability of RWE in the Polish healthcare system. Limited access to high quality data from Electronic Health Registries in Poland, due to poor IT infrastructure for example, may impair expected RWE utility.

Finally in Italy many managed entry agreements are in place and RWE is used in the reimbursement process. As a result RWE plays a key role in cost efficacy models and may be used to fine-tune guidance for in-market products in future. In terms of registries Italy has many regulatory registries which are not currently being used, however there is potential for this to change as familiarity and experience with the data improves.

Discussions from this session suggested that RWE tends to play a role in two situations:

- Accelerated regulatory review and conditional licencing – accelerating the route to market for patient benefit.
- Re-review occurring at year one, two or five with ongoing data collection.

These two distinct roles were analysed in more detail in session two.

Session 2: RWE processes and implementation in decision making

Discussion in session two was framed around the two themes that became evident in session one – accelerated access and reassessment/re-review – with the impact, challenge and opportunity being discussed. Top line results for each of these themes can be seen in **Figure 2**.

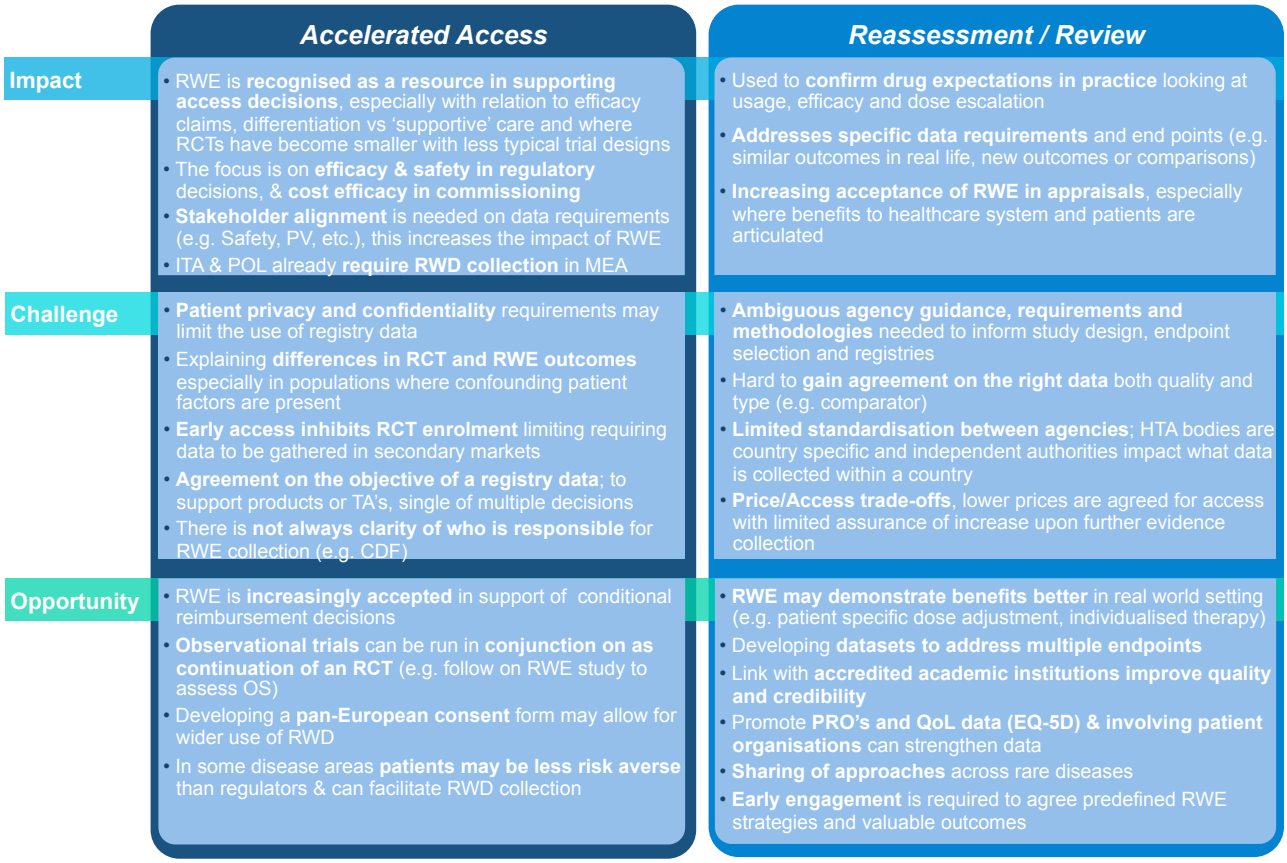
Accelerated access:

RWE was recognised by all stakeholders involved in the discussion as a resource for the support of access decisions, particularly where RCTs have become smaller with less typical trial designs, and is known to be increasingly accepted in support

of conditional reimbursement decisions. Regulatory decisions tend to focus on efficacy and safety whilst commissioning is more concerned with cost effectiveness. If a drug receives a conditional licence it can be adopted for use whilst the collection of outcomes data continues. Commissioners must then review the evidence base presented and approve its use.

Challenges around the use of RWE for accelerated access exist. Patient privacy and confidentiality requirements may limit the use of registry data. Furthermore, if a drug is made available via the conditional approval method patient recruitment for additional studies may become an issue if the drug is already reimbursed – patients may not want to be involved in an RCT if they already have access to the drug in question via their health system which is why RWE from other types of studies is essential. Such a challenge may be addressed by conducting trials in other markets (for example, China) although this may raise questions around the generalisation of the data and the acceptability at a local level due to differences in populations and treatment standards, among other reasons. There may also be problems explaining any differences seen between RCT and RWE outcomes, particularly if the RWE population is less healthy than the RCT population, which is usually the case. If so then RWE data will be more relevant.

Figure 2: Reflections on two settings where RWE is used



In some disease areas collection of RWE may be facilitated by the fact that patients with a significant risk of morbidity or mortality as a result of a condition may be less risk averse than regulators and may be more likely to accept a higher level of uncertainty due to an immature evidence package. Furthermore there is the possibility that developing a pan-European consent form for patients may allow for the wider use of RWE. Early engagement between pharma companies and regulators as well as commissioners to garner an understanding of data needs will also support its use in accelerated access.

Reassessment/re-review:

There is a clear role for RWE in the re-review setting where it can address specific data requirements and end points. It can generally be used to confirm drug expectations where important factors include usage, efficiency and dose escalation, as well as safety. Despite concerns that 'interference', for example from confounding factors, in the real world may impact benefits it is also possible that RWE may demonstrate benefits more effectively in a real world setting due to issues such as patient specific dose adjustment and individualised therapy.

There are three main objectives in terms of RWE for re-review:

- Consistency of outcomes between RCT and real life, i.e. RWE
- A requirement for specific additional data, or validation of new outcomes measures
- Comparison data

Whilst there is potential for enhanced benefit there are a number of areas where improvement would boost the possible impact RWE could have. As in the situation with accelerated access, it can be hard to reach an agreement on the type and quality level of data required for such re-review processes as well as where responsibilities lie in terms of data collection. There also tends to be limited consensus and standardisation across agencies which are country-specific and influence the data collected within a country.

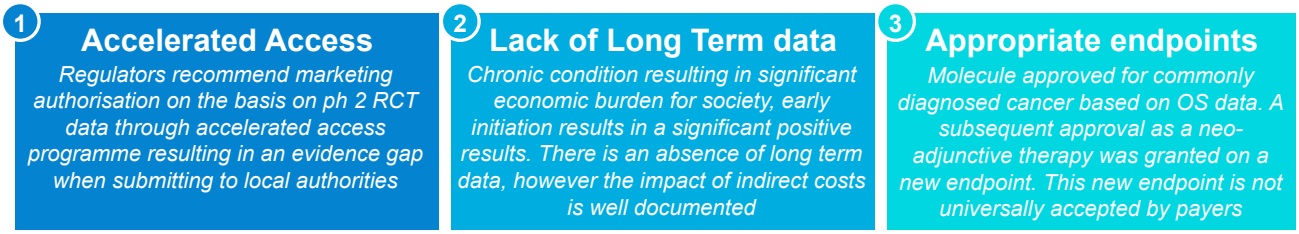
The ideal would be for regulatory authorities to be explicit in outlining what data is required for re-review–both in terms of quality and type. Such early engagement would ensure that industry starts the process knowing exactly what is expected of them. There also needs to be a focus on patient reported outcomes, for example via the EQ-5D and disease specific quality of life measures, which should be routinely collected, as well as involving patients and patient organisations to ensure a multi-stakeholder process. There is also a need to encourage a certain level of consistency across databases, with the ability to link data across countries and sectors to enhance data-usability. Again issues around patient confidentiality can play a role here. Registries should be designed and viewed as clinical trials with clarity in the questions asked of the registry, as opposed to focusing on the

traditional 'data fishing' role of the registry. Finally, the publication of data on RWE and its utilisation needs to be encouraged and supported to improve familiarity of the use of RWE amongst healthcare communities' and related stakeholders, as well as the potential value gained as a result of the use of RWE. Such a step can be supported via linking with academic institutions in order to build the credibility and reputation of RWE.

Session 3: Meaningful outcomes from RWE

This session focused on the analysis of three separate case studies in order to identify some criteria for meaningful outcomes. Case studies are described in **Figure 3**. Discussion of each of the three case studies centred on how RWE can support RCTs in meaningful outcomes, which endpoints would be used as evidence and what is currently inhibiting RWE from providing meaningful outcomes and what can be done to address these issues.

Figure 3: Three case studies analysed with key stakeholders



Case study 1:

This case reviewed the use of RWE as a direct contributor to product approval and access in the absence of conventional RCT evidence. In the example regulators have recommended a drug for EU-wide marketing authorisation via an accelerated assessment programme on the basis of Phase 2 RCT data, with a lack of Phase 3 data due to ethical issues arising from withholding treatments to certain patients.

General consensus amongst stakeholders taking part in the discussion was that the role of RWE in this context is to conduct observational trials for the targeted claim in subpopulations – to facilitate this a structured observational trial design is needed with the ability to follow a patient cohort and allow for sub-set analysis. RWE can also support patient access schemes, provide insights on adherence and aid in the development of local data to confirm benefits for commissioning. However, whilst additional RWE data are useful for approval in this adaptive pathways procedure Phase III data should still be provided in a second stage if RCTs are possible.

Relevant endpoints/outcomes will generally centre around survival or progression free survival alongside quality of life measured via EQ-5D. There is also the opportunity for biomarker validation, or relevance checking.

Challenges include issues around the statistical power of data resulting from small populations, cost/benefit trade-offs where a biomarker/diagnostic approach is concerned and the quality of data collection – for example NICE approval data may be used to support commissioning decisions later in the product's life cycle but there needs to be ongoing guidance sought to ensure data used is sufficient.

Case study 2:

This case looks at building an evidence based case for patient access with the consideration of broader societal benefit. For example, a chronic condition which results in significant economic burden for society. Early initiation of a novel treatment has been found to result in significant positive results, with strong levels of evidence to justify approvals, but there is an absence of long term data for cost effectiveness, although the impact of indirect costs (such as work productivity losses) is well documented.

In such cases RWE can be used to validate models where use is limited or based on intermediate outcomes. It can also be used to generate intermediate to long term data on a broader set of outcomes and create data on indirect costs that can support commissioning decisions. Outcome measures can include overall survival, morbidity, avoidable morbidity, quality of life over two years and overall patient experience alongside long term safety data, compliance/adherence and overall clinical and economic benefits.

Challenges include the fact that the inclusion of indirect benefits may not be considered relevant by all authorities. For example, in France and Italy indirect costs are excluded from any cost benefit analysis by law, whereas in the UK NICE may allow the inclusion of such data in special cases, for example, it may include the cost of a carer required by a patient. Additionally the length of trials or follow-up periods required in chronic, progressive conditions, may cause problems.

Case study 3:

This case reviews the use of RWE as a direct contributor to product approval and access in the absence, or impossible nature, of conventional RCT evidence. In such situations the role of RWE was seen to be in the support of commercial deals to facilitate ongoing data collection. RWE would also assist with the validation of either new mechanisms of action, new population groups or new treatment strategies. It could also be used to link or correlate endpoints and clinical outcomes as well as demonstrate savings or reduce uncertainty in treatment via long term observational studies.

There are challenges around the development of agreements on reimbursement, access and ongoing data collection as well as understanding the rate of efficacy at which point a drug becomes cost effective. There are also issues based on the data used – for example, countries may be more comfortable using universally available health service data to support RWE in the form of joint data sets. Using an 'item club'1 style process, whereby companies pay for subscriptions to specific databases developed by an expert group gathering and publishing data based on specific requests from subscribers, may work towards tackling this issue.

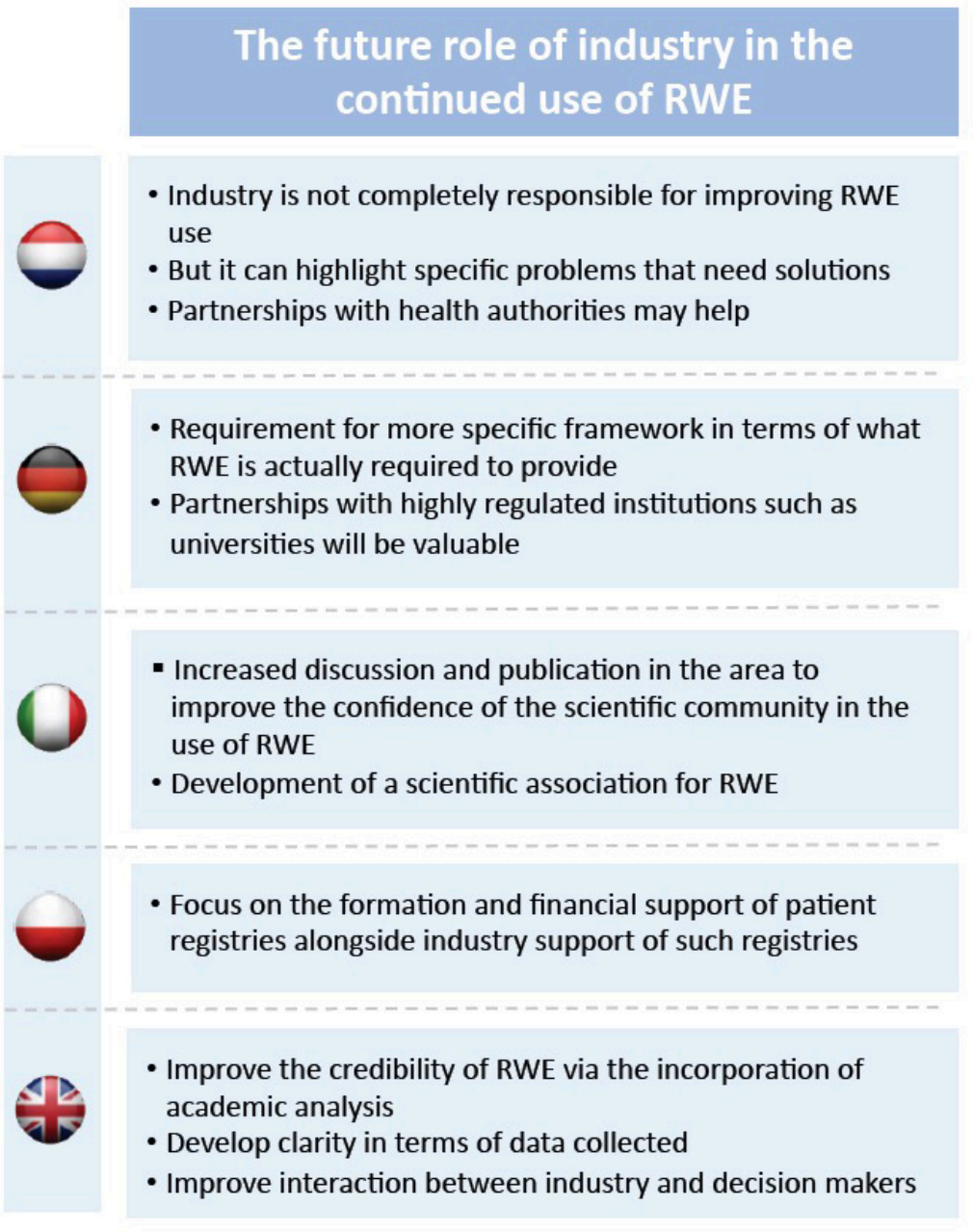
A common thread across all three of the analysed case studies was that RWE tends to be used as complimentary data, although there may well be differences in the requirements between the licencing authority and what commissioners would be willing to accept.

1 Item Clubs involve companies paying a subscription to access specific databases. These databases have been developed by expert groups tasked with gathering and publishing data based on specific requests from their prescribers.

Session 4: Priorities for focus and opportunities for industry cooperation and support

This session focused on the role of industry in the future use of RWE for licensing and commissioning decisions. There were three areas where KOL saw a role for industry – becoming the leader; developing the data; and creating the community. Country specific responses to the question of future industry role can be seen in **Figure 4**.

Figure 4: The future role of industry in the continued use of RWE



Becoming the leader

Companies could draw on their internal expertise, for example in areas such as oncology or diagnostics, and use the breadth of its organisation to use RWE to solve a specific problem. They could also utilise, or create, the mechanisms by which industry as a whole can collaborate with decision makers in a more timely and effective manner. They should also ensure that any support or funding of RWE is highly transparent to ensure it maintains its high standards of credibility. Finally building reputation and trust by working with academic institutions may also be valuable.

Developing the data

The experts consulted suggested a number of ways in which industry could work towards developing the RWE available. For example, by supporting the formation and co-financing of registries in countries like Poland, where one of the main obstacles to the use of RWE is a lack of good epidemiological data. They could also play a role in providing design expertise for registries, improving the quality and consistency of data collected, promote the consistency and universality of use and address issues around confidentiality of patient data held within registries.

Creating the community

Promotion of collaboration between academic institutions, industry and health authorities, alongside the encouragement of the publication of high quality RWE may improve the credibility of RWE and confidence within the scientific community around its use. There may be the opportunity for the development of a scientific association for RWE which will also increase confidence in its use. Collaborations, and initiatives like a scientific association for RWE may also enable the improvement of transparency, communication and information sharing which could work towards defining the explicit purpose of RWE both in terms of commissioning and licencing.

Conclusions

The discussions with European-wide RWE experts developed understanding of the current role of RWE in both commissioning and licencing decisions. The benefit of RWE is becoming more prominent, but the landscape is currently fragmented and may require more focused leadership and collaboration across countries and institutions. There are still a number of questions to answer. For example, can the use of RWE address any gaps between licencing and commissioning?; how do we ensure that we are not asking RWE to do something that it is not designed for – what is the most appropriate role for this type of data?; and how do we incorporate patient data in the most effective way possible? Answering these questions may lead to the underpinning of a RWE strategy for the future.

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Author affiliations

This paper was written by Jennifer Gill (LSE Health, London School of Economics and Political Science, UK), Bernard Avouac (Rheumatologist, Past President Transparency Committee, France), Robert Duncombe (Christie NHS Foundation Trust, Manchester, UK), John Hutton (York Health Economics Consortium, University of York, UK), Karina Jahnz-Różyk (Military Institute of Medicine, Warsaw, Poland), Wolfgang Schramm (University of Munich and Rudolf Marx Stiftung, Germany), Federico Spandonaro (Dept. of Economic and Finance University of Roma Tor Vergata and Chair C.R.E.A. Sanità (Consortium for Health Economics Applied Research), Italy), Michael Thomas (Partner, A.T. Kearney, London) and Panos Kanavos (SE Health, London School of Economics and Political Science)

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