ARWEN

ARWEN RWE perspectives

How can real-world evidence be used to solve unwarranted variation in drug uptake and clinical guidelines?

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About the ARWEN RWE perspectives

This series is meant to bring you snippets of our latest ideas, reflections and opinions on the real-world evidence world. Our goal is to show innovative angles to interpret our healthcare systems and their future, stimulating thinking and further investigation. The series collects organic perspectives from our ARWEN experts, and it is not meant to be a scientific publication. All statements represent the opinions of the authors.

Introduction

The matter of drug uptake is raising great interest amongst European healthcare policymakers and the industry. The number of novel active substances, both in research pipelines and on the market, has grown exponentially over the past two decades. Also, with the use of new biomarkers and data sets, the ability to divide a patient population into distinct groups – each with specific needs, characteristics, and behaviours – is dramatically improving1[1,2]. Today, there are more medicines, for more and more specific patient segments than ever before.

Healthcare regulators seek to guide the prescribing behaviour of physicians, but with innovative therapeutic options, the need to adequately update and develop timely and accurate guidelines is increasingly challenging. One result of this is the large variation in the use of medicines within and across European countries.

To get a grip on this variation, regulators, biopharma, and providers are turning their attention to real-world data (RWD). More and more, the real-world uptake of medicines is considered essential, not just to detect treatment variation, but to learn what medicines are most effective for specific classes of patients. This way, drafting guidelines is shifting from a top-down exercise (from regulators to physicians) to an industry-wide learning cycle. Policymakers can continuously learn from the physicians' prescription habits and therapy outcomes, making their clinical indications always up-to-date, and constantly evolving.

Not surprisingly, the concept of "living guidelines" is gaining popularity in healthcare: a format of guidance that is constantly being updated and also evolves based on recent evidence, with RWD as a core enabler[3]. It was the recent growth in quality and availability of real-world evidence (RWE) that is enabling "living guidelines" to move from being a theoretical concept to an actionable decision support tool for caregivers.

Treatment guidelines affect drug uptake, but they are not the only factor

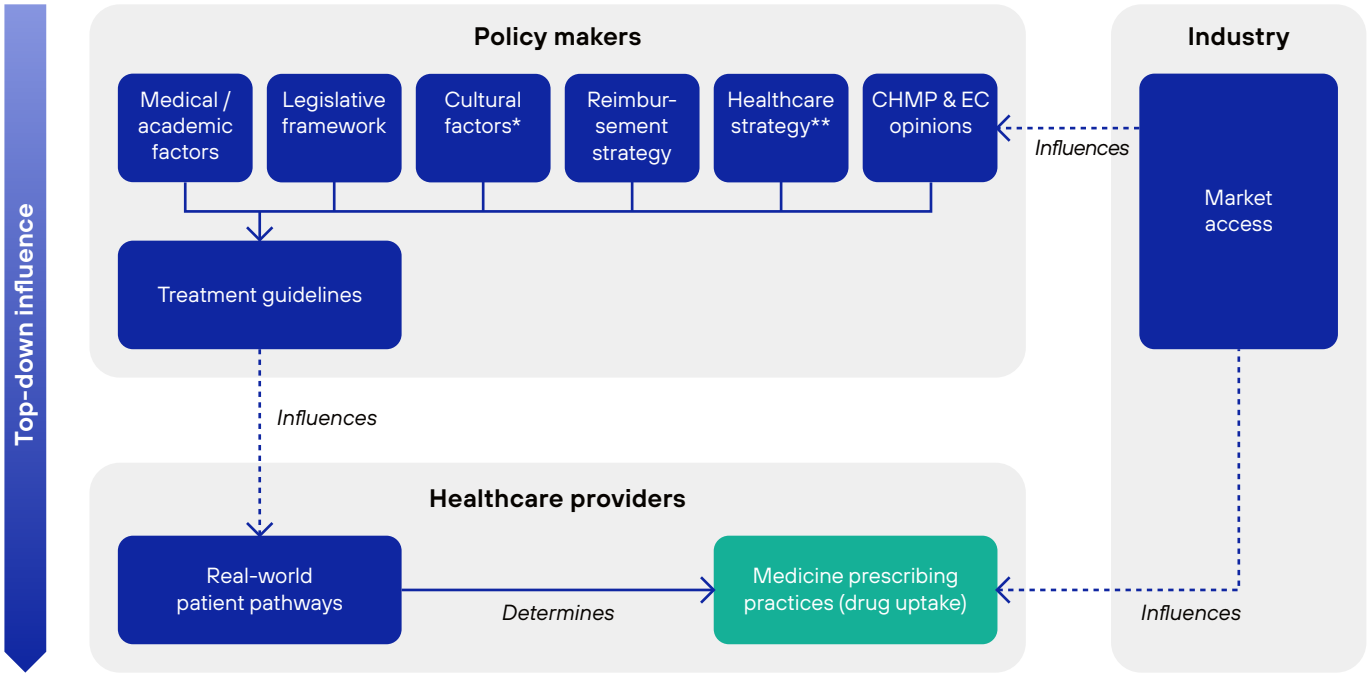
Clinical guidelines and recommendations are tools that healthcare policymakers use to convert the evidence on treatment modalities into organically curated advice to influence physicians. Healthcare professionals use treatment guidelines that support decision-making around treatment options, including specific

interventions, diagnostics or screening in specific patient cohorts. In other words, policymakers affect the decisions of caregivers in a top-down manner.

A variety of factors influence, support, and in some cases help evolve the process of guideline development by regulators. These include academic literature, national heritage, the local legislative framework, cultural factors and beliefs, disposition to novelty, the reimbursement strategy of the payer, national healthcare strategy, and more[4]. Drug manufacturers play a part too. Market access and medical communication departments of life science companies complement the role of policymakers, generating evidence that can support physicians in choosing the best drug for their patients or screening in specific patient cohorts.

In figure 1, the process is illustrated through a visual framework that displays the factors influencing the guidelines as well as influencing relationships between uptake, industry, and policymakers.

Interpretative framework for medicine prescribing practices



* Risk appetite, relationship with the life science industry
** First mover / laggard, incentivization of specific medicine class, policy strategy, etc.

Figure 1: Conceptual framework of drug uptake dynamics and their correlations – the top-down influence of treatment guidelines and market access activities on drug uptake

Treatment guidelines and information from the drug manufacturers provide a standard direction to clinicians for the treatment of patients with certain conditions. At the same time, they do not fully explain the prescribing behaviours of physicians.

For instance, Lugtenberg et al. discovered that in a cross-sectional electronic survey among 703 GPs in the Netherlands, that guideline recommendations were followed by GPs in an average of 77% of the relevant decisions[5].

In a recent broad systematic review, de Guzmán et al. discovered that in Europe only 54 to 69% of the overall treatment process in breast cancer adhered to the

applicable guidelines[6]. In other studies, adherence is frequently registered at ratios below 50%[7].

Several elements influence the decisions of physicians, beyond guidelines. This is especially true in complex disease groups, such as cancer, where treatment pathways become highly intricate with wider and constantly updating options of treatments available. As illustrated in figure 2, factors such as the medical background of physicians, personal experiences, and internal hospital guidelines can play a role in shaping the thinking and preferences of doctors.

Treatment guidelines experience variation or lags across geographies

The creation of guidance by policymakers is characterised by diverse methods of synthesising influencing local and country-level healthcare imperatives. As a consequence, we experience high heterogeneity in guidelines across Europe and within countries.

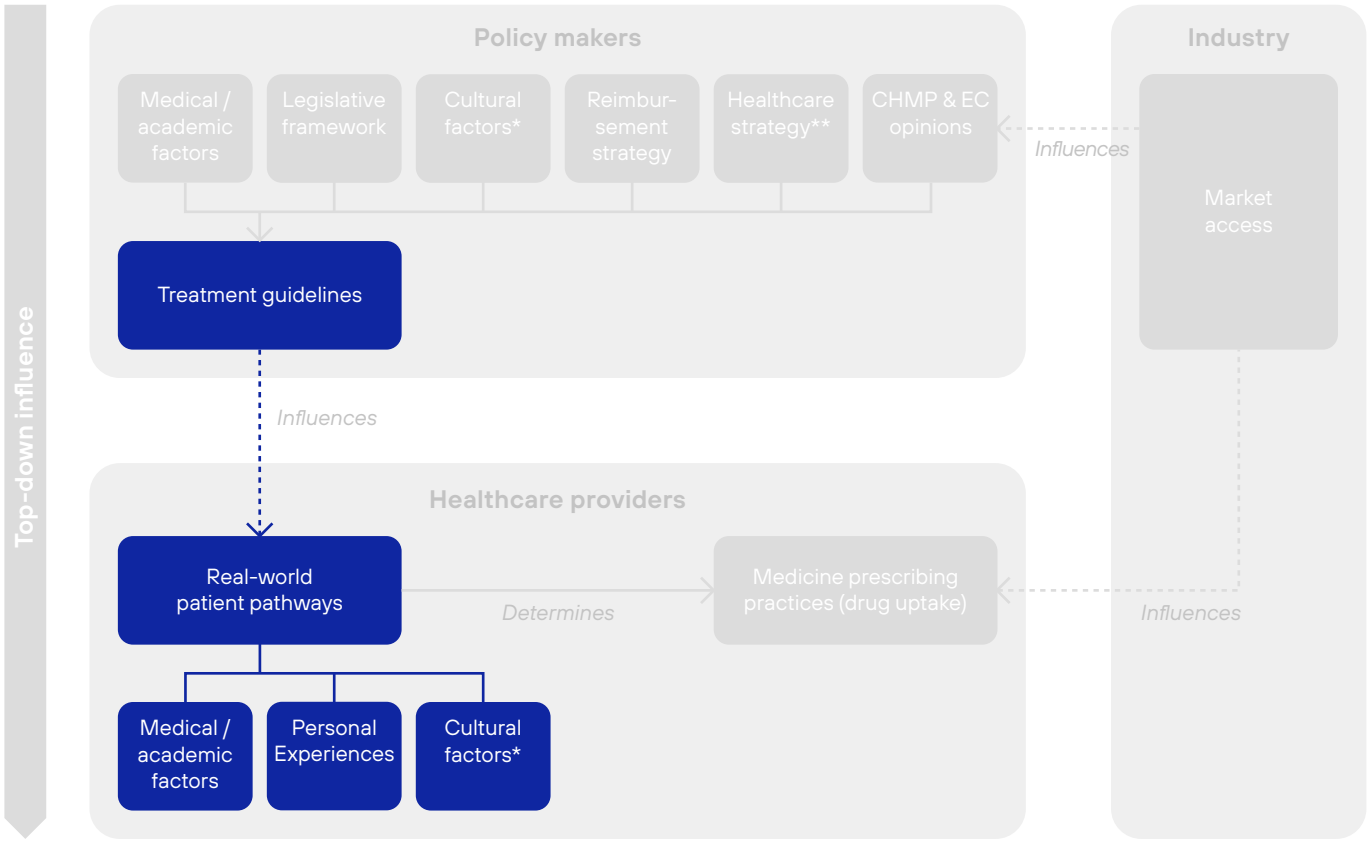


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Figure 2: Conceptual framework of drug uptake dynamics and correlations – influences of variation in treatment guidelines and personal factors on real-world patient pathways

To explain this point, an analysis of European guidelines was carried out for breast cancer. Advisories were observed at the country level (and in some cases at the regional level) on the use of selected breast cancer drugs. In the analysis, a relatively novel group of breast cancer drugs, known as CD4/6K Inhibitors palbociclib and ribociclib, were taken into consideration, as well as the more established and widely prescribed targeted drugs such as pertuzumab, trastuzumab and trastuzumab emtansine (figure 3).

Treatment guidelines on selected breast cancer medicines across 5 European countries (May 2022)

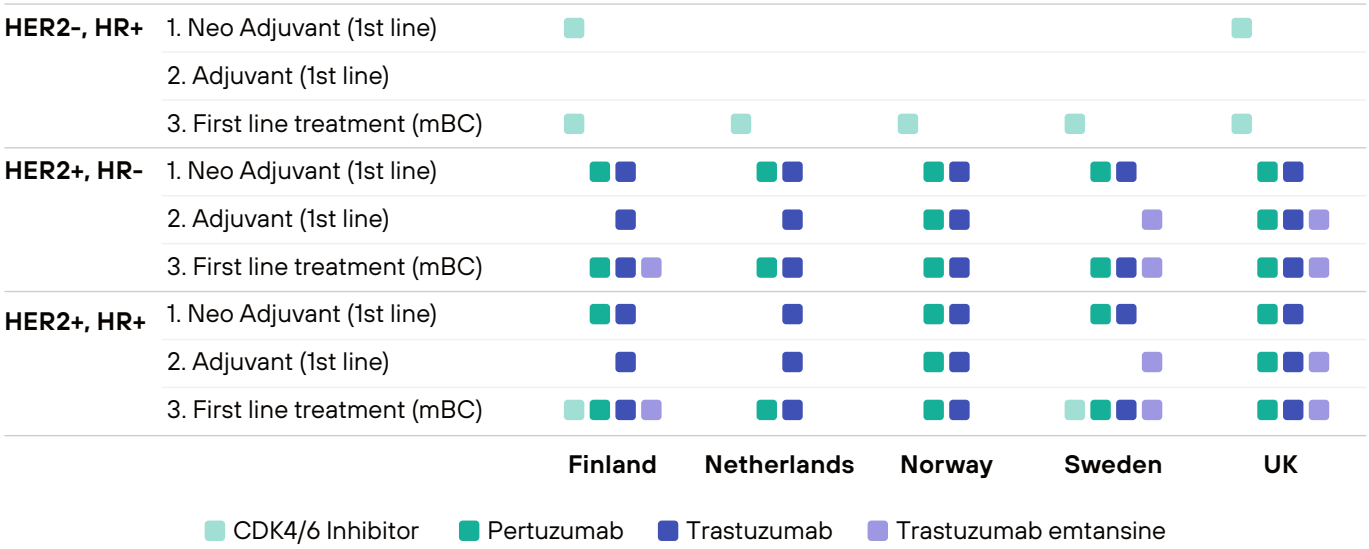

Figure 3: Overview of guideline recommendations on breast cancer drugs

- HER2-/+ status indicates the presence of the human epidermal growth factor receptor 2 in the cancer cells
- Neo Adjuvant treatment refers to any treatment delivered before the primary treatment
- Adjuvant treatment refers to any treatment delivered in addition to or after the primary treatment
- First line treatment (mBC) refers to the first treatment delivered after metastasis have been diagnosed

It appears that some countries lag in the protocolisation of both new and old therapies, even when a medical consensus on safety and effectiveness is established. It is also interesting to notice that countries endorse different indications, even in the case of established medications. In some instances, guidelines leave doctors a broad leeway to determine the medicines to use, while others are stricter. This is especially the case when driven to compliance with reimbursement agreements.

This simple example indicates that a global consensus on therapeutic modalities across therapeutic areas is often missing, causing variations in the guidelines.

Drug uptake varies significantly, resulting in suboptimal patient outcomes

Alongside some diversity at the regulator level, there is also a wide variation in the eventual use of therapeutics, even in highly developed academic centres[8].

A report that clearly shows the differences in drug uptake across borders is the Comparator Report on Cancer in Europe 2019 published by The Swedish Institute for Health Economics (IHE)[9]. A central insight highlighted in this report is the patient's access to both traditional and new medicines in Europe. We will be focusing again on a breast cancer example using the same set of countries (figure 4). Significant international differences in drug uptake levels of CDK 4/6 inhibitors, Pertuzumab, Trastuzumab and Trastuzumab Emtansine can be observed.

The role of treatment guidelines is indicated by the authors of the study as one of the main explanations of the variation. However, it is interesting to note that variations in terms of drug uptake do not directly correlate to variations in terms of guidelines. In some cases, uptake of drugs yet to be protocolised

Medicines sales of selected breast cancer medicines across 5 European countries (2018)

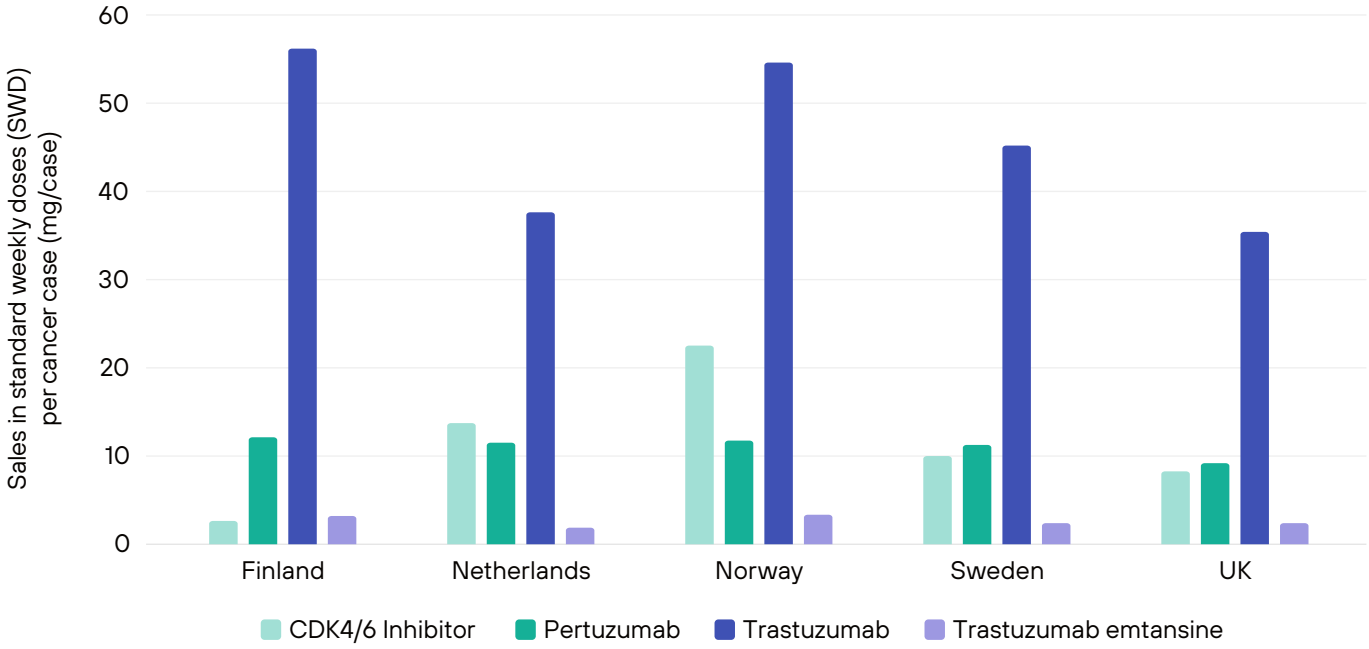

Figure 4: Drug uptake of breast cancer drugs in 2018

in the guidelines was recorded[10]. This proves that the real-world behaviours of healthcare actors seen in the light of uptake are only partially influenced by top-down guidelines.

It should be noted here that the drug uptake levels as shown in figure 4 are based on sales figures and may not be representative of the actual use of the medicines as drugs may be used for inventory, or dosage may differ per guideline recommendation.

Another analysis carried out by LOGEX can be used to showcase the variation in medicines uptake. LOGEX was commissioned by NHS England to help form a sound methodology to determine and compare medicines uptake across several markets[11]. We delivered a medicines uptake methodology that was applied to compare England for five different medicines against ten other European countries. The method and analysis were recognised as a step up

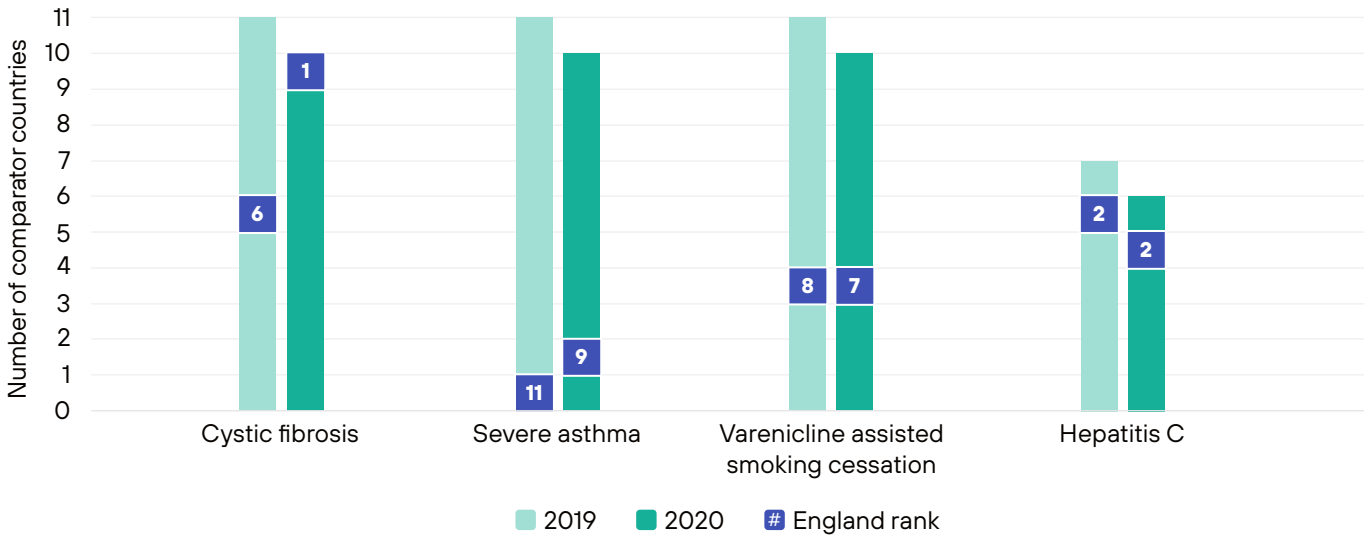

Figure 5: Number of comparator countries and England rank in the International Medicines Uptake Comparator (IMUC)

in how one can objectively compare medicines uptake across countries and disease areas.

In the above figure, we see how England fares in terms of medicines uptake as compared to 10 different European markets in cystic fibrosis, severe asthma, smoking cessation, and hepatitis C.

Variation in medicines uptake is recognised as one of the main drivers of patient costs as it prevents the creation of economies of scale and transparent prices[14]. It can also cause inefficiencies in the purchasing and use of medicines, diagnostics, supplies and devices at primary and inpatient level[12]. This in turn is related as well to suboptimal patient outcomes, such as increased mortality, higher reoperation rates, and less time to next treatment[13].

It should therefore be a top priority for all healthcare systems to eliminate variation in uptake.

The role of real-world evidence in reducing unwarranted drug uptake variation

It is understood that unwarranted uptake variation is causing a great detriment to both healthcare outcomes and finances – but how can real-world data be used to tackle it and steer away from the risks of empiricism?

In our framework presented above, we see how treatment guidelines, shaped by a variety of influencing factors, attempt to influence prescribing behaviours and patient pathways.

We can also observe that:

1. Guidelines are a top-down way for regulators to influence real-world clinical decision-making. But other drivers, such as physicians' personal experiences, medical/academic factors and cultural elements, may influence doctors' decisions. As a consequence, treatment guidelines are therefore only partial influencers of treatment pathways.
2. There is cross-country (or cross-regional) variation also in terms of guidelines as often there is no consensus across countries on what therapeutic regimes could provide the best patient outcomes, or there is a lag in the protocolisation of effective therapies due to reimbursement reasons or other factors.
3. There is significant variation in the use of medicines across countries and disease groups. We find that unwarranted treatment variation is frequently related to poor patient outcomes and increased costs, causing great damage to the systems and patients.

Luckily, healthcare stakeholders can benefit from an ever improving quality of data, availability of highly advanced data analytics tools and sophisticated algorithms. This has corresponded with a surge in the utilisation of real-world evidence, as physicians and policymakers seek to understand the difference in clinical practice and tackle variation.

Through real-world data, regulators can learn from the physicians, understanding what therapies are the most effective and in what time/sequence for a granular cohort of patients. Clinicians themselves can even better understand what prescribed medicines are the most efficacious and cost-effective, benchmarking their performance with peers.

Drug manufacturers, that are interested to learn more about the use of their therapies beyond mere sales figures, via RWE have the possibility to better understand where the care gaps are in the patient treatment journeys and develop better-targeted products.

Observatories on drug uptake and prescription patterns can help establish a virtuous learning cycle, where drug uptake and outcomes influence the "living guidelines" which in turn guide clinicians in a reliable, constantly updated way.

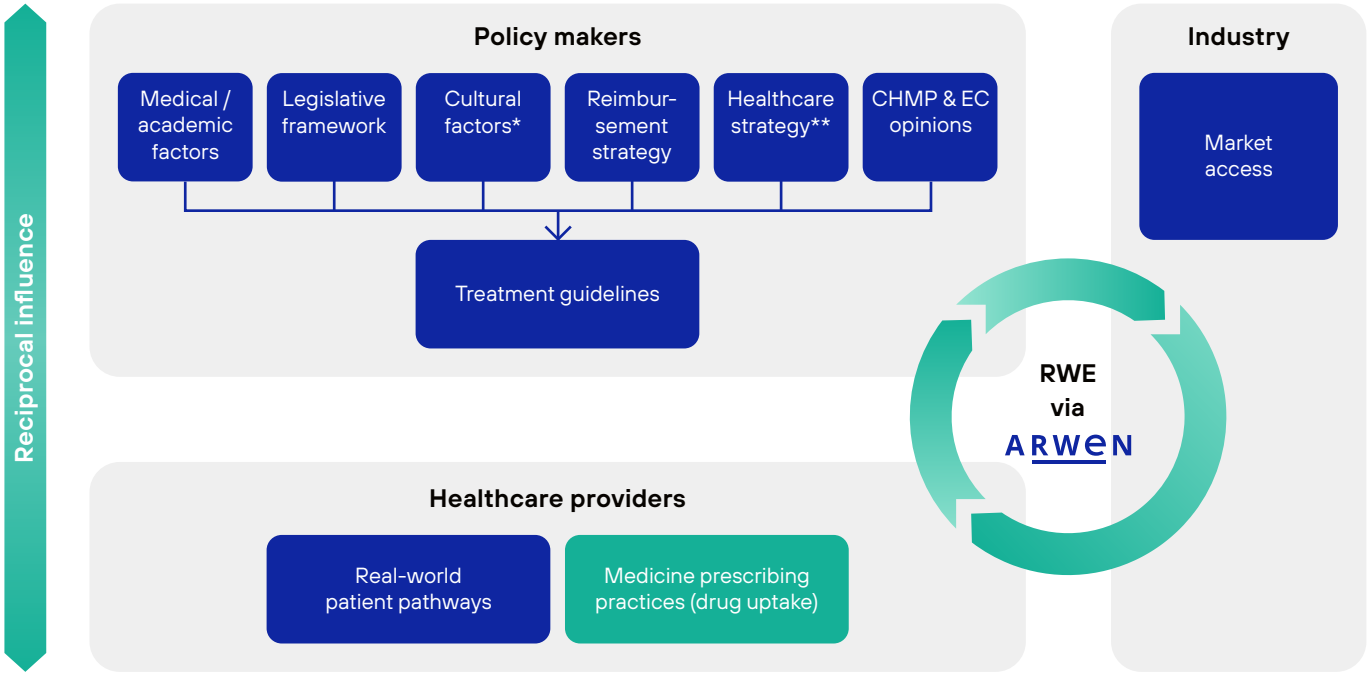

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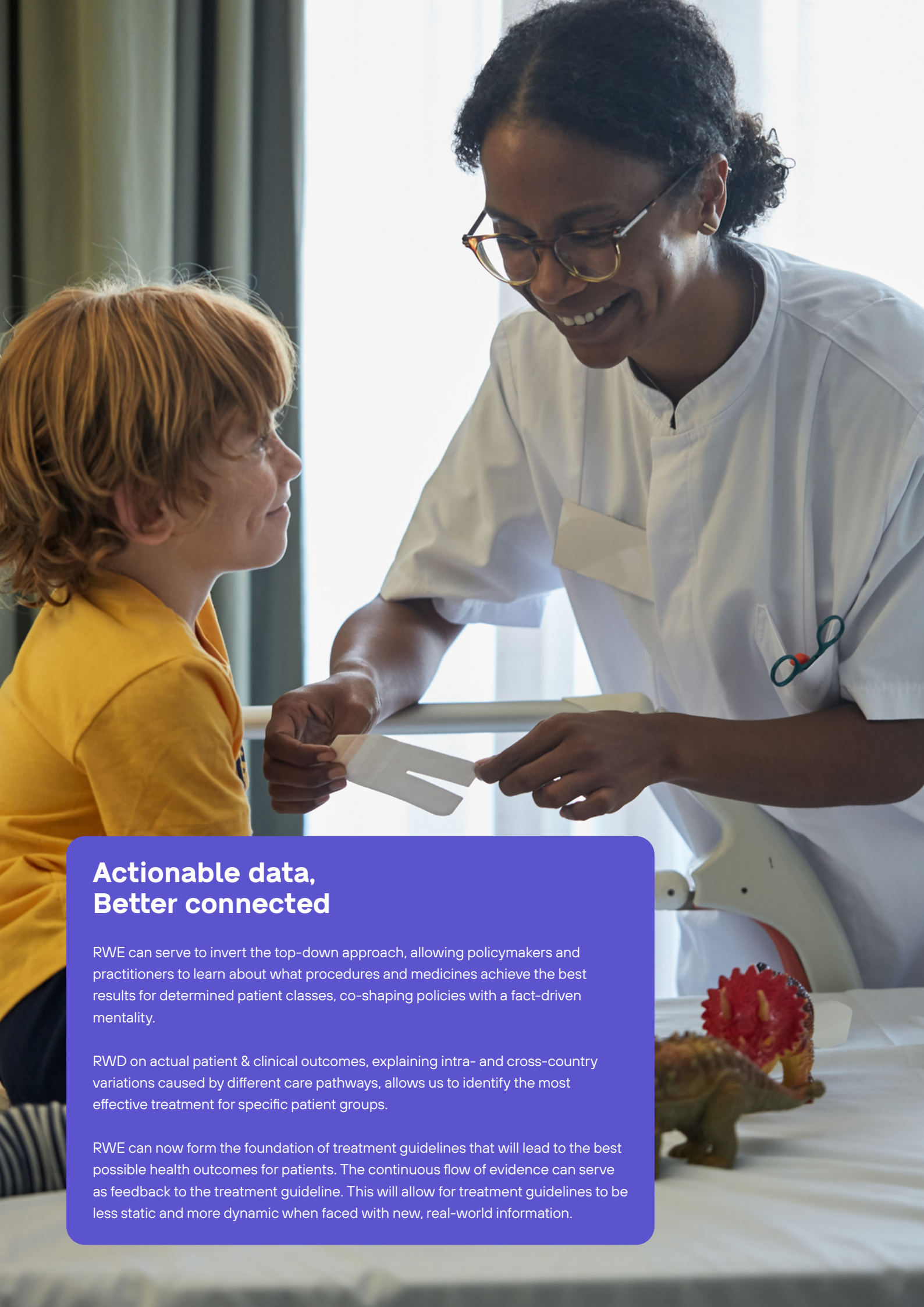
Figure 6: Conceptual framework of drug uptake dynamics and correlations – real-world evidence as an enabler for establishing best practices in healthcare and creating reciprocal influence between policy makers, healthcare providers, and industry

How real-world evidence differs from randomised controlled trials

In traditional life sciences research, patient data is collected during randomised controlled trials (RCTs) that are designed to only collect pre-defined data types during a limited period. This way, data is collected in a standardised and structured manner from a specific, defined and randomized patient population. This approach has been the golden standard to study the efficacy and safety of medical treatments for regulatory approval and market authorisation purposes. However, RCTs can be limited and challenged in explaining the variation in guidelines and its impact on drug uptake as it is in essence experimental rather than the real world.

Real-world evidence (RWE) is the evidence derived from real-world data (RWD). It includes any data gathered outside of the highly-controlled clinical trial conditions and captures the context in the actual setting of medicine prescribing and its use. Some of the RWD sources include patient health records, administrative records, insurers' claims data, patient surveys, observational cohort studies and digital health technologies.



Actionable data, Better connected

RWE can serve to invert the top-down approach, allowing policymakers and practitioners to learn about what procedures and medicines achieve the best results for determined patient classes, co-shaping policies with a fact-driven mentality.

RWD on actual patient & clinical outcomes, explaining intra- and cross-country variations caused by different care pathways, allows us to identify the most effective treatment for specific patient groups.

RWE can now form the foundation of treatment guidelines that will lead to the best possible health outcomes for patients. The continuous flow of evidence can serve as feedback to the treatment guideline. This will allow for treatment guidelines to be less static and more dynamic when faced with new, real-world information.

The world is diverse, real-world data is diverse
It is important for users of RWE to understand its nature and purposes. Such data is often not registered for analytical purposes. Instead, it often comes from administrative, financial or logistic IT infrastructures. Dealing with RWD means dealing with the heterogeneity of the real world. Critical to quality RWD is the ability to handle big hospital datasets and harmonise and validate these complex real-world datasets for healthcare measurements. Once this is accomplished, RWE can disclose a set of deep, longitudinal and actionable insights that RCTs cannot achieve, expanding the possibilities of how data can support care givers in their daily practice.

Essential evidence
RWE will not only help policymakers and physicians determine and choose the optimal care pathway. It can also lead to the improvement of the optimal care pathway. When used appropriately, RWE also dramatically improves drug development, pricing, and access.

The true power of RWE
As we discussed, the use of RWE can lead to better treatment guidelines, improved standards of care and prescription habits. All of these benefits are immensely important for improving healthcare. The widespread use of RWE in medical decision-making at all levels grows the knowledge about what works and what does not work quite as well. This knowledge consolidates consensus around best practices that can then be reflected in treatment guidelines. As a consequence, unwarranted variation can be truly understood and reduced with a conscious and proactive approach.

Making an impact with RWE
Our belief in the central role of RWE in today's healthcare system is based on extensive work around treatment pathways in diseases such as breast cancer. For breast cancer, we found that real-world patient pathways can capture an objective, holistic, quantitative view of the real-world journey of the patient from physical examination in a breast clinic leading to diagnosis to assessment that involves pathology, clinical, radiological, and biopsy by multi-disciplinary teams (MDT). It exposes details on treatment strategies and lines of treatments deployed in different settings – neoadjuvant, adjuvant, and post adjuvant. It lists specific surgical treatments, local or systemic, biologic therapy or chemotherapy. It details follow-ups and subsequent hospital visits in both inpatient and outpatient settings, including surgeries such as breast reconstruction. Holistic determination of best practice guidance and improvements to prescribing practices over time can therefore be made with confidence.

Overcoming the challenges and making RWE accessible around Europe
We do realise RWE is not necessarily easy to come by. Some of the biggest challenges with generating RWE today include the limited availability of RWD and the poor quality of available data for many diseases. Besides that, RWE currently lacks well-established methodological standards and regulatory frameworks. As a consequence, RWE tends to suffer from overly complex project designs.

In an attempt to increase the availability and usability of RWD, LOGEX recently introduced ARWEN, the Actionable Real-World Evidence Network. This network aims to make it easier for hospitals to safely and efficiently share RWD for research. At the same time, the network helps researchers secure the RWD they need for their studies. More information about ARWEN can be found on www.arwen.eu.

Conclusion

We have seen that unwarranted variations in clinical outcomes across Europe are caused mainly by variations in national treatment guidelines and by insufficient adherence to the treatment guidelines. In turn, guidelines are generally set in a top-down way and do not learn from real-world clinical practice.

We believe RWE can play a vital role in addressing these variations. The study of real-world patient pathways in the context of treatments delivered to patients can help address this vacuum of knowledge of underlying drivers of pathway variations and their impact on patient outcomes. It allows doctors to be better informed of which treatments have been most effective, and for policymakers to understand how to best organise access to treatments within different care settings. It can provide the feedback necessary for changes to guidelines and further access to patients based on evidence of medicines' effectiveness in real-world settings.

Real-world evidence of patient pathways can shape a virtuous cycle that closes the gap in understanding what policymakers, providers and industry face. This cycle will, over time, allow for refinement of treatment guidelines, maintain relevance to prescribers and better inform and drive continuous service improvements in patients' pathways with ever more specific knowledge.

The way forward:
ICDU, a tangible and open approach to measure drug uptake and tackle un-warranted variation with RWE

Based on data from LOGEX's ARWEN hospitals, LOGEX will study and report on various matters of uptake with a series of reports – International Comparator of Drug Uptake (ICDU). With this, we commit to inform European healthcare stakeholders, from regulators to clinicians to life sciences, how medicines are being used in different countries. This is made possible thanks to the commitment of our ARWEN members that allow us to generate vital insights that will help us understand and reduce the unwarranted variation in drug uptake, improving the lives of patients.

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