trial data and provide different insights into how a drug works."

Ultimately, when striving for an accurate valuation of a drug, RWE provides a much more complete picture. The sheer heterogeneity of the potential user base of any drug means that we will never fully understand the full breadth of its benefits and risks on feasible timelines through RCTs alone.

In NICE's 'Statement of intent', these are identified as "contextual factors", and would be crucial in accurately determining the value of a product in particular sub-populations of patients.

The statement reads: "The observed discrepancy between the effects of a health intervention in routine clinical practice (effectiveness) and the effects demonstrated in RCTs (efficacy) is known as the 'efficacy effectiveness gap'.

"Contextual factors that interact with the effect of an intervention are known as drivers of effectiveness. These factors can contribute to an efficacy effectiveness gap. There are three levels of contextual factors:

- The actual use of the intervention (for example, adherence, co-medication, dose/intensity, duration of use)
- Patient and disease (for example, age, gender, behavioural factors, baseline risk, genetics, severity of disease, comorbidities)
- Healthcare system (for example, implementation, medical practices, screening policies)"

These are factors which, by nature, cannot be evaluated in randomised controlled trials, given their purpose of providing a controlled microcosm of the real-world intent-to-treat population, and these microcosms are not always proportionately representative. This can lead to distorted evaluations of a product's efficacy, which in turn can skew any potential assessment of its value.

"RCTs may not always reflect these contextual factors, and high-quality observational data may better indicate the expected effectiveness in routine clinical practice," the statement continues. "For most decisions relevant to NICE guidance, the expectation is that the efficacy measured in well-designed trials will be greater than the effectiveness derived from analysis of broader types of data. This is because in routine practice characteristics such as age, comorbidities and adherence are more likely to reduce the effectiveness of the intervention compared with trial settings than enhance it. Qualitative data sources may also provide useful contextual information, for example by providing detail on any challenges in delivering an intervention or on the experiences of patients."

Seeking guidance

The benefits that RWE can bring to transforming the value equation in drug access are clear and the wheels are turning on ever-increasing adoption from trial designers and regulators. But what still needs to be done to bring this invaluable data source into the spotlight?

As the MHRA explained, the Academy of Medical Sciences convened a roundtable in 2018 to determine the next steps for the use of RWE in regulatory decision-making. It found that the industry is still looking for external guidance on how best to apply it, and this may prove to be one of the most pressing needs to be addressed in future if we are to fully harness its potential.

Medical devices and their growing regulatory challenges

NDA

Tina Amini, Division Director Medical Devices at NDA Group and former Head of Notified Body and Certification Authority at LRQA, explains what companies need to look out for in the growing area of device regulation:

Recent scientific advances and improvements in enabling technologies have opened new avenues for convergence among medicines, diagnostics, and devices. The medical technology industry continues to be one of the most diverse and innovative sectors.

Major shifts in the health care environment including regulatory requirements make it increasingly difficult for medical technology companies to sustain traditional growth and profitability.

Why can we say that the regulatory challenges in the medical device field are growing?

"With the introduction of the new Medical Device Regulation (MDR), and the pending In Vitro Diagnostics Regulation (IVDR), the regulatory landscape in the EU has undergone tremendous change. The new situation gives rise to uncertainties and unknowns and it will take time before it settles and becomes predictable again."

Why was the new regulation introduced?

"The new regulation aims to boost patient safety and effectiveness of all the medical devices that are commercialised but also to increase transparency to make the process clearer to everyone involved.

"Shortcomings in the Directive in divergent interpretations also resulted in different output from the notified bodies. The new regulation attempts to address this as well."

How does the new regulation change the European device market?

"The situation is currently uncertain. The delay in the database EUDAMED, an insufficient number of designated notified bodies, and lack of sufficient guidance documents are all causing challenges. There is a lot of guess work awaiting official decisions and guidance. It is, however, certain that the new regulations will bring substantial change to how medical devices are brought to and maintained in the market.

"The regulation also impacts the notified bodies as they have to be re-designated under new regulations. The time and cost associated with this has actually resulted in some notified bodies not applying for designation under the new regulations.

"Up until now only eleven notified bodies have been designated under MDR, and three under IVDR and not all with full scope, compared to about 80 notified bodies that were operating under the MDD in the early 2010s. Today, there are not enough notified bodies to pick up all the work. For companies this means longer timelines as you queue to have your product reviewed. We're already seeing the manufacturers struggling to find a notified body to take them on."

How is all this affecting the manufacturers?

"Much greater emphasis has been placed on clinical data, clinical evaluations and post-market surveillance and this must be reflected in the manufacturer's technical documentation and quality management system.

"The regulation has also resulted in up-classification of several medical devices such as medical device software and certain devices with ancillary medicinal substances for instance.

"The in vitro Diagnostic Devices Regulation will have an even greater impact, with over 80% of IVDs requiring notified body involvement."

How will pharma and biotech be affected?

"Pharmaceutical companies supplying drug delivery devices in combination with their medicinal products, such as pre-filled syringes and pen injectors are directly impacted. It will also impact device manufacturers supplying these drug-delivery devices to pharmaceutical manufacturers for inclusion in medicinal products.

"To date, these companies only got approval from the competent authorities or European Medicine Agency (EMA), but will now have to seek opinion from the notified bodies for the device aspect as well. For most, interaction with notified bodies is a new process and they are unfamiliar with the data package that must be submitted to notified bodies. This can impact the total project timelines."

How does NDA's Medical Device Division support companies with these challenges?

"There are some specific challenges that we can help with, such as support with notified body interactions and assessing the product from a scientific, technical, and regulatory perspective to be adequately prepared to meet the requirements. At the backend of this is our extensive experience with both medicines and medical devices. At NDA Group, we understand the challenges and have the solutions.

"We have expertise to help manufacturers to implement the requirement of the MDR and IVDR regulations. That's fundamentally why we formed this new division – to expand our support to both pharma and medtech companies."

Do you think that NDA can help to minimise the waiting time for the notified bodies?

"Yes – purely by identifying gaps and making sure that the quality systems and submitted documentations are per regulations' requirements. With the long queues it is better knowing exactly what documentation to submit. Then you get less questions from the notified bodies and this can save a lot of time."

What do you think the future holds in this space?

"The challenges we are seeing right now will not disappear in the near future – it will take time. But longer term there should be safer and better performing devices in the market and a more harmonised approach by the Member States and the notified bodies.

"The situation may lead to manufacturers reducing their product portfolios as the cost of maintaining the devices on the market under new regulations have increased or the medical devices prices might change. Delays in market entry can introduce risks to the SMEs that could reduce their willingness to innovate and bring new products to the market.

"I do not envisage too many certificates being issued under MDR short term. But we will see a rush in 2023 and early 2024 as we get closer to the end of validity of certificates issued under the directive.

"Eventually, we will reach a new status quo where the new practices are more evenly harmonised and the process more predictable. We have however entered a time where device regulation has raised the bar for anyone who wants to enter the market and the need for the right expertise and advice will not go away."