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Adaptive Pathways and Real-World Evidence: Three Perspectives

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With a healthcare landscape driven by the advent of precision medicine and empowered patients, it would seem that "science has overtaken the system". This includes the recognition that patients are often willing to accept greater risks from treatment of life-threatening and severely debilitating diseases in return for earlier access, especially when there are no alternative treatments available. This underlines a "need for speed" in biomedical innovation: more rapid development, accelerated approval and – crucially – timely access to transformative medicines. These developments challenge established clinical development pathways and put pressure on regulatory and particularly HTA (health technology assessment) processes.

In response, paradigms of biomedical innovation are being transformed with "Adaptive pathways", which encompass earlier crisis-stakeholder engagement, including patients, early access regulatory tools, and iterative evidence generation through the life cycle of the medicinal product with an expanded toolbox: pragmatic and real-world studies complementing RCTs where the collection of data through traditional routes is difficult, e.g. in rare diseases and in increasingly fragmented populations.

In order to achieve equitable and timely access to transformative medicines for patients with unmet needs, rapid market access and reimbursement in step with earlier conditional marketing authorization is just as essential. However, the uncertainty about whether the anticipated clinical benefit will be verified in clinical practice and the possibility of undiscovered risks pose serious challenges to payers and HTA bodies. With greater uncertainty, a novel medicine's lifetime price should no longer be determined at first market entry for a limited population, but be governed by more flexible and adaptive approaches to pricing and reimbursement that reflect the emerging evidence generated.

Patient-centered real-world evidence (RWE) presents a significant opportunity to enhance early access regulatory decision-making as well as adaptive value-based contracting centered on mutually agreed outcomes. Technological advances permit the collection of real-world data (RWD) from an increasing number of sources and platforms, while refined observational methodology and next generation analytics enable the translation of these data into RWE. Nonetheless, opinions on RWE remain diverse. Questions raised by stakeholders concern the methodology, reliability and the usefulness of RWE in decision-making, particularly regarding treatment effects. Based on these criticisms, it seems that RWE still has some way to go before becoming established as a universally accepted complement to ransmoized controled trial (RCT) data for benefit/risk and value decision-making.

At last year's ISPOR 20th Annual European Congress in Glasgow, UK, a panel offering "three diverse perspectives" — patients, payers, and biopharma — debated how the spectrum of stakeholders can improve the process of demonstrating benefit/risk and value in the challenging environment of adaptive pathways with less data and greater uncertainty; the role of real-world evidence (RWE) to support conditional authorization and early market access; the current limitations to implementing value-based MEAs in Europe and potential ways forward; and the role of the patient community to enhance early access initiatives as mediators and decision-makers on national and European levels. Highlights from the panel debate are presented below.

Nicola Bedlington, Secretary General, European Patients' Forum and Co-Founder, The Patient Access Partnership PACT, Brussels, Belgium ("the patients' voice"): Adaptive Pathways, as defined by ADAPT SMART, foster access to beneficial treatment for the right patient groups at the earliest appropriate time in the product life-span in a sustainable fashion. They are of interest to patients as they offer the opportunity to address the bottlenecks evident in standard pathways. Patients have a role throughout the entire development lifecycle. Participation in early dialogues is crucial, given that patients have different perspectives on benefit/risk from the other stakeholders. Patients – and caregivers – are willing to accept greater risks, however not at any cost. We cannot be cavalier regarding safety and need to consider patient preferences for trade-offs between earlier access and potential risks. These preferences are not static or linear. Expectations and perceptions of benefits and risks change over time and according to age, illness, role in society, culture.

Patients equally have a role in defining the value of an innovation, in determining the significant added benefit of a novel treatment. Patient empowerment is thus part of the drive towards sustainability of our health systems.

Ad Schuurman, MA, Senior Medical Officer, EMA, London, UK, Head of the International Department, National Health Care Institute (ZIN), The Netherlands ("the payer perspective"): Payers share the concerns regarding sustainability. The pace of biomedical innovation is higher than it has ever been before. These faster advances are good for patients, and we welcome the patient voice. But there needs to be a balance, some patient groups are very organized, however, we are also responsible for those patients that are not as vocal. It is our responsibility to have control over costs, and what you spend on one patient, you do not have for the other. The dynamics are so quick and the standard of care changes so rapidly, that we are at risk of losing control, not knowing what we are paying for in the hospital setting.

This is also connected to the ways we assess data and the quality of evidence, which is becoming quickly outdated in this highly dynamic environment. And we do not have new ways of assessing RWD in place in Europe. There is a lot of promise in real-world evidence, but we do not see it, cannot use it yet. So Adaptive Pathways are of interest to payers if we can regain a measure of control in the funding of innovations. They should be restricted to special cases, where there is a high unmet patient need, or an urgent public health requirement, and where we expect a major improvement over current options.

Rob Thwaites, MA, MCom., Senior Director, Takeda, London, UK ("the Biopharma Viewpoint"): It has traditionally been industry's role to generate data, and we should produce evidence on the unmet needs as well as the value a new compound is expected to bring in addressing the patient needs. This real-world evidence (RWE) complements the randomized clinical trial data and supports an iterative scientific development in Adaptive Pathways. Companies in the pharmaceutical industry have been introducing more systematic approaches for effectiveness planning, incorporating real-world research into the activities of the project teams for drugs in development. This includes engaging earlier in scientific advice processes, not only with regulators but also with HTA agencies and patient organizations, even where the range and disparity of evidence needs may well give rise to concerns that the manufacturer will not be able to meet all needs.

At the same time there are a number of areas of RWE that require further development, including the methodological approaches, the quality of the evidence, and the data sources. There is also the issue of acceptability of RWE, which differs between stakeholders and countries.

Bedlington: This is a key issue, while stakeholders can generally agree on the unmet need, their evidence requirements differ substantially. Can we align regulatory with HTA/payer data needs, and develop a fair framework to define the value and the pricing of innovations, as well as a set of basic principles that all stakeholders can agree on? We should utilize the opportunities and all the work that is ongoing, for example within IMI's Big Data for Better Outcomes (BD4BO) program.

Schuurman: There are many reasons for the differences between countries, and these will persist. Alignment is relatively unlikely. Payers are often not involved, and even though there is 80-90% overlap in data needs between HTAs and payers, priorities differ. Some countries will assess RWE, while others do not, and may never do so. Perhaps for orphan drugs there is a chance for greater consensus as there is a culture of international collaboration within the European rare disease networks.

Adaptive Pathways will require new and adaptive reimbursement strategies with mutually accepted prices. This could be managed entry agreements (MEAs) with conditional reimbursement at an initial level, which will be re-assessed once the data has matured, leading to a higher or lower price, or no reimbursement, if the initial promise of the innovation is not confirmed. This also includes realistic exit strategies which are clearly agreed upon in advance between all stakeholders. Especially patients and doctors need to be aware of this.

The main problem is that the payers do not have the resources to manage these MEAs in a proper way, which is why we must focus on the most urgent cases with the greatest unmet need. In addition, as mentioned, we do not have the structure to assess the outcomes data. This is why most of the current MEAs are financial- and not outcomes-based in Europe. We must therefore re-think the assessment of value of therapeutic innovations, focused on the outcomes achieved.

Thwaites: Agreed, we still have a long way to go regarding value-based MEAs. We have seen from the Italian experience with these agreements that building the infrastructure to collect the necessary data is not straightforward. Is there an appetite for MEAs within senior levels of management in pharma? I think so, but we need to see positive examples of how MEAs could work.

Schuurman: Payers will need to push the issue by increasingly saying "no" to the traditional pricing models.

Bedlington: The patients' role in MEAs is to share their health outcomes data. Particularly those with serious and chronic conditions are willing to do so. Wider citizen groups are more critical, and we should make greater efforts to shift public opinion toward a more positive approach to research. EUPATI is doing this with a multi lingual toolbox on medicines R&D.

EUPATI has also educated about 100 patient-experts through an expert level course, and 60 more patients will graduate later this year. We are fostering patient engagement throughout the development life-cycle, with patient advisors as equal partners at the table with EMA, HTAs, payers and pharma.

There is much to do: massive challenges persist across Europe to equitable and timely access, not just to innovative medicines but also to the most basic care. This "post-code lottery" is unacceptable in the 21st Century and we must address this. It's a human rights issue, nothing more, nothing less.

David Schwicker, MA, Principal, ORPHA Strategy Consulting, Basle, Switzerland, was the panel's moderator.

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