

***How Can Health Technology
Assessments in the Asia-Pacific Area
Respond to Increased Clinical
Uncertainty as a Consequence of
Expedited US and EU Regulatory
Processes?***

... Is Risk-Sharing the Answer?



HTAi Conference, Tokyo, May 2016

Panel session presenters:

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Professor Arnold Chan – Health Data Research Center, Taiwan

Professor Adrian Towse – Office of Health Economics, UK

Chaired by: Dr Franz Pichler – Eli Lilly & Company, Australia

About HTAi

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About this report

The HTAi 2016 annual meeting was held in Tokyo on 10–14 May, with the theme “Informing Health Care Decisions with Values and Evidence”. This report summarises a panel session entitled “**How Can HTAs in the Asia-Pacific Respond to Increased Clinical Uncertainty?**” which took place on Thursday, 12 May. The session was developed by the Regulatory Interactions and Conditional Coverage Interest Group (RICC IG); instrumental to the development of the panel was the RICC vice chair Professor Urs Brügger. The concept for this panel stems from a discussion initiated by Adriana Platona (Australian Department of Health) and Michelle Mujoomdar (CADTH) during a workshop on Adaptive Pathways held at the 2015 HTAi Annual Meeting in Oslo. This workshop was developed in collaboration between two former interest groups that have since merged to form the RICC IG.

The report has been approved by all presenters to be put forward as a public record of the HTAi panel session.

Funding was received by OHE from Eli Lilly and Company, to produce a record of this panel session in the form of this report.

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1. INTRODUCTION

This report provides a detailed summary of a panel session which took place at the HTAi 2016 annual meeting, Tokyo. The panel session was entitled “How Can HTA in Asia-Pacific Respond to Increased Clinical Uncertainty as a Consequence of Expedited US and EU Regulatory Processes?” and was chaired by Franz Pichler (Eli Lilly & Company).

2. BACKGROUND

The research and development (R & D) pipeline for new medical treatments is evolving. One important factor is that therapies are becoming increasingly stratified, with the result that treatments are being made available for smaller patient populations who have high unmet need. Governments are therefore being challenged to establish regulatory pathways that can accommodate the clinical uncertainty associated with many of these treatments, paired with the urgency of their demand, for patients who currently have no treatment alternatives.

Across the globe, but in the US and Europe in particular, regulators have responded by developing regulatory pathways that can expedite patient access. In the US, an important scheme introduced by the Food and Drug Agency (FDA) is the “Breakthrough Therapy Designation” (BTD). In the EU, the European Medicines Agency (EMA) has introduced various mechanisms. These are introduced briefly below.

2.1. Regulatory mechanisms to expedite patient access

2.1.1. FDA “Breakthrough Therapy Designation” (BTD)

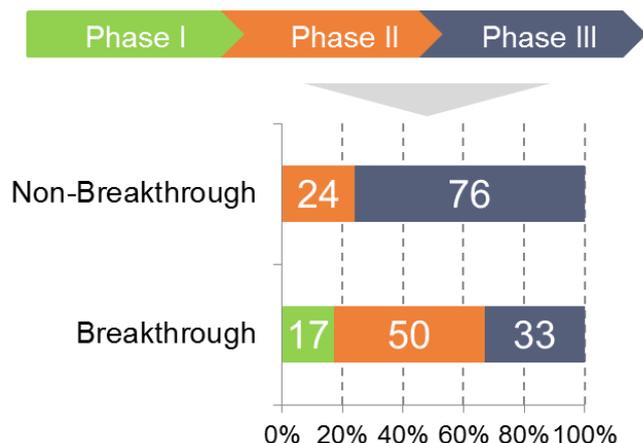
The FDA introduced BTD in 2012 as part of the Safety and Innovation Act: FDASIA. To be eligible for BTD, the drug must treat a serious or life-threatening disease or condition, and preliminary clinical evidence must indicate substantial improvement over existing therapies in one or more clinically significant endpoints (FDA, 2014). Preliminary clinical data are generally from Phase I or II clinical trials. For therapies that receive BTD status, intensive guidance is offered by the FDA on efficient drug development, which is intended to make the development programme significantly shorter without compromising the need to generate adequate data to demonstrate safety and efficacy for marketing-authorisation purposes. This includes advice and support for efficient (smaller and/or shorter) trial design. The FDA assigns senior managers and experienced project management staff, and offers rolling review which can allow portions of the application to be reviewed as they become available.

By providing intensive guidance and collaboration between the FDA and developers, the aim is for development times to be reduced and therefore access to be brought forward. Of the over 100 drugs granted BTD, over 30 had gone on to receive marketing approval by the end of 2015 (Shea et al., 2016). One-third of these were anti-cancer agents. By comparing the characteristics of novel anti-cancer drugs approved with and without BTD between 1 January 2013 and 31 December 2015, Shea et al. (2016) determined that, of the 29 anti-cancer drugs approved, 12 (41%) had been granted BTD. This means that a significant portion of new cancer drugs are being routed through this expedited

programme, for which pre-market development time has been shown to be reduced by 2.2 years (median of 5.2 years, versus 7.4 years for non-designated drugs).¹

While it is purported that criteria for marketing approval are not affected by BTD status, in reality 66% of oncology drugs with BTD are obtaining approval based on Phase I or Phase II clinical trial data (n = 8), versus 24% of non-designated oncology drugs (n = 4) that were approved based on Phase II data and none on Phase I data. This is shown in Figure 1.

Figure 1. Phase of development at FDA market authorisation of oncology drugs



Source: Shea et al. (2016).

2.1.2. EMA mechanisms: PRIME, CMA, Adaptive Pathways

The EMA formally launched PRIME (PRiority MEDicines) in March 2016 which, similarly to BTD, supports the development of medicines that target unmet medical need. The scheme is voluntary, and based on enhanced interaction and early dialogue between the EMA and developers to optimise development plans and speed up evaluation, with the aim of securing earlier access for patients (EMA, 2016b). Within its first month (up until 6 April 2016), the EMA had received 18 applications for PRIME, of which four medicines had been accepted onto the scheme. Given that the scheme has only recently been launched, it is difficult to anticipate its impact on evidence availability and development times.

In addition to PRIME, the EMA is able to provide temporary marketing authorisation which is valid for one year, through their existing Conditional Marketing Authorisation (CMA) scheme. The CMA holder is obliged to complete specific data-collection obligations to confirm that the benefit–risk ratio is positive.

More innovative is the EMA’s Adaptive Pathways, which was launched in March 2014 as a pilot project. This programme is also aimed at improving timely access to new medicines, but through an iterative development process. This involves approval in stages, beginning with approval for restricted patient populations, and then gradually expanding the license as further data are collected (EMA, 2016a). Another key element to this pilot is the early involvement of patients and health technology assessment (HTA) bodies, who must be willing and able to work with regulators to support this iterative

¹ Pre-market development time is defined as the number of years between investigational new drug application, and submission of new drug application or biologics license application.

expansion of license. The report from this pilot project is expected to be released in 2016. ADAPT-SMART is an Innovative Medicines Initiative (IMI) project that is investigating the conceptual framework that could support Adaptive Pathways, including tools and methodologies.

2.2. Implications for HTA globally

It is likely that the same medicines will be applicable for both the new FDA and EMA mechanisms for expedited access, as they have various criteria in common. It is therefore imperative that HTA bodies and payers are able to adapt and respond to this changing regulatory environment, and be ready to deal with the greater clinical uncertainty that may be present at the time of launch of those medicines. This applies not only to the countries for which the regulatory changes are under way, but also to countries outside the US and Europe, as pharmaceutical companies may tailor their development plans to meet the needs of the expedited programmes of those two large markets. Consequently, HTA bodies and payers across the globe may face new challenges in dealing with products for which the value proposition is based on greater clinical uncertainty, and in recognising and adapting to the collection and utilisation of more (real-world) observational data.

Various mechanisms for the “managed entry” of medical products are available, for example coverage with evidence development, whereby products are granted temporary reimbursement status, to be revisited following a period of data collection on use in real-world settings, or other performance-based risk-sharing arrangements which link payment explicitly with outcome. These mechanisms go by many names:

- performance-based risk-sharing arrangements (PBRSA)
- outcomes-based schemes
- coverage with evidence development (CED)
- risk-sharing agreements (RSA)
- patient access schemes (PAS)
- pay-for-performance (P4P).

The panel session summarised in this report considered how HTA bodies in the Asia-Pacific region can respond, and whether risk-sharing arrangements may be the way forward. By obtaining insight from three experts in the field, we explore the various challenges to be considered, and outline possible solutions.

After introducing the topic, Franz Pichler introduced the presenters, who were all asked to address the following:

- The changing evidence base and how an Asia-Pacific HTA body can respond.
- Opportunities for using claims data to help address clinical uncertainties by monitoring the performance of products in the real world.
- Consideration of outcomes-based risk-sharing mechanisms as a potential means to address this challenge.

Below, a summary is provided of each presentation.

3. MANAGING UNCERTAINTY WITH RISK-SHARING AGREEMENTS: A CANADIAN PERSPECTIVE

Dr Michelle Mujoomdar, Director of Scientific Affairs, CADTH.

As an organisation based outside Europe and the US, the Canadian Agency for Drugs and Technologies in Health (CADTH) also faces the challenges posed by the changing regulatory landscape externally, which impacts the evidence base available for HTA in Canada. By way of disclosure, Dr Mujoomdar outlined that CADTH is funded by federal, provincial and territorial ministries of health, and receives application fees for three programmes: CADTH Common Drug Review (CDR), CADTH pan-Canadian Oncology Drug Review (pCODR) and CADTH Scientific Advice. To the best of Dr Mujoomdar's knowledge, no aspect of her current role might reasonably be expected to affect her views on the subject matter of this panel session.

An introduction to CADTH

In Canada, there are two national drug review processes: Common Drug Review (CDR) and the pan-Canadian Oncology Drug Review (pCODR). There are 18 participating public drug plans. However, price negotiation (through the pan-Canadian Pricing Alliance, pCPA) is undertaken outside CADTH.

The following provides a CADTH perspective on the changing evidence base, evidentiary requirements, any subsequent uncertainty, and the challenges for HTA that arise from this uncertainty. It seeks to explore whether (and if so, how) these challenges should be addressed.

Issues from a Canadian perspective

Clinical development plans for large pharmaceutical companies are developed primarily for the European and US markets. As a result, smaller markets are affected by the signals that the regulatory agencies in those large markets send. However, the resulting evidence packages and data collection plans for medicines that have been developed through these alternative regulatory pathways, such as BTD or Adaptive Pathways, may not meet the needs of Canada (or other countries) from multiple perspectives: Health Canada, CADTH, payers, patients and clinicians.

While there is a priority review process in Canada's regulatory system, there is no progressive licensing programme that mimics the Adaptive Pathways pilot under way in Europe. However, there are some tools available which provide a way to collect further data on products and their use in medical practice after licensing. For example, typically Health Canada issues a "notice of compliance" (NOC) when granting marketing approval for a drug, but the agency is also able to issue a notice of compliance with conditions (NOC/c), which is authorisation to market a drug subject to the condition that sponsors undertake additional studies to verify clinical benefit (Health Canada, 2016a). In addition, Bill C-17 ("Vanessa's Law") was introduced in 2013 to amend the Food and Drugs Act, by improving Health Canada's ability to collect post-market safety information and take appropriate action to reduce harm where risk is identified (Health Canada, 2016b). This includes the ability to require information, tests and studies. However – where further evidence has been demanded – it is difficult to know the extent to which developers have complied with these requirements. In addition, these measures are somewhat passive; more active measures are required in order to have an impact on HTA.

From an HTA perspective, the evidence packages for new drugs often have a high degree of uncertainty attached, particularly those for cancer and rare diseases where often the evidence is only up to Phase II. In addition, trials are often of short duration and use alternative clinical endpoints. The question, therefore, is whether drugs with this degree of uncertainty should be considered by CADTH, and if so what options are available to deal with that uncertainty.

Risk-sharing agreements: challenges and opportunities

One way of managing uncertainty is with RSAs, which require collaboration between the HTA and payer communities. These can promote access to beneficial drugs, and reward value and performance in real-world settings. However, there are some challenges.

The first major challenge of RSAs is that they can be resource-intensive to initiate and agree upon, requiring much negotiation. In some cases, agreements simply cannot be reached. Another major issue is the data requirements for implementing such arrangements, which rely upon the collection of high-quality real-world data. In Canada, there are pockets of good data that are collected alongside clinical practice, but coverage is patchy and a coordinated approach to data collection across Canada is lacking. Electronic health records (EHRs) are important, and while the infrastructure in some areas exists to support these, other regions are lagging behind and require vast expansion and improvement of the infrastructure.

Another issue is one of trust. Where agreements require the collection of *de novo* data, manufacturers are often required to contribute to this data collection activity. However, there is some resistance in the HTA and payer community to utilising industry-generated data. Additionally, there is a prevailing feeling within the payer community that payers bear the burden of the “risk” associated with RSAs. In particular, the “managed exit” of products, for example where further data have demonstrated that new treatments are not cost-effective, can be very difficult to implement in practice.

There are various measures that can overcome some of these challenges. Agreements are resource-intensive, so there should be a prioritisation mechanism that recognises the types of clinical situation that these agreements would be more amenable to. There should also be a true willingness to negotiate and to share risk. In order to make agreements feasible, there must be further emphasis and investment in the collection of health data, and a collaborative approach between Canadian jurisdictions should be taken. In addition, there should be greater trust and increased acceptance of data collection that is facilitated by industry, and management of expectations which allows for drug de-listing to be feasible and followed through if necessary.

In summary, expedited processes of approval can increase access to potentially beneficial treatments, but this is generally accompanied by higher uncertainty of the clinical evidence at launch. RSAs may be one solution to assist with managing this clinical uncertainty. The associated challenges should be acknowledged and potential ways to overcome these explored, for which we must think globally.

4. MANAGING UNCERTAINTY WITH RISK-SHARING AGREEMENTS: A TAIWANESE PERSPECTIVE

Prof. K. Arnold Chan, Health Data Research Center, Taiwan.

By way of background and disclosure, Professor Chan outlined his professional experience, which includes being a member of the Pharmaceutical Benefit and Reimbursement Scheme Committee (National Health Insurance Administration within the Ministry of Health and Welfare in Taiwan), being Deputy Chair of the Drug Safety Committee within the Taiwan Food and Drug Administration, acting as a consultant for private companies (mostly pro bono) and being involved in conducting industry-sponsored observational studies. Professor Chan has been involved in HTA in the past, but in recent years has dealt mostly with drug safety, from a global perspective.

New medical products in Taiwan

Taiwan is a small country, and follows guidelines from the International Council on Harmonisation of Technical Registration of Pharmaceuticals for Human Use (ICH). However, local data are sometimes required for medical product registration. Most products are approved following FDA, EMA and Japanese approval, but independent reviews are undertaken by the Taiwan Center for Drug Evaluation and Taiwan FDA before market approval. HTA dossiers submitted for listing and reimbursement at the National Health Insurance Administration are also independently reviewed.

Many therapies are coming onto the global approved market and diffusing through the Asia-Pacific market, including target therapies for cancer, biologics for auto-immune diseases, anti-PD-1 antibodies, lipid-lowering drugs (such as PCSK-9 inhibitors), treatments for hepatitis C, antibiotics and drugs for heart failure; some of these are being reviewed by the National Health Insurance Administration now. However, two “new” drugs have been approved in Taiwan. Taiwan was the first to approve afatinib in 2013 for non-small-cell lung cancer as many trial patients were from Taiwan (Sequist et al., 2013). In addition, nemonoxacin – a quinolone antibiotic – was approved first in Taiwan in 2014 as it was developed by a domestic drug company. Others could have been approved early in Taiwan due to trials being conducted there, but were not, such as AZD9291 (osimertinib) for T790M mutation-positive metastatic non-small-cell lung cancer (Jänne et al., 2015).

Uncertainty at the time of review

It is common to encounter some level of uncertainty at the time of new drug application, and similarly at the time of reimbursement review in Taiwan: uncertainty in the efficacy of a product, its effectiveness in local populations, safety (particularly in the long term), performance and value. There are two options in dealing with this uncertainty. The default option has been to delay approval and reimbursement until more data become available. However, there is another option: conditional approval, with collection of post-marketing data alongside risk-sharing or pay-for-performance. This is new territory for Taiwan and the Taiwan government authority has not indicated what option is the preferred solution.

The types of new data required to facilitate such arrangements are multiple. Peri-approval clinical trials that are conducted to address HTA as well as regulatory approval needs are required. Post-approval registries are similarly needed, to collect information on and monitor the effectiveness, safety and value of therapies that have been introduced. These need to be based within the hospitals/clinics, and can utilise the

infrastructure for electronic medical records. Finally, health insurance claims data are required. These data are managed by the National Health Insurance Administration, and provide a national, comprehensive database with population coverage. Currently only academics have access to that data, which may need to be made more widely available to facilitate better understanding of long-term effectiveness.

Hypothetical examples

We can consider an example of a very effective cancer drug for patients who have no treatment alternatives, which is, however, only effective in 20% of those patients; there is no valid predictive marker. Cost per unit dose is high and budget impact would be large. The decision would be to either deny or delay the decision, at great cost to those patients who could benefit greatly from the drug, or to enter an RSA.

The solution that could be most beneficial would be to share risk and collect additional information. This could begin with a hospital-based registry, to collect information on the drug being used in very sick patients (who are being treated in just a handful of hospitals in Taiwan). Clinical specimens could thus be collected to find potential biomarkers to predict effectiveness, and clinical outcomes data monitored to determine long-term effectiveness and outcomes. Alongside this, health insurance claims data can be utilised to examine cost-effectiveness.

Another hypothetical example could be for a new biologic for systemic lupus erythematosus, which is common in the Chinese population. The biologic is efficacious but expensive. Given that treatment could potentially be lifelong, there would be strong concerns around budget impact. A PBRSA would be optimal in this scenario, alongside a post-approval registry to be supplemented by electronic medical records and health insurance claims.

Challenges of risk-sharing

Important barriers to RSAs in Taiwan are the data infrastructure requirements and expertise necessary to analyse and interpret clinical trial and/or registry data. In addition, there is currently a lack of dialogue between the drug approval agency (the Taiwan FDA, whose remit includes clinical trials) and the health insurance agency (interested in budget impact). The two agencies would need to work together to facilitate such arrangements, and be willing to replace the current "binary" decisions they make with conditional and iterative decisions. In addition, RSAs would be seen as a high commitment, involving prolonged periods of data collection, and de-listing is viewed as difficult. While scientists are ready for the changes, and the National Health Insurance Administration also seem interested in the approach, a change in the law would be required, and it is not clear whether all parties would be on board.

5. THE POTENTIAL FOR PERFORMANCE-BASED RISK-SHARING ARRANGEMENTS

Prof. Adrian Towse, Director of Office of Health Economics (OHE), UK

In order to explore how expedited review and consequent clinical uncertainty can be addressed, Professor Towse explained the current context in Europe, the EU's Adaptive Pathway, the potential for performance-based risk-sharing, and the implications for the Asia-Pacific region.

Demand for expedited access in the US and Europe

In Europe, the IMI “Get Real” project was launched in 2013 to consider how robust new methods of real-world evidence (RWE) collection and synthesis could be adopted earlier in pharmaceutical R & D and the health care decision-making process (GetReal, 2016). At the beginning of this project, the prevailing question was: can more be learnt about a product pre-launch, or should we get to post-launch sooner and learn more there? It has been evident for some time that health systems in the US and Europe – payers in particular – are interested in obtaining more evidence in a post-launch setting. This has been explored, for example, in a project undertaken by the OHE in collaboration with the Center for Medical Technology Policy (CMTP) entitled “New Drug Development Paradigm” (NDDP), where plausible scenarios were projected to 2020 for the US and Europe exploring the future demand for comparative effectiveness research (in the US) and relative effectiveness research (in the EU) (Messner, Mohr and Towse, 2015a; Messner et al., 2015b; Towse et al., 2015). The appetite for RWE was thus already on the rise; the early-access debate has enhanced concerns about the degree of uncertainty in the evidence of effectiveness available at launch.

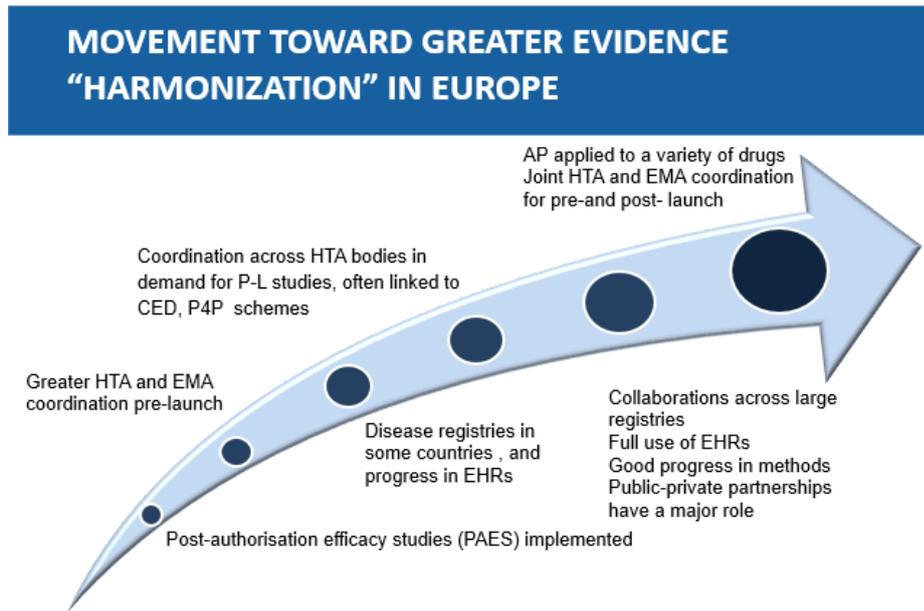
EMA Adaptive Pathways

Under Adaptive Pathways, the point at which an “initial license” for some groups of patients is issued will be brought forward for promising new drugs meeting certain criteria, and granted in some cases for some indications at Phase II. This means that, during Phase III, participation by patients in randomised controlled trials (RCTs) will be reduced, and more patients will be monitored at this stage through observational studies and registries.

There are some misconceptions around Adaptive Pathways, the first of which is that evidence standards are lower. By contrast, Adaptive Pathways provide the opportunity for evidence to increase over time, and provide multiple decision points which impact the timing of patient access for different groups of patients. This means that, for developers, earlier market access is granted, in exchange for continuous monitoring and changes in licensed indications based on the data generated from monitoring. Another myth is that, for developers, development time is necessarily cut and costs are therefore lowered. In reality, this only holds to the first decision point. Costs may increase if ongoing monitoring (which has associated costs) does not lead to further approvals; more research is needed to understand the real impact of Adaptive Pathways on the costs and benefits to payers, developers, regulators and patients, though some modelling work has been undertaken (Baird et al., 2013; Berdud et al., [forthcoming]). A final myth is that patients gain unfettered early access. In reality, patients obtaining early access are likely to be required to provide consent to be included in tracking activities such as registries and observational studies.

Figure 2 provides an analysis from the aforementioned NDDP project. Moving towards the right of the diagram represents the scenario most conducive to relative-effectiveness research and Adaptive Pathways (Towse et al., 2015). We are already starting to observe a dialogue between regulators and HTA bodies with regard to what information is required from manufacturers post-launch as well as pre-launch. For Adaptive Pathways and other early-access arrangements to be successful, payers must also be on board and prepared to coordinate common requirements with regulators and HTA bodies, particularly with data collection plans. Conditional agreements may be the key to facilitating this for payers.

Figure 2. NDDP project: movement toward health system harmonisation in Europe

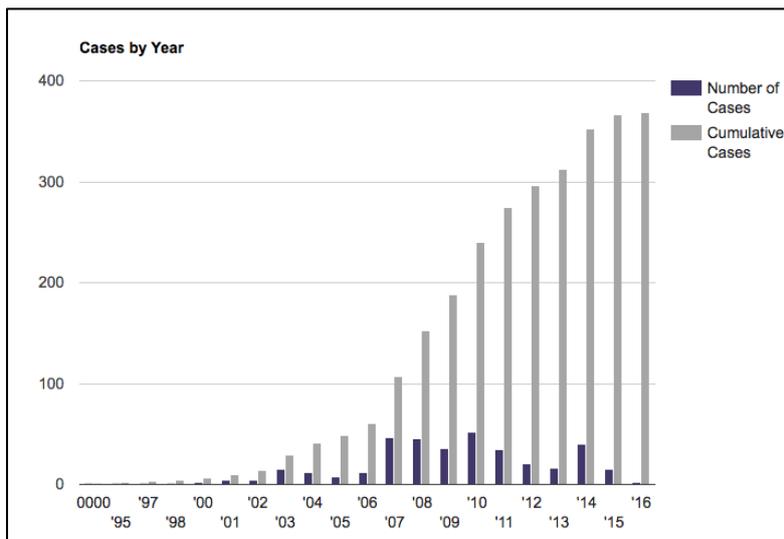


Source: Adapted from Towse et al. (2015)

The potential and reality of performance-based risk sharing

The University of Washington’s performance-based risk-sharing arrangement (PBRSA) database collects information on RSAs that have been implemented globally. These are captured in Figure 3 both cumulatively and by year. There have been a total of 369 PBRSA implemented up until early 2016. It can be observed that the use of PBRSA appears to be maturing, as their rate of growth has slowed.

Figure 3. PBRSA schemes by year

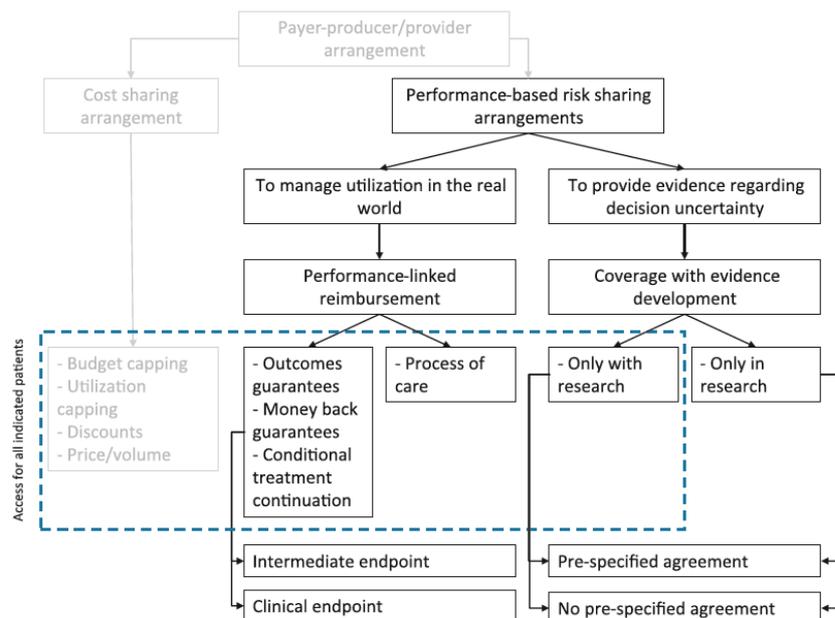


Source: University of Washington PBRSA database

PBRSA can be used to give access to new technologies where traditional reimbursement is deemed inappropriate. PBRSA can perform three key functions as part of a Managed Entry Agreement (MEA): to manage uncertainty regarding clinical effectiveness or cost-

effectiveness, to manage utilisation in order to optimise use of the drug, or to manage budget impact. Any form of MEA should be accompanied by a formal written arrangement between stakeholders which identifies the rationale for the agreement, aspects to be assessed, methods of data collection and review, and criteria for ending the agreement (Klemp, Frønsdal and Facey, 2011). Figure 4 presents a taxonomy for PBRSA generated by an ISPOR good-practice task force.

Figure 4. PBRSA Taxonomy - ISPOR Good Practice for PBRSA Task Force



Source: Garrison et al. (2013)

MEAs exist on a patient- or population-level basis, and can be outcomes- (PBRSA) or non-outcomes-based (e.g. budget capping or price/volume agreements). There are many examples of the use of PBRSA and other MEAs in practice, for example in Sweden, Italy, the Netherlands and Australia. Presented here are examples from the US and Europe.

Examples of PBRSA utilisation: the US and Europe

In the US, there is very little PBRSA activity in the private sector, with perceived barriers including the significant additional effort required in negotiating and monitoring an agreement, data infrastructure requirements in order to deliver the evidence, and the lowest-price rule for some public payers, which means that there is a risk that a PBRSA may trigger requirements to cut prices elsewhere (Garrison et al., 2015). Thus most recent interest in PBRSA in the US has been from the public sector. For example, the Centers for Medicare and Medicaid Services (CMS) have proposed testing a new “Medicare Part B Drug Payment Model” to improve quality of care and deliver better value for Medicare beneficiaries, through value-based purchasing tools (CMS, 2016).

In the UK, an example of a specific PBRSA is that implemented for the drug Velcade for multiple myeloma, where the initial cost per quality-adjusted life year (QALY) was above the acceptable threshold applied by the National Institute for Health and Care Excellence (NICE). A resubmission to NICE took place with a performance-related scheme, whereby continuation of treatment was conditional upon achieving an acceptable outcome, in

effect an outcomes guarantee. A rebate was offered for non-responders. Under these conditions, NICE was able to approve the product for reimbursement, as the scheme was able to mitigate the negative consequences of the uncertainty that existed around the product's value for non-responders. The agreement has now evolved, and been replaced by a simple discount applied to the product. This was made possible by the collection of further information around the proportion of non-responders, which allowed for the complicated reimbursement arrangement to be replaced by a price discount that accounts for its value and does not require long-term follow-up for all patients.

A further UK example is Votrient for renal cell carcinoma. The manufacturer claimed equivalent effectiveness to a comparator product, and NICE accepted the price on that basis, provided a rebate was offered if equivalence in the ongoing RCT was not proven. This has also subsequently turned into a simpler scheme, once non-inferiority was proven. A more complicated example can be seen in the UK's Multiple Sclerosis Risk Sharing Scheme (MSRSS), which was a 10-year scheme initiated in 2001 for four multiple sclerosis (MS) drugs for relapsing-remitting MS. The cost-effectiveness of the drugs was highly dependent on long-term outcomes, and therefore dependent upon the time horizon of the models. A time frame of at least 20 years was required for the drugs to be cost-effective, but the companies were only able to offer follow-up data for two years. Therefore a 10-year performance-based scheme was developed and implemented in 2002, with actual outcomes reviewed every two years and a price adjustment mechanism applied to maintain a cost-effectiveness threshold of £36,000/QALY. The scheme generated much discussion and criticism, after early data collection suggested that the drugs had no significant effect after two years, and no price adjustment was implemented despite these findings (Delamothe, 2010; Raftery, 2010; McCabe et al., 2010). The most recent 2016 results suggest that after six years of evidence collection the drugs are effective (Duddy and Palace, 2016), but the scheme raises many questions. Ten years is a long time frame for a PBRSA, and parties who sign up must be prepared for ups and downs over the course of the scheme. Given the then untreated nature of MS, there was pressure from all sides to make the right decision about access. However, collecting evidence on a therapy for a chronic disease inevitably can take time.

Challenges of risk-sharing

Overall, the literature suggests that there is an important gap in structured ex-post evaluation of PBRsAs (Puig-Peiró et al., 2011; Neumann et al., 2011). Schemes that focus on utilisation appear to have been more successful than coverage-with-evidence-development schemes. However, the evidence is limited, mixed, qualitative and partial.

A major challenge in the implementation of PBRsAs is the cost and practicality of evidence collection. Transaction costs are large, and derive mainly from the evidence collection that is required alongside any scheme. Most studies require bespoke data collection infrastructure to be developed, and there is little overlap or coordination between schemes. Negotiation between parties also takes time and resources, but standard templates can be implemented in order to reduce transaction costs. It is also imperative that the evidence to be collected in a PBRSA will resolve the uncertainty present and thereby address the needs of the payer. Another important issue is that, for many PBRsAs, prices need to be able to vary according to the outcomes achieved. However, a movement upward in price could be difficult to implement (though, arguably, optimal to ensure correct incentives), so a withdrawal of discount may be easier, or there may be other ways to change effective revenue, e.g. expansion of approved sub-groups for use.

Implications for the Asia-Pacific region

The options for payers in the Asia-Pacific region, in response to the changing levels of evidence available for new drugs seeking approval in local markets, are multiple. Alternatives to outcomes-based risk sharing include:

- Adopting now with no further evidence collection – this would mean that access is offered straight away, but it could then become increasingly difficult to resolve any remaining uncertainties.
- Coverage with evidence development, with no agreement – renegotiations could take place at later time points with additional information, but this would mean there is no commitment to collect information.
- Delay adoption and collect further information – however, this would mean that patients lose the benefits of early access.

For the implementation of PBRsAs in the Asia-Pacific region, there is a greater need for institutional flexibility; payers and HTA bodies must be in a position to work together, which in some cases may require legislative changes. Post-launch data collection capability must be improved, both for registries and for pragmatic trials. The transferability of real-world evidence is an important issue, as it is unlikely that companies will conduct post-launch studies in all countries.

6. PANEL DISCUSSION

The panel session presentations were accompanied by panel and audience discussion, both following each presentation and at the end. These are summarised by theme below.

The mechanics of “managed exit”

There is an ethical dimension to managing the exit of a product from the market, which must be feasible for some RSAs to work (e.g. coverage with evidence development). The key is to make this transparent in the set-up arrangements for the scheme.

A related issue is that of “indication creep”, from which any conditional approval/reimbursement must be protected.

Price flexibilities

Linked to the issue of managed exit, there should be recognition that, if risk-sharing schemes can be accompanied by price flexibilities, then price could simply be adjusted to reflect findings and make a positive reimbursement decision worthwhile. If effectiveness was found to be so poor that this could not be addressed by price changes, then it would in any case be of benefit to the patient to withdraw the product.

The importance of trust in RSAs

Dialogue is required to make RSAs work. Trust is an important issue. High prices can make constructive conversations difficult. However, along with the challenges there are also opportunities, with ever-increasing ways to collect and analyse data and new contractual mechanisms to address uncertainty that were not previously available.

Observational data and transferability of evidence

For randomised controlled trials there has been much work done on studying the transferability of results across populations. Little is known about the transferability of

observational studies, and there is likely to be a high degree of local variability. Even within countries, such as Canada, there is reluctance to make decisions based on data from other provinces, let alone other countries. These issues are being explored by projects such as the “GetReal” project. The ambition for collection of real-world (observational) data is to understand utilisation and impact in real practice, which is bound to differ according to local context. Therefore some locally collected data is likely to be a necessary supplement to experimental evidence, in order both to understand utilisation and impact in real practice and to facilitate RSAs.

7. SHARED PERSPECTIVES AND CONCLUSIONS

The regulatory landscape is changing. The calls for more streamlined introduction of innovative therapies are being answered, with regulatory agencies such as the EMA and FDA adopting ways to provide earlier access to therapies which have the potential to help patients in the most need. These programmes are unlikely to be successful if the issue of cost benefit (reimbursement) is not tackled alongside risk benefit (regulation). For HTA agencies and payers, the level of evidence available at the time of launch is likely to be affected by the earlier introduction of medicines and an increased reliance on observational rather than experimental data.

The implications for HTA agencies extend beyond the US and Europe, as the tailoring of development plans for these markets will have an important impact on the evidence available globally. We have seen examples of how these challenges manifest in markets such as Canada and Taiwan, and explored the implications for HTA agencies in the Asia-Pacific region more broadly.

RSAs can offer payers a way to provide access to promising technologies with high uncertainty, while limiting their risk of providing unlimited and indefinite access to high-cost drugs that may prove to be ineffective. They can be used to manage uncertainty regarding clinical effectiveness or cost-effectiveness, to manage utilisation in order to optimise performance, and also to manage budget impact. However, there are various challenges associated with these schemes. The first is the trust and collaboration required between HTA bodies and payers, as well as industry. All parties must be willing to make the commitments necessary, some of which can be long-term in nature. A second challenge is the collection of high-quality data alongside clinical practice; in many countries, a vast improvement in the infrastructure for data collection is required in order to successfully implement RSAs. Finally, an expansion in expertise and methods to analyse and interpret observational data is required, globally.

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