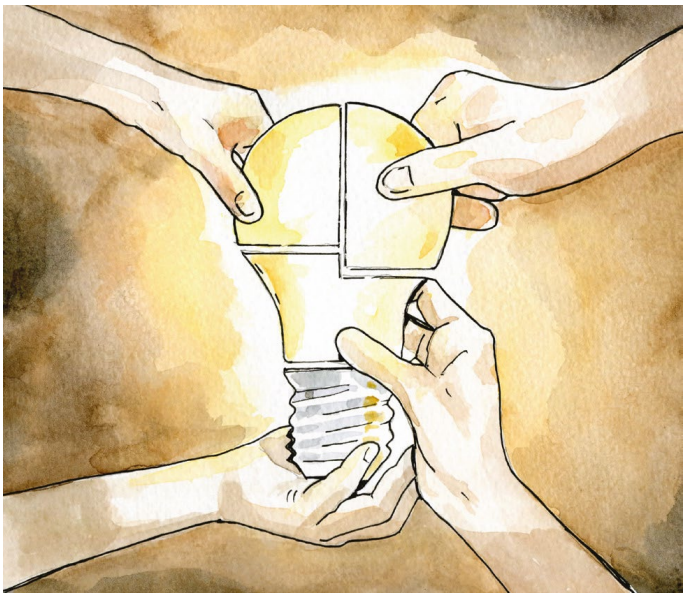


Identifying and understanding regulatory and reimbursement uncertainty during development:

How can this improve predictability of regulatory and HTA outcomes?

9 – 10 October 2019

Surrey, UK

WORKSHOP REPORT

CIRS Centre for Innovation in Regulatory Science

Contacts

Dr Jamie Munro, *Executive Director* jmunro@cirsci.org
Dr Neil McAuslane, *Scientific Director* nmcauslane@cirsci.org
Tina Wang, *Manager, HTA Programme* twang@cirsci.org

The Centre for Innovation in Regulatory Science (CIRS) is a neutral, independently managed UK-based subsidiary company, forming part of the Clarivate Analytics group. CIRS' mission is to maintain a leadership role in identifying and applying scientific principles for the purpose of advancing regulatory and HTA policies and processes. CIRS provides an international forum for industry, regulators, HTA and other healthcare stakeholders to meet, debate and develop regulatory and reimbursement policy through the innovative application of regulatory science and to facilitate access to medical products through these activities. This is CIRS' purpose. CIRS is operated solely for the promotion of its purpose. The organisation has its own dedicated management and advisory boards, and its funding is derived from membership dues, related activities, special projects and grants.

Centre for Innovation in Regulatory Science (CIRS)
Friars House, 160 Blackfriars Road, London, SE1 8EZ
Email: cirs@cirsci.org
Website: www.cirsci.org

Report date: 14 February 2020

Prepared by: Dr Jenny Sharpe, *Senior Scientific Writer, CIRS*

Section 1: Executive Summary

Background to the workshop

Driven by complex requirements and divergent stakeholder needs, uncertainty is always present in the development, review and reimbursement of new medicines. Moreover, three types of uncertainty have been identified specifically related to early-access pathways: uncertainty resulting from unpredictable conditions, from lack of available information and from the decision-making process, with each of these types requiring different approaches [1]. However, understanding the degree of uncertainty and applying appropriate risk-mitigation strategies in either the pre- or post-approval space may help to provide needed predictability to companies, regulators, health technology assessors, payers and patients in the generation of evidence for new treatments for diseases, especially those with inadequate or no treatments.

At a recent Institute of Medicine meeting to discuss regulatory uncertainty around benefit-risk decisions, regulatory uncertainty was said to be driven by human variability, as clinical trials cannot provide full information about harm and effectiveness in real-world populations, cannot measure the effect of chronic use, nor determine the unknown or “unknown unknown” where data are missing or not studied [2]. In addition, it should be recognised that medicines have uncertainties that arise from both clinical and/or economic evidence. HTA uncertainty can be categorised around indirectness, imprecision, unavailability of evidence and systematic error or bias.

Companies use scientific advice to provide more aligned evidence requirements for specific products, but this task is made more complex because of differing regulatory and HTA remits. Different jurisdictional considerations result in a lack of homogeneity across HTA that may be found in the regulatory space. HTA decision making includes economic analysis, the uncertainties of which go beyond the need or scope of regulators. In addition, HTA decisions rely on estimating the extent of differences among comparators and on assumptions, analysis and modelling beyond the clinical evidence available to the regulators. It needs to be determined if there are common lessons from both the HTA and regulatory spheres to help address the issues of increased uncertainty for early-access medicines.

At a CIRS/Utrecht joint meeting in 2018 it was recommended that “It would be valuable to research how to eliminate known uncertainties, not just in the regulatory and HTA contexts but also for payers and clinicians. These are not just uncertainties in terms of safety but also in efficacy, effectiveness and clinical use” [2]. This workshop will bring together different stakeholders to advance this research and to discuss how the knowledge of regulatory and HTA uncertainties identified prior to or during development can be avoided or mitigated to improve the probability of positive regulatory and HTA outcomes.

Workshop objectives

1. Discuss the types of uncertainties that can be identified and, in theory, resolved during clinical development as well as those for which data will be unavailable for early-access medicines
2. Identify potentially resolvable uncertainties as perceived by companies, HTA bodies, payers, patients and regulatory agencies and how to better manage these for early-access medicines
3. Recommend appropriate approaches that build management or resolution of regulatory or HTA uncertainties for early-access medicines into the development space

References

[1] What new research can enable a joint approach by regulatory and HTA agencies to manage uncertainties for products using early access pathways? CIRS/Utrecht Forum report 2018.
[2] Characterizing Uncertainty in the Assessment of Benefits and Risks of Pharmaceutical Products, 2014 National Academy of Science

Key points from presentations

Dr Lawrence Liberti, *Head, Regulatory Collaborations, CIRS*, opened the workshop with an overview of previous CIRS work on early access medicines and flexible regulatory access pathways, which has led to the identification of three key types of uncertainty. He explained that the aims of the workshop were to assess how to describe and understand uncertainties, how to put certain weight behind these uncertainties, and how to communicate them.

Role of uncertainty across different contexts

Dr John Patrick Stewart, *Director General, Therapeutic Products Directorate, Health Canada*, spoke about the significant role that uncertainty has in Health Canada's decision-making. Benefit-risk decisions are challenging, particularly when there is a lot of uncertainty. Decision-making in larger economies directly impacts Canada, so Health Canada has had to adapt and develop a dynamic approach to uncertainty. Lines of communication between stakeholders are integral to all aspects of Canada's conditional approval pathway, the Notice of Compliance with Conditions (NOC/c). It is important to remember that not all confirmatory studies will be positive, and that early access must be balanced with patient safety and wellbeing.

Niklas Hedberg, *Chief Pharmacist, Dental and Pharmaceutical Benefits Agency (TLV), Sweden,* followed with an HTA perspective of the role of uncertainty. HTAs are concerned with uncertainties partly because they could become risks and are likely to reach different conclusions/decisions compared to regulators. TLV categorises uncertainty in a transparent and coherent way according to different levels i.e. low to very high. Internal discussions about Advanced Therapy Medicinal Products (ATMPs) have particularly focused on identifying the greatest uncertainties, understanding how the use and effectiveness of approved products could be monitored, and determining the need for new evaluation and payment models.

Dr Michael Ermisch, *Specialist, National Association of Statutory Health Insurance Funds (GKV-Spitzenverband), Germany,* then gave a payer's perspective on the role of uncertainty. Insecurities in the quantification of added benefit mean that the value of a medicinal product cannot be established, which causes problems for value-based prices. Real-world evidence generation may not be a sufficient solution, unless its methodological problems are solved and the responsibility shift from developers to payers and society is addressed.

Reducing uncertainty in the development space

Dr Alicia Granados, *Head of Global HTA Strategy, Sanofi, Spain,* gave an overview of some of the challenges companies face when trying to manage or resolve uncertainties during development. Uncertainties can be reduced as more evidence is generated over time, ideally informed by iterative multi-stakeholder dialogue and assessment. While early scientific dialogues offer a valuable opportunity to optimise development programmes, there is often poor alignment between regulatory and HTA evidentiary requirements. Further research on the impact of seeking advice on prospective HTA recommendations and patient access is needed.

Types of unresolvable uncertainties during development

Adam Heathfield, *Senior Director, Patient and Health Impact, Pfizer, UK*, gave an overview of uncertainties that cannot be resolved and why companies should acknowledge these early in development. While many uncertainties could be resolved via randomised controlled trials (RCTs) and other data, they may be difficult to resolve at a local level in every health system or resolve via standard means if the therapy is eligible for early access. To facilitate better management of uncertainties, companies should have a cross-functional understanding of all evidence gaps. While there can be issues around the clarity and feasibility of HTA advice, companies should ensure they are asking the right questions and consider taking consolidated parallel consultation pathways.

Prof Hans-Georg Eichler, *Senior Medical Officer, European Medicines Agency,* then described how a framework for classifying uncertainties and coping strategies was applied to oncology products approved between 2011-2017. Not enough data was the main source of uncertainty, requiring submission of post approval data. However, for ultra-rare indications, uncertainties were frequently due to unreliable data, rather

than not enough data. Further studies could be directed towards understanding longitudinal evolution of uncertainties in a product and to evolve the framework and pilot it within guidelines and templates.

Andrew Mitchell, *Strategic Adviser, Evaluation, Department of Health, Australia,* then gave an HTA viewpoint on types of unresolvable uncertainties. While some uncertainties can be managed through post-market data collection, the issue for companies and HTA-informed payers is that many important decisions must be made with pre-market data only. Uncertainties related to statistics (precision), attribution (bias), indirectness (assumption) and value (price) cannot be fully eliminated but may be possible to manage through sample size, science, modelling and HTA-informed negotiation, respectively.

Scientific advice for mapping uncertainty

Jeanette Kusel, *Director for Scientific Advice, National Institute for Health and Care Excellence (NICE), UK,* described how scientific advice allows early dialogue between stakeholders and the mapping of where uncertainties can and should be resolved. The current paradigm is for companies to seek regulatory advice first and plan trials to resolve uncertainties that are important to the regulators, leaving limited scope for changing these trials to resolve uncertainties that are important to HTA bodies. A new paradigm should be explored where joint HTA and regulatory advice is sought early and on entire clinical development plans, rather than individual trials.

A framework approach to resolving uncertainty

Dr Robyn Lim, *Senior Science Advisor, Health Products and Food Branch, Health Canada,* spoke about Structured Evidence Planning, Production, and Evaluation (SEPPE), a context-adaptable practice framework proposing that evidence be treated much like manufactured goods, with global, built-in quality processes and proactive, iterative feedback from key decision-makers at critical, pre-identified points in product R&D. Although it is not possible to eliminate all evidence uncertainties under SEPPE, it could curtail moments where avoidable uncertainty becomes the issue tipping towards negative decisions.

Tools for addressing clinical uncertainties during development

Dr Michael Kulig, *Scientific Advisor and Head of Working Group Pharmaceuticals at the Medicine Department, Federal Joint Committee (G-BA), Germany,* described how the inclusion of RCT data in G-BA assessments does not necessarily address uncertainties related to long-term evidence. Requirements for further evidence from HTA and regulatory bodies may be sufficient in managing or reducing uncertainty, however, generating relative effectiveness data after market access can be very difficult as there is bias by indication, and at least in Germany, reimbursement of the new drug may limit the availability of controls. Early advice and dialogues involving all stakeholders can provide tools for reducing uncertainty.

Prof Anthonius de Boer, *Chair, Medicines Evaluation Board (MEB), The Netherlands,* gave an overview of tools being explored to close the regulatory and HTA gap and streamline decision making, such as joint scientific advice and parallel procedures. Joint scientific advice can help to meet stakeholder needs with regards to addressing clinical uncertainties during development for both market access as well for reimbursement. Benefits of the Netherlands' pilot parallel procedure include expedited patient access, more synergised procedures and increased sales revenue for the company. However, challenges remain such as pricing in the Netherlands, which is not listed as one of the 'first wave countries' for market introduction, and the need to be cautious about the influence that regulators have on HTA decision making and *vice versa*.

Shane Kavanagh, *Vice President, Health Economics, Janssen, Belgium,* then gave a company perspective on tools to address clinical uncertainties during development. Although it can take years to identify and validate appropriate surrogate endpoints in oncology, they must play a central role in value-assessment processes. Innovative payment models and outcomes-based risk-sharing approaches must become more widely accepted, with multi-stakeholder discussions starting before new treatments are approved so that all options are considered and access solutions co-created.

A life cycle approach to manage uncertainties for early-access medicines

Dr Brian O'Rourke, *President and CEO, Canadian Agency for Drugs and Technology in Health (CADTH),* spoke about the need for a broader approach to HTA, shifting towards health technology management across the medical product life cycle. A life cycle approach to HTA can facilitate the management of uncertainties for early-access medicines but relies on several key elements and practical considerations, such as early awareness of impending disruption, engagement of key stakeholders, a framework for conditional reimbursement, outcomes-based Managed Entry Agreements, reassessment programmes based on real world evidence and payer receptivity.

Managing uncertainty using post licensing evidence generation

Dr Magdalini Papadaki, *Associate Director, Business Strategy & Operations, MSD, UK,* discussed how real world evidence (RWE) can address some of the challenges of traditional RCTs, if stakeholders agree on data quality standards, evidence design principles and characteristics. Leveraging the promise of RWE and new trial designs calls for operational adaptations, new data-driven strategies, and an integrated partner ecosystem that captures high quality data, minimising gaps and allowing long-term follow up. To move forward with utilising different ways of managing uncertainty post-licensing, innovator companies, regulators, HTA agencies and other stakeholders need to build capabilities and partnerships to better understand and use RWE.

Communicating uncertainty and risk to key stakeholders

Dr Claus Bolte, *Head of Sector Marketing Authorisation, Swissmedic,* gave an overview of tools used to help stakeholders understand uncertainties. Communication approaches should involve the target audience and be tailored appropriately. To effectively communicate the basis of a decision, it is important to provide a record trail and explain the criteria and process used. Swissmedic provides active, passive and reactive information to its national and international stakeholders, including patients, healthcare professionals, professional societies and government colleagues.

Dr Alan MacDonald, *Chairman, Scottish Medicines Consortium,* then gave an HTA's perspective on communicating uncertainty and risk at the time of product approval for early-access medicines. When communicating with key stakeholders, uncertainty should be embraced and not confused with a lack of rigour. Maximum possible transparency is critical to ensure public confidence when decisions are based on incomplete information. HTA has a key role in identifying uncertainties in evidence for early access medicines in a "coverage with evidence" setting and its role in directing how these gaps should be filled needs further thought.

Valentina Strammiello, *Programme Manager, European Patients' Forum,* then spoke about the importance of a strong, clear and transparent communication strategy when engaging with patients and the general public. This should describe and promote the concept of early access, provide sound evidence in lay language, mitigate risks of misinterpretation and manage the expectations of patients. Patient organisations and advocates have a key role as information providers and resources like the European Patients' Academy on Therapeutic Innovation (EUPATI) can also assist with patient engagement.

Managed entry schemes to manage uncertainty

Dr Wim Goettsch, *Associate Professor of HTA, WHO Collaborating Centre for Pharmaceutical Policy, Utrecht University, The Netherlands,* spoke about a four-year pilot scheme of conditional financing in the Netherlands, which showed numerous shortcomings related to procedural, methodological and decision-making aspects of implementation. Learning from this pilot and others' experiences is key to moving forward with managed entry schemes for early access medicines. Well-designed registries are also critical but better structural governance/funding models need to be developed and ethical and technical issues resolved.

Dr Vanessa Schaub, *Global Access Senior Health Systems Strategy Leader HTA & Reimbursement, F.Hoffman-La Roche, Switzerland,* then gave a company perspective on outcome based agreements, which are usually set up as a co-creative approach or partnership with external stakeholders. This allows for early alignment on defined clinical outcomes, data gathering and monitoring, and expected/desired cut-offs. A multi-

stakeholder approach is also needed to foster system-wide change and ready the necessary legal frameworks and IT infrastructure. In order to move forward with using managed entry schemes to improve patient access, we need to work together to start and pilot agreements that are truly based on clinical outcomes, keeping them as simple as possible.

Vinciane Knappenberg, *Adviser (Directorate Pharmaceutical Policy), National Institute for Health and Disability Insurance (NIHDI), Belgium,* then gave a payer's perspective on managed entry schemes for managing uncertainty. NIHDI is evolving from purely financial schemes towards patient-based outcomes schemes, which allow reimbursement that is clinically justified and focus on both value and budget control. Although they are subject to less political criticism, patient-based outcomes schemes can be difficult to conclude due to scientific, logistical and financial reasons. NIHDI is also considering new methods for negotiation, new approaches to payment systems and horizon scanning, as well as participation in international collaborations to pool resources and increase negotiating power.

Managing the outcome of conditional approvals and reimbursement

Dr Nithyanandan Nagercoil, *Medical Assessor, Medicines and Healthcare products Regulatory Agency (MHRA), UK,* spoke about challenges regulators face in balancing early access with decision uncertainty. In order to manage expectations and address unexpected findings, there must be early engagement between companies and regulatory agencies. Companies should form proactive and well-considered proposals that consider the relevant clinical and societal context and expectations of the specific target populations, while regulators must carry out prompt reviews and endorsements with/without modifications. Quick communication and implementation of agreed action plans should provide reassurance to patients and stakeholders, hopefully pre-empting issues.

Dr Jacqueline Brown, *Research Fellow, Health Outcomes, Eli Lilly and Company, UK,* then presented Lartruvo as a case study for learning about decision making when post-approval evidence does not support a product's initial potential, as well as the role of exit strategies and disinvestment plans. Lartruvo was the first drug to be withdrawn following accelerated/conditional marketing approval. Despite very promising phase II results, the phase 3 study testing Lartruvo, which was well-controlled and conducted, failed to meet its primary endpoint. When the unexpected does happen, it is essential that patients are put first; stakeholders need to work together to make decisions about how patients are managed between the time of data read out and market authorisation withdrawal, and after market authorisation withdrawal.

Evert Jan van Lente, *Director EU Affairs, AOK-Bundesverband, Germany,* then gave a payer's perspective on conditional reimbursement and adaptive pricing, which could be potential solutions to the considerable pressure to make promising new therapies available (even if uncertainty is very high). However, conditional reimbursement and adaptive pricing cannot yet be implemented in Germany because of a lack of legislation, pricing methodology, satisfactory framework for methodological conditional approval and reimbursement, and payer expertise. In addition, high costs for post-marketing evidence generation and a lack of infrastructure can result in data of unknown quality.

Recommendations from across the syndicate discussions

Managing the uncertainty in evidence development for regulators and health technology assessors for early-access medicines – can a list of areas of uncertainty be agreed by stakeholders for early-access medicines?

- Apply learning from one therapeutic area to another to understand uncertainties to be addressed regarding unexpected safety concerns.
- Develop a regulators' risk management programme to potentially address HTA uncertainties including post-launch scientific advice (EUnetHTA/EMA) and phase 3 designs to address both HTA/regulator needs and that accommodates the level of uncertainty in development pathway at timing of interaction.
- Develop global standardisation of surrogate endpoints, biomarkers and historical controls.
- Create incentives for Wave 2+ regions so that they can access early access products and ensure regulatory oversight; include recommendations for sharing risk management programmes.
- Improve quality of real world evidence and standardised medical data collection and develop a methodology to extrapolate real world evidence into clinical outcomes.
- Develop HTA frameworks to manage early access programme uncertainties.

Can we develop a high-level framework to systemically identify and calibrate the type or degree of uncertainty?

In the short term, carry out a mapping exercise on current context, in order to inform an Integrated Uncertainty Management Plan (IUMP) framework:

- Map existing activities / models across current stakeholders (industry, regulators, HTA, payer) with a view to understand potential for optimising use or combining in the context of an IUMP framework.
- Map different payer / HTA systems for better understanding of potential 'global' approach to IUMP.
- Map existing advice pathways to understand timing and purpose in relation to the development timeline and which type of uncertainties are in scope.

In the longer term, discuss and refine IUMP scope and methodology:

- Recommend on structured methodology for assessing and aligning on uncertainties and mitigation activities.
- Re-visit current advice / interaction framework with recommendation on potential need for changes, including patient and prescriber perspectives.
- Assess and address gaps in incentives for data collection (uncertainties mitigation) in relation to IUMP framework.

Can we develop a high-level framework to systemically identify and calibrate the type or degree of uncertainty?

- **Now:** All stakeholders should choose a champion to take part in a coalition to continue discussing and moving the topic forward.
- **Within 1 year:** Jointly agree on a framework for common data collection across jurisdictions. Important considerations include:
  - Making it fit-for-purpose, ensuring quality/consistency and a governance model acceptable to all stakeholders.
  - Feasibility and acceptability should be informed by a multi-stakeholder survey, potentially through CIRS.
  - Results should be published / publicly available and aligned with/informed by other initiatives e.g. EMA registry (qualification) initiative.
  - Multiple data sources are needed for different purposes (not all have to adhere to RCT gold standard).
  - Determine who is going to pay for real-world data collection.
- **After 1 year:** Ensure multi-stakeholder prospective life cycle planning through adaptive and flexible risk management plan-like document/agreement. Make use of existing concepts but involve all key aspects relevant to all stakeholders.

Workshop Programme

SESSION: IDENTIFYING AND ARTICULATING TYPES OF UNCERTAINTIES DURING DEVELOPMENT OF EARLY ACCESS MEDICINES – CAN THIS IMPROVE OUTCOME PREDICTABILITY?	
Chair's welcome and introduction	**Dr Sean Tunis,** *Senior Strategic Adviser, Center for Medical Technology Policy, USA*
Managing uncertainties for products using early access pathways: why this and why now?	**Dr Lawrence Liberti,** *Head, Regulatory Collaborations, CIRS*
Early access vs routine medicines – what role does uncertainty play across the different contexts in framing evidence generation needs and decision-making considerations?	**Regulatory viewpoint – Dr J Patrick Stewart,** *Director General, Therapeutic Products Directorate, Health Canada*
	HTA viewpoint – Niklas Hedberg, *Chief Pharmacist, TLV, Sweden*
	Payer viewpoint – Dr Michael Ermisch, *Specialist, GKV-Spitzenverband, Germany*
Reducing uncertainty in the development space – is it possible for companies to identify the priorities from regulators, health technology assessors and payers as to which clinical uncertainties need to be managed or resolved during development?	**Dr Alicia Granados,** *Head of Global HTA Scientific Strategy, Sanofi, Spain*
What are the types of uncertainties that cannot be resolved during development and why is it important to acknowledge these early in development?	**Company viewpoint – Adam Heathfield,** *Senior Director, Patient and Health Impact, Pfizer, UK*
	Regulatory viewpoint – Prof Hans-Georg Eichler, *Senior Medical Officer, European Medicines Agency*
	HTA viewpoint – Andrew Mitchell, *Strategic Adviser, Evaluation, Department of Health, Australia*
What type of scientific advice/early dialogues enable a company and agency to potentially map stakeholder perceptions regarding resolvable versus unresolvable uncertainties?	**Jeanette Kusel,** *Director for Scientific Advice, NICE, UK*
Could the utilisation of a context adaptable framework approach e.g. SEPPE be used to identify gaps in stakeholder evidentiary requirements and resolve uncertainties?	**Dr Robyn Lim,** *Senior Science Advisor, Health Products and Food Branch, Health Canada*

SESSION: WHAT ARE THE STRATEGIES, METHODOLOGIES AND ACTIVITIES THAT CAN BE USED TO MANAGE OR MITIGATE PREDICTABLE AND UNPREDICTABLE UNCERTAINTY SO AS TO IMPROVE REGULATORY AND REIMBURSEMENT OUTCOMES?	
Chair's introduction	**Dr Tomas Salmonson,** *former Chair CHMP, EMA and Partner, Consilium Salmonson & Hemmings, Sweden*
Are today's tools for addressing clinical uncertainties during development sufficient to meet the stakeholder's needs or are new approaches required to bridge the regulatory HTA gap?	**HTA viewpoint – Dr Michael Kulig,** *Head of Working Group Pharmaceuticals, Medical Consultancy Department, G-BA, Germany*
	Regulatory viewpoint – Prof Anthonius de Boer, *Chair, Medicines Evaluation Board, The Netherlands*
	Company viewpoint – Shane Kavanagh, *Vice President, Health Economics, Janssen, Belgium*
Utilising a life cycle approach as the way forward to manage uncertainties for early access medicines: what are the practical considerations?	**Dr Brian O Rourke,** *President and CEO, CADTH, Canada*
How to manage uncertainty and mitigate risks identified at the time of approval and reimbursement using post-licensing evidence generation – what are the future opportunities and current barriers?	**Dr Magdalini Papadaki,** *Associate Director, Business Strategy & Operations, MSD, UK*

SESSION: SYNDICATE DISCUSSIONS	
Syndicate A: Managing the uncertainty in evidence development for regulators and health technology assessors – can a list of areas of uncertainty be agreed by these stakeholders for early access medicines?	**Chair: Dr Sean Tunis,** *Senior Strategic Adviser, Center for Medical Technology Policy, USA*
	Rapporteur: Dr Shalu Ramrakha, *Director, Global Regulatory Affairs, GlaxoSmithKline, UK*
Syndicate B: Can we develop a high-level framework to systemically identify and calibrate the type or degree of uncertainty?	**Chair: Dr Thomas Lönngren,** *Independent Strategy Advisor, PharmaExec Consulting Filial SE, Sweden*
	Rapporteur: Anders Blaedel Lassen, *Senior Director & Head of Patient Insights, Lundbeck, Denmark*
Syndicate C: Is there another way? Utilising a life cycle approach for early access medicines to manage uncertainties – what are the considerations?	**Chair: Dr Luc Boileau,** *President and CEO, INESSS, Canada*
	Rapporteur: Lourens Bloem, *PhD candidate, Utrecht Institute for Pharmaceutical Sciences Utrecht University, the Netherlands*

SESSION: SYNDICATE FEEDBACK	
Chair's introduction	**Prof Adrian Towse,** *Director Emeritus and Senior Research Fellow, Office of Health Economics, UK*
Feedback of syndicate discussions and participants' viewpoints	
How should the level of known and unknown uncertainty and risk be communicated to key stakeholders at the time of product approval for early access medicines?	**Regulatory viewpoint – Dr Claus Bolte,** *Head of Sector Marketing Authorisation, Swissmedic*
	HTA viewpoint – Dr Alan MacDonald, *Chairman, Scottish Medicines Consortium*
	Patient viewpoint – Valentina Strammiello, *Senior Programme Manager, European Patients' Forum, Belgium*

SESSION: WHAT ARE THE ROLES OF DIFFERENTIAL PRICING BASED ON LEVELS OF UNCERTAINTY, EXIT STRATEGIES, AND DISINVESTMENT PLANS IN EARLY ACCESS MEDICINES AND HOW DO THESE WORK IN PRACTICE?	
Chair's introduction	**Prof Adrian Towse,** *Director Emeritus and Senior Research Fellow, Office of Health Economics, UK*
Managed entry schemes to manage uncertainty and ensure added value: is this the future for all new early access medicines, what has been the experience and what should be the key considerations?	**HTA viewpoint – Dr Wim Goettsch,** *Associate Professor HTA, WHO Collaborating Centre for Pharmaceutical Policy, Utrecht University, The Netherlands*
	Company viewpoint – Dr Vanessa Schaub, *Global Access Senior Health Systems Strategy Leader HTA & Reimbursement, F.Hoffmann-La Roche, Switzerland*
	Payer viewpoint – Vinciane Knappenberg, *Advisor (Directorate Pharmaceutical Policy), National Institute for Health & Disability Insurance (NIHDI), Belgium*
Addressing the expectations: how to manage the outcome of conditional approvals and reimbursement	**Regulatory viewpoint – Dr Nithyanandan Nagercoil,** *Expert Medical Assessor, MHRA*
	Company viewpoint – Dr Jacqueline Brown, *Research Fellow, Health Outcomes, Eli Lilly and Company, UK*
	Payer viewpoint – Evert Jan van Lente, *Director EU-affairs, AOK-Bundesverband, Germany*

Section 2: Presentations

Please note, the slide featured in each of the following summaries is attributed to the individual presenter and has been reproduced with his/her permission.

Managing uncertainties for products using early access pathway: why this and why now?

Dr Lawrence Liberti, *Head, Regulatory Collaborations, CIRS*

Over the last few years, CIRS has held a number of workshops on early access medicines [1-3], with the goal to increase understanding of the limits of our knowledge and provide a lifecycle framework to manage this uncertainty. Outputs from these workshops, in addition to a joint meeting with Utrecht University [4], have informed the objectives and programme for this workshop.

In the context of regulatory decision making and early access pathways, there are three types of uncertainty that need to be addressed in different ways [4]:

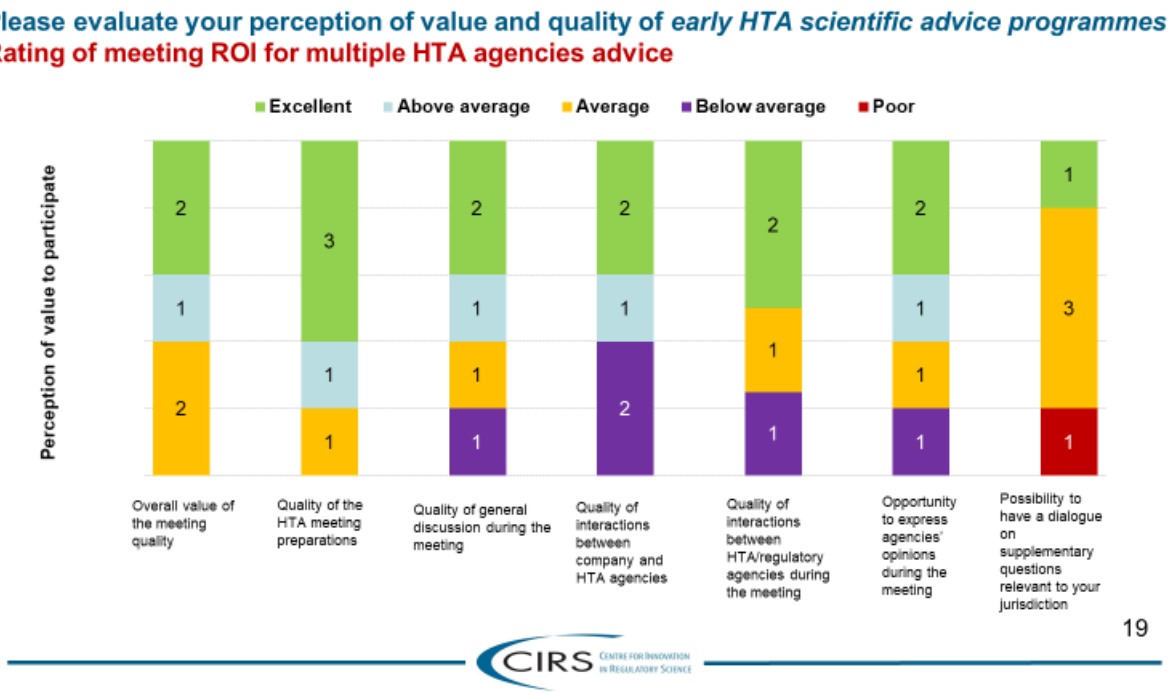
- Stochastic – uncertainty resulting from unpredictable conditions
- Epistemic – uncertainty that can be mitigated by additional information
- Decision-related – uncertainty that is inherent in decisions made with the best available knowledge weighed in the light of specific external parameters, such as budgets or specific patient needs.

Transparency and open communication with external stakeholders are key to understanding how much uncertainty is acceptable at product launch. CIRS research has shown that companies are seeking scientific advice earlier and earlier (see figure below), which creates an opportunity for multi-stakeholder involvement in identifying uncertainties early on and understanding if and how these uncertainties could be mitigated.

Integrated evidence generation plans offer a structured process to manage uncertainties throughout the life cycle of a product. Pulling information together into a single repository allows internal stakeholders to better understand uncertainties and the development programme designed to mitigate them. This in turn can enhance internal communication, encouraging a more cross-functional approach and potentially more internal alignment.

There are several ways to link uncertainty to reimbursement (and thus the price of a pharmaceutical product), but it can be difficult to know how well this works for early access medicines. For example, in the case of new antibiotics, clinical trials aim to show noninferiority, which often results in lower prices than existing generic drugs. Therefore, there is a need for new contractual arrangements and better HTA models to capture public health benefits beyond the immediate health gain to a treated individual [5]. The Institute for Clinical and Economic Review (ICER) in the US has also recently questioned whether value-based pricing should be modulated by uncertainties in the context of potential cures and short-term transformative therapies.

This workshop brings together different stakeholders to discuss how the knowledge of regulatory and HTA uncertainties identified prior to or during development can be avoided or mitigated to improve the probability of positive regulatory and HTA outcomes.



References:

[1] CIRS Workshop (2017) Flexibility regulatory / access pathways: are we there yet?

[2] CIRS Workshop (2018) Advancing the on-market evaluation of early access medicines: evolving post-approval assessments for efficacy to enable a life-cycle approach to medicine evaluation

[3] CIRS Workshop (2018) Enabling innovation: early upstream interactions to enhance downstream decision making

[4] CIRS / Utrecht University WHO Collaborating Centre for Pharmaceutical Policy and Regulation Workshop (2018) What new research can enable a joint approach by regulatory and HTA agencies to manage uncertainties for products using early access pathways?

[5] Neri, M., Hampson, G., Henshall, C. and Towse, A. (2019) HTA and payment mechanisms for new drugs to tackle AMR. OHE Research Paper, London: Office of Health Economics. Available at: https://www.ohe.org/publications/hta-and-payment-mechanisms-new-drugs-tackle-amr

Early access vs routine medicines – what role does uncertainty play across the different contexts in framing evidence generation needs and decision-making considerations?

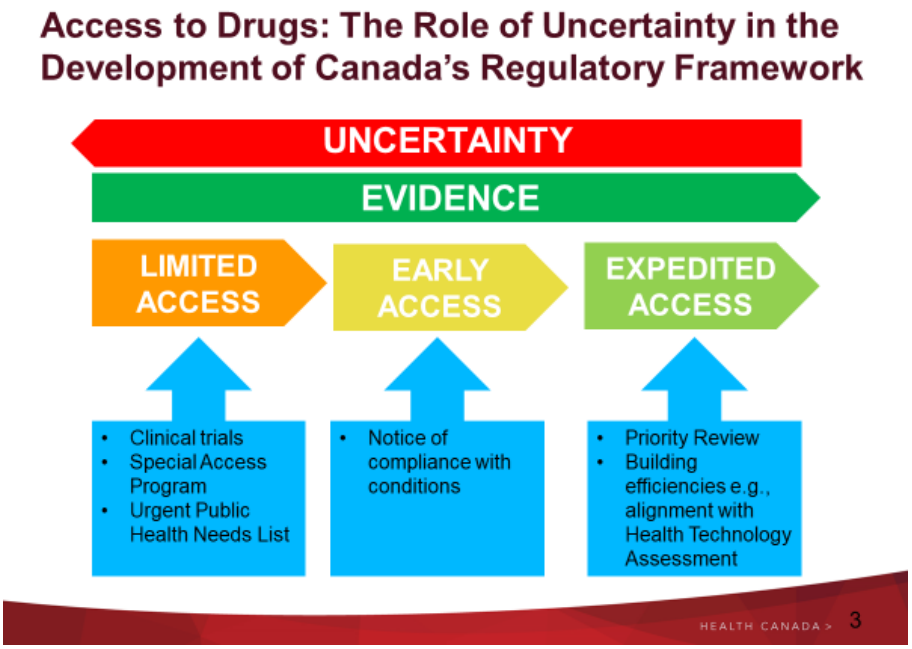
Regulatory viewpoint – Dr J Patrick Stewart, *Director General of Therapeutics Products Directorate, Health Canada*

Uncertainty plays a significant role in Health Canada's decision-making. Like many other regulatory jurisdictions, Health Canada has a drug approval system based on the quantity and quality of evidence, where access is on a continuum inversely related to uncertainty (see below). When robust evidence is lacking and uncertainty is high, the agency's preferred approach is to provide limited access through a clinical trial authorisation. However, other routes are possible, including Special Access Programmes (where practitioners can request unauthorised medicines for individual patients with serious or life-threatening conditions), and the Urgent Public Health Needs List (for drugs authorised in specific foreign jurisdictions that address urgent public health needs).

In Canada, early access refers to access through the Notice of Compliance with Conditions (NOC/c). Since this pathway was introduced in 1998, Health Canada's approach has evolved and adapted with regards to uncertainty and early access. Advancements in basic science, surrogate markers, real world evidence collection and a better understanding of patient and physician perspectives have in some cases "reset the evidentiary bar". However, it's important to consider that confirmatory studies with long-term expectations do not always yield relevant data or can take too long to produce data.

Since sponsors typically go to US and European markets first, Health Canada has a limited ability to influence drug development designs or push back on uncertainties. The agency has had to adapt to this reality, and as a result, has granted approval to several products with some evidence uncertainty. However, approval is not synonymous with access, as Canadian HTA bodies and payers have different evidentiary needs and requirements.

In order to better manage uncertainty, we must have a dynamic approach and be willing to evolve in response to experience and an ever-changing environment. The pressure to provide early access must always be balanced with patient safety and wellbeing, and early engagement between sponsors, physicians, patients and international regulators are integral to this.



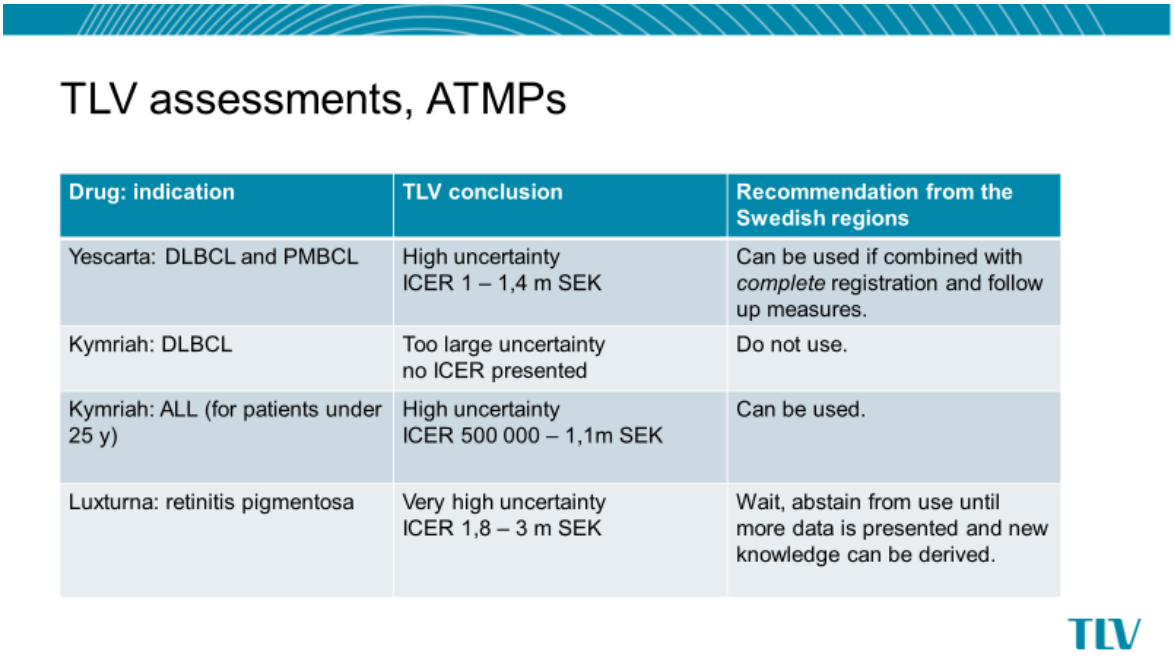
HTA viewpoint – Niklas Hedburg, *Chief Pharmacist, TLV, Sweden*

When you have to make a decision e.g. about reimbursement, a little data, or even *some* data, is better than no data. However, *any* data isn't better than no data, and the role of the HTA is to find the difference between *some* and *any*. While HTA bodies have become used to studying one group of patients and drawing conclusions about other groups, they are now faced with the new challenge of studying individual patients (or very small groups of patients) and drawing conclusions for other individuals, or perhaps the same individuals in a later stage of disease.

HTA bodies are concerned with uncertainties partly because they could become risks. Risk is the *probability* of an event occurring and the *consequence* of the same event. Even if the uncertainty and the probability are the same for different stakeholders, their consequences and therefore risks might differ. Therefore, regulators and HTA bodies may come to different conclusions or decisions, based on the same uncertainty.

Decision-makers must pay attention to the two possibilities of failure: Type A, saying yes to something that later proves to be bad; and Type B, saying no to something that later proves to be good. Waiting for more information or less uncertainty is not always the answer, and will increase the number of Type B errors.

TLV typically tries to categorise uncertainty in evaluation as *low, moderate, high,* or *very high.* There is a continuous effort to make this categorisation transparent and coherent. High or very high uncertainties are most significant in TLV's decision-making, and often apply to Advanced Therapy Medicinal Products (ATMPs) (see below). Internal discussions within TLV about these products have particularly focused on identifying the greatest uncertainties, understanding how the use and effectiveness of approved products could be monitored, and determining the need for new evaluation and payment models.



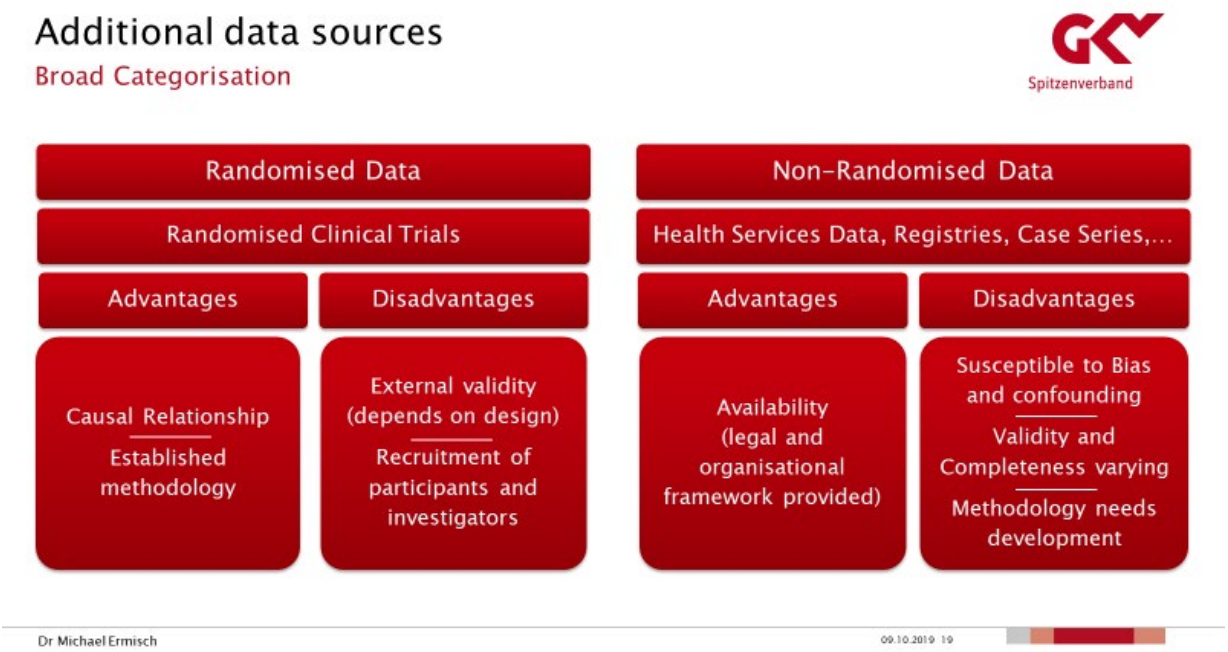
Payer viewpoint – Dr Michael Ermisch, *Specialist, GKV-Spitzenverband (GKV-SV), Germany*

Reasons for uncertainty include incomplete efficacy/safety data upon approval, questions around the external validity of clinical trials, and insufficient consideration of differences in healthcare systems. The European Medicines Agency granted 26 conditional marketing authorisations between 2011-2018, all of which used surrogate endpoints that had not yet been shown to reliably predict clinical outcomes [1]. Although payers must accept the societal need for early access in indications of high unmet medical need, such authorisations create significant uncertainty that does not always resolve with time.

In Germany, reimbursement is automatically granted for authorised medicinal products and HTA decisions establish whether a product provides 'additional benefit' over current treatment availability. A recent study has shown that over half of drugs entering the German market have not been proven to have added benefit [2]. This means that, for most drugs, German payers must either accept the unknown or use it to leverage price, which can be challenging. Final negotiated prices are always made public and may influence other European markets. In addition, conditional reimbursement is not yet feasible within the German system due to legal constraints.

Additional data can be collected from randomised or non-randomised sources (see below). Non-randomised data collection should be prospectively planned and registered, otherwise it could be susceptible to publication bias. Payers are not able to accept these new methods unless they've been proven to comparable validity as randomised control trials. [3]

In summary, uncertainties in studies supporting marketing authorisation expose patients, physicians and payers to therapies that are thus far experimental. Insecurities in the quantification of added benefit mean that the value of a medicinal product cannot be established, which causes problems for establishing value-based prices. Real-world evidence generation may not be a sufficient solution, unless its methodological problems are solved and responsibility shifts from the developers to payers and society are sufficiently addressed.



References:

[1] Schuster Bruce C, Brhlikova P, Heath J, McGettigan P (2019) The use of validated and nonvalidated surrogate endpoints in two European Medicines Agency expedited approval pathways: a cross sectional study of products authorised 2011-2018, *PLoS Medicine* 16(9). Available at https://doi.org/10.1371/journal.pmed.1002873

[2] Wieseler B, McGauran N, Kaiser T (2019) New drugs: where did we go wrong and what can we do better? *BMJ* 366. Available at https://doi.org/10.1136/bmj.l4340

[3] Hans-Georg Eichler, Franz Koenig, Peter Arlett, et al. (2019) Are Novel, Nonrandomized Analytic Methods Fit for Decision Making? The Need for Prospective, Controlled, and Transparent Validation, Clinical Pharmacology & Therapeutics (online). Available at https://doi.org/10.1002/cpt.1638

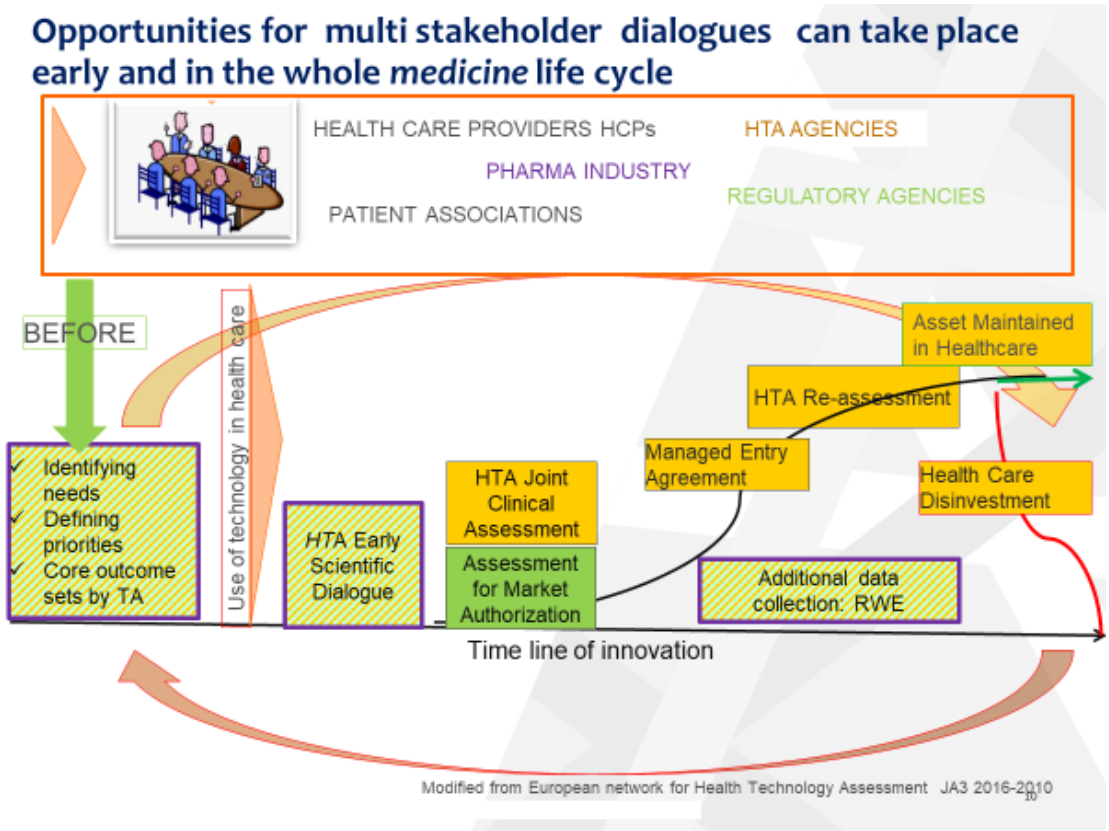
Reducing uncertainty in the development space – is it possible for companies to identify the priorities from regulators, health technology assessor and payers as to which clinical uncertainties need to be managed or resolved during development?

Company viewpoint – Dr Alicia Granados, *Head of Global HTA Scientific Strategy, Sanofi, Spain*

Uncertainty must be managed earlier in therapeutic development, without neglecting healthcare priorities. While early scientific dialogues offer a valuable opportunity to optimise development programmes, there is often poor alignment between regulatory and HTA evidentiary requirements, making it difficult for technology developers to know which to follow. Referring to an internal value framework can assist with these decisions. For example, Sanofi has developed a holistic framework featuring six value dimensions (unmet needs, population, outcomes, intervention, economic impact and context) to ensure that evidence generation is relevant to patients, physicians and healthcare authorities.

Further research on the impact of seeking advice on prospective HTA recommendations is needed, though emerging evidence suggests that it is beneficial. Companies are unlikely to have the capacity to undertake the increasing number of HTA early dialogue opportunities, so will need to prioritise on where to put their resources. Horizon scanning for HTA can facilitate understanding of the diversity in value frameworks and potentially identify commonalities in evidentiary requirements.

Uncertainties can be reduced as more evidence is generated over time, ideally informed by iterative multi-stakeholder dialogue and assessment (see below). In the context of early access in the EU, there are several collaborative initiatives to improve both evidence generation and assessment, including adaptive pathways, the priority medicines (PRIME) scheme, EMA-HTA parallel advice and the SEED (Shaping European Early Dialogues for health technologies) project facilitating multi-HTA advice.



What are the types of uncertainties that cannot be resolved during development and why is it important to acknowledge these early in development?

Company viewpoint – Adam Heathfield, *Senior Director, Patient and Health Impact, Pfizer, UK*

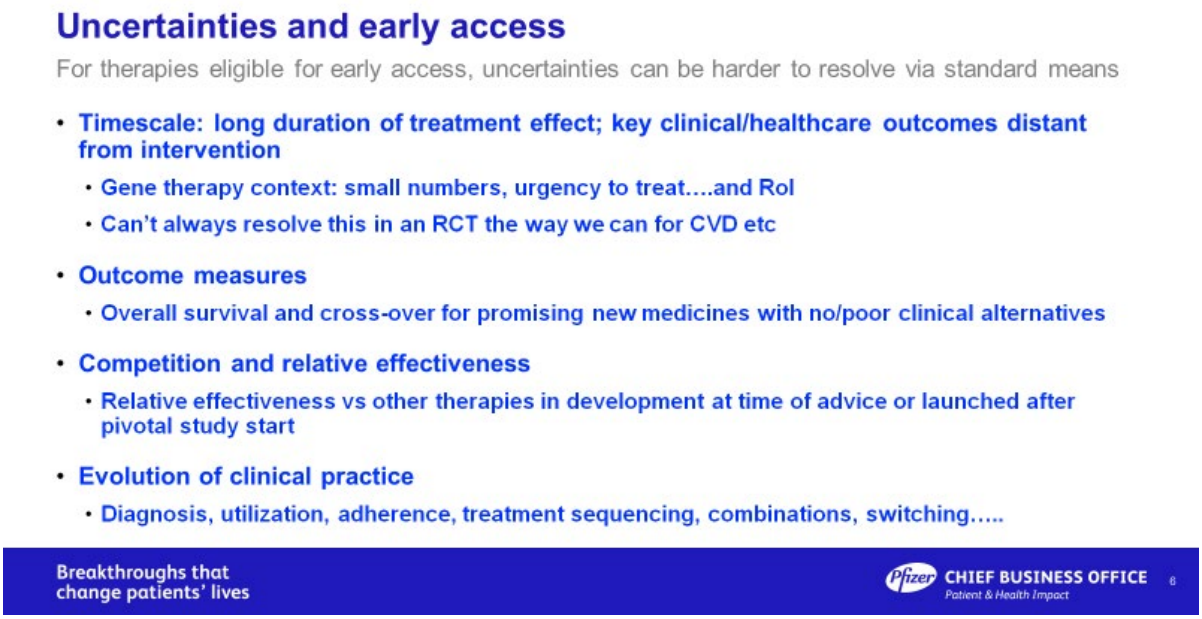
In the overall healthcare landscape, there is a willingness to accelerate access for medicines that address high unmet need, tackle serious/life-threatening disease and have promising early data. In addition to regulatory conditional marketing authorisations, there are many early access compassionate use programs that have been set up by governments in various countries in recent years. While dialogue with regulators appears to be supporting the conversion of conditional marketing authorisation into full marketing authorisations, HTA and payers have different questions or evidence standards that are harder to agree on.

Many questions throughout the medical product life cycle could be resolved via randomised controlled trials (RCTs) and other data e.g. epidemiological studies, real-world evidence (RWE) [1]. However, it may be difficult to resolve some of these uncertainties at a local level in every health system, so developers may need to prioritise on what is the best use of time and resources.

For therapies eligible for early access, uncertainties arising from issues such as shortened timescale, outcome measures, competition and relative effectiveness, and evolution of clinical practice can be harder to resolve via standard means (see below). For example, a typical RCT cannot demonstrate the duration of effect of a gene therapy for a rare disease.

HTAs do not always give clear, actionable advice to companies, particularly regarding RWE where both sides are still learning. This can sometimes lead to a “courtesy loop” where neither side wants to be the first to give direction on the use of RWE. As a result, companies may be unsure as to the business case for implementing HTA advice and be concerned about “mission creep”, or greater access burdens.

To facilitate better management of uncertainties, companies should have a cross-functional understanding of all current and future evidence gaps. While there can be issues around the clarity and feasibility of HTA advice, companies should ensure they are asking the right questions and consider taking consolidated parallel consultation pathways.



References:

[1] Bate et al. (2016) Designing and incorporating a real world data approach to international drug development and use: what the UK offers, *Drug Discovery Today*, 21(3):400-405

Regulatory viewpoint – Prof Hans-Georg Eichler, *Senior Medical Officer, European Medicines Agency (EMA)*

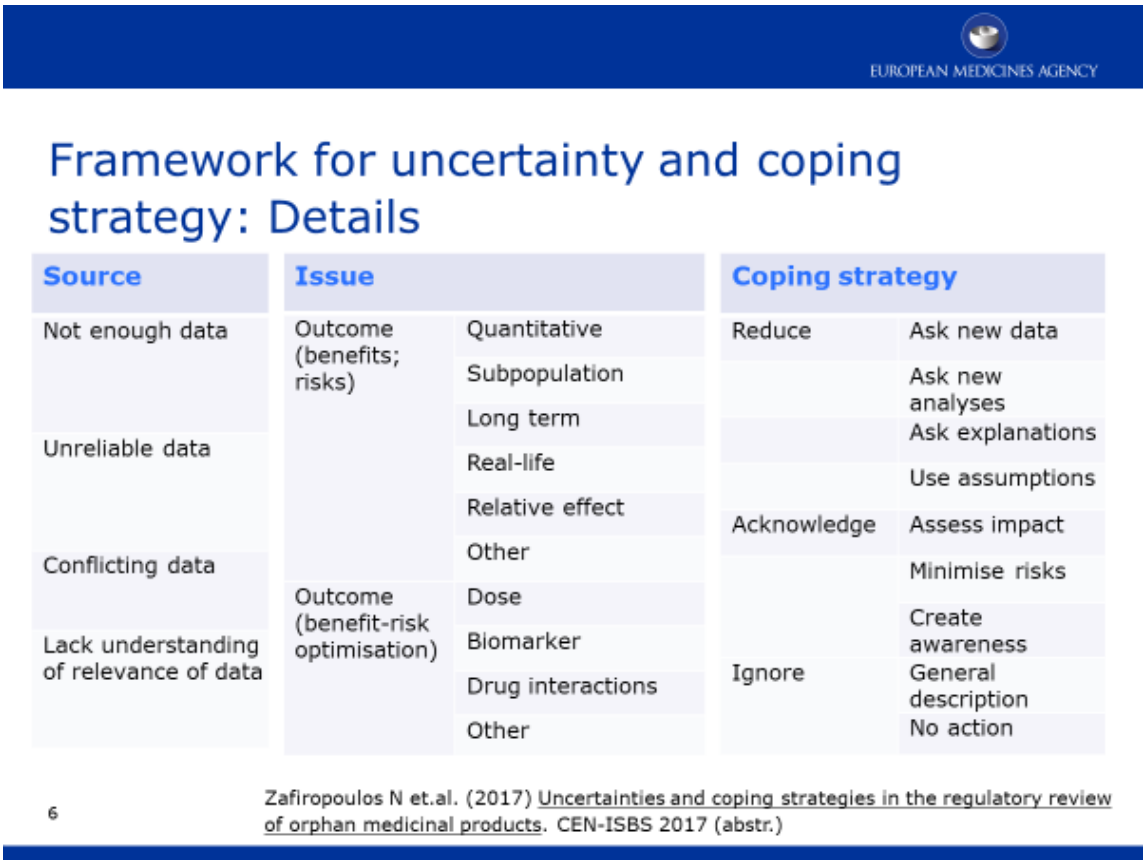
Many uncertainties within drug development are scientific, but there can also be behavioural uncertainties that should be considered. For example, the uncertainty around how a drug will be used in clinical practice (physicians might prescribe a higher dosage or for a different patient group), or the uncertainty that a company will deliver on promises made at launch.

Uncertainties are well-recognised in regulatory decisions and their acceptability depends on context. Regulators need to describe the source of uncertainty, communicate surrounding issues and identify and communicate coping strategies. For example, if there is uncertainty around treatment effect because of unreliable data, a patient registry could be a potential coping strategy. Known, scientific uncertainties at the time of approval can be found in the benefit-risk section of European Public Assessment Reports (EPARs) and coping strategies are presented in Annex II and the Risk Management Plan.

A framework for classifying uncertainties and coping strategies (see below) was applied to all oncology products approved by the EMA between 2011-2017 [1]. This showed that a lack of randomised control trials was associated with a higher number of uncertainties about safety issues. Not enough data was the main source of uncertainty, requiring submission of post approval data. The highest number of uncertainties were observed in ultra-rare orphan indications, and somewhat surprisingly these were frequently due to unreliable data, rather than not enough data.

To date, EMA's track record of accepting higher levels of uncertainty is reassuring. Of the 38 conditional marketing approvals granted since 2006, half have been converted to full authorisations, one has been withdrawn from market and the rest remain conditional. However, this could be interpreted in several ways: is this a chance finding? Are regulators reluctant to change their own assessments? Are regulators really good at picking the 'winners'? Or are regulators (at least in Europe) too risk averse and the threshold for accepting higher uncertainty is too high?

Further studies could be directed towards understanding longitudinal evolution of uncertainties in a product, with a focus on the initial phases of assessment and post-approval. It would also be beneficial to explore therapeutic areas outside of oncology and rate the impact of uncertainties, as well as evolve the framework and pilot incorporating it into guidelines and templates.



References:

[1] Zafiropoulos N et.al. (2017) Uncertainties and coping strategies in the regulatory review of orphan medicinal products [poster]. CEN-ISBS, 28 Aug – 1 September 2017, Vienna. Available at: http://www.asterix-fp7.eu/media/uploads/file/CEN-ISBS%20Poster%2028-08-2017.pdf

HTA and payer viewpoint - Andrew Mitchell, *Strategic Adviser, Evaluation, Department of Health, Australia*

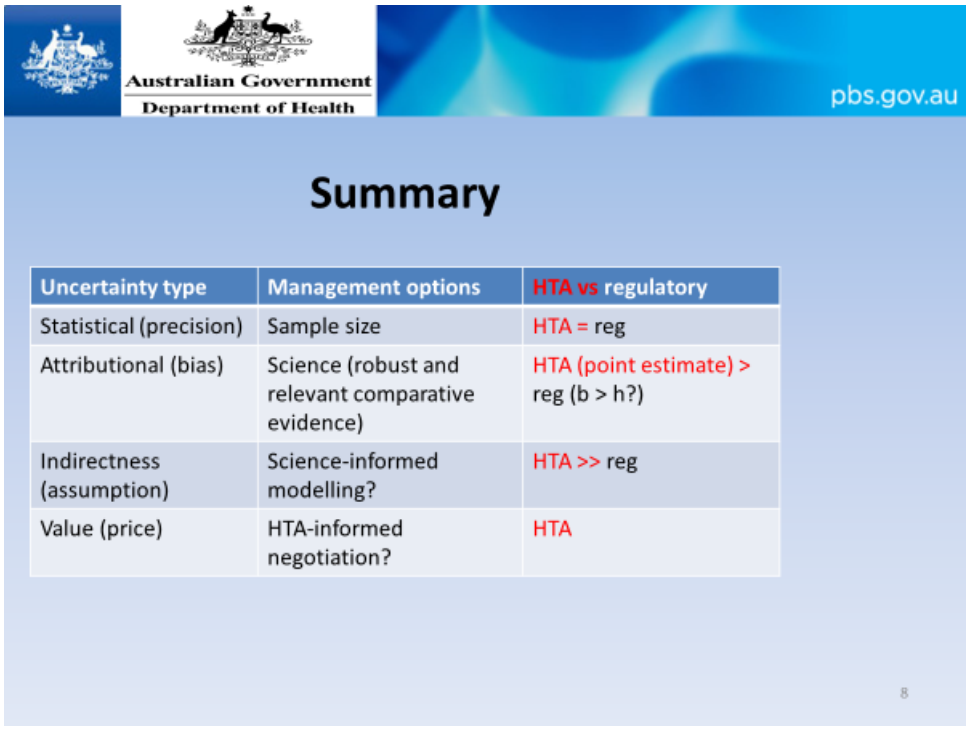
Unresolvable uncertainties during development include long-term patient-relevant health outcomes, infrequent health outcomes, price and therefore, cost per patient. Although some of these uncertainties can be managed through post-market data collection, the issue for companies and HTA-informed payers is that many important decisions must be made with pre-market data only.

It may be possible to resolve uncertainties such as random and systematic error, incremental health outcome estimates and incremental healthcare resource consequences. Adequate sample size and scientific rigor can reduce imprecision and bias, respectively. To resolve incremental outcome estimates, there needs to be a 'counterfactual' comparison available e.g. in addition to the quantified estimate of the outcomes from a single-arm study, the quantified estimate of the outcomes for patients who would not have received the proposed medicine is required. This may be challenging in the case of rare diseases where prognostic data is often scarce or nonexistent.

Science cannot provide all information needed by HTA-informed payers; assumptions are made to cover gaps in available evidence and price is never generated by science alone. Management of the 'evidence to assumption' ratio is dictated by how large the incremental cost is, particularly the incremental cost per patient. In addition, many third-party payers are concerned with the related incremental costs per year to their budgets. In general, the larger the incremental costs, the smaller the evidence to assumption ratio and the harder it is for payers to justify paying for a medicine. Although a lifecycle approach will help to mitigate these difficulties, the most acute pressure point remains at the time of market entry, when the launch of a medicine can be greatly affected by whether a third-party payer decides to subsidise the cost to the patient.

The main HTA toolkit to address uncertainty is the modelled economic evaluation, a mathematical composite developed by a modeller using computer software. These models, which are subject to scenario and sensitivity analyses for robustness, identify uncertainty drivers and their consequences for decision making. Reaching a common position on the model is usually a prerequisite to reaching agreement to subsidy.

Although it may not be possible to eliminate uncertainties or resolve them, we must be able to manage uncertainties to the point where defensible decision-making functions can proceed in a systematic way. It's important to recognise that some uncertainties may be more difficult to manage than others and may be perceived differently between HTA bodies and regulatory agencies (see below).



What type of scientific advice/early dialogues (joint, parallel, multi HTA) enable a company and agency to potentially map stakeholder perceptions regarding resolvable versus unresolvable uncertainties?

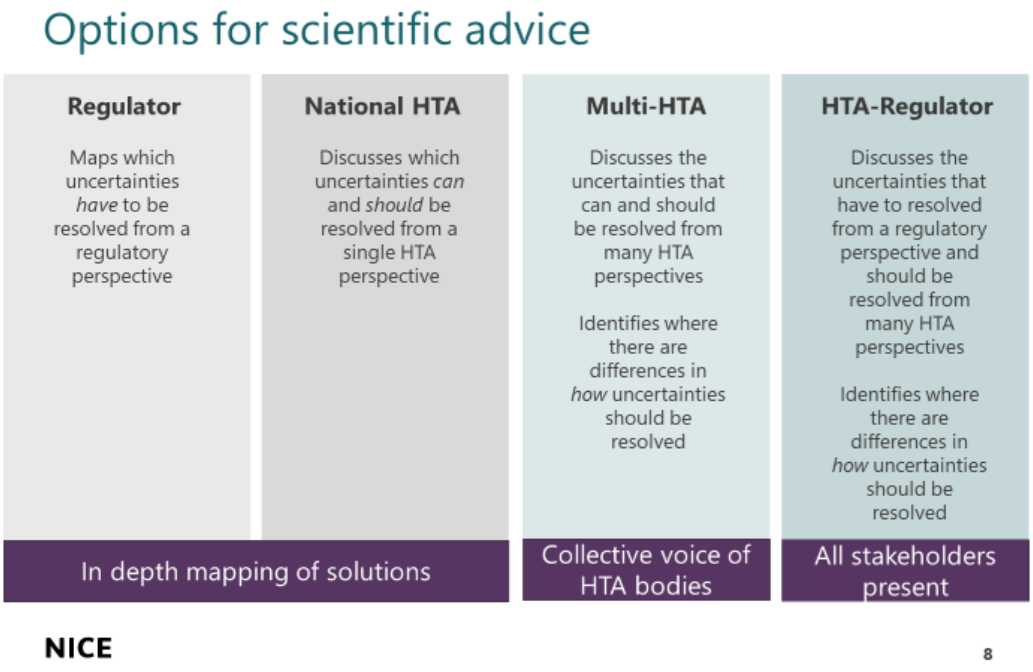
HTA viewpoint – Jeanette Kusel, *Director for Scientific Advice, NICE, UK*

Scientific advice allows early dialogue between stakeholders, to map where uncertainties can and should be resolved. In addition to companies, regulators and HTA bodies, healthcare professionals and patients are important stakeholders in scientific advice processes, though there may be more effective ways to capture their perceptions and feed these into clinical development.

Most uncertainty during clinical development is resolvable, but not necessarily within a single trial framework to satisfy all stakeholders. Regulators and HTA bodies often have different concerns about the trial population, intervention, comparator and outcomes. For example, regulators might be concerned about heterogeneity within the comparator, whereas HTA bodies might be more concerned about whether that comparator is equivalent to a relevant comparator used in clinical practice in their jurisdiction.

There are several types of scientific advice available that map which uncertainties have/can/should be resolved (see below). When NICE first initiated its scientific advice ten years ago, most projects were NICE-specific, but this is slowly shifting towards joint advice e.g. MHRA-NICE, EUNetHTA Multi HTA, EMA-EUNetHTA.

The current paradigm is for companies to seek scientific advice from regulators first and plan trials to resolve uncertainties that are important to the regulators. This leaves limited scope for changing these trials to resolve uncertainties that are important to HTA bodies. A new paradigm should be explored where joint HTA and regulatory advice is sought early on and on entire clinical development plans, rather than individual trials. Once trial protocols are developed, there could potentially be another round of advice with individual regulators and HTA bodies to make any final adjustments. The output may be a portfolio of evidence collection studies of different types, designed to resolve the full range of necessary uncertainties across stakeholders.



Could the utilisation of a context adaptable framework approach e.g. SEPPE be used to identify gaps in stakeholder evidentiary requirements and resolve uncertainties?

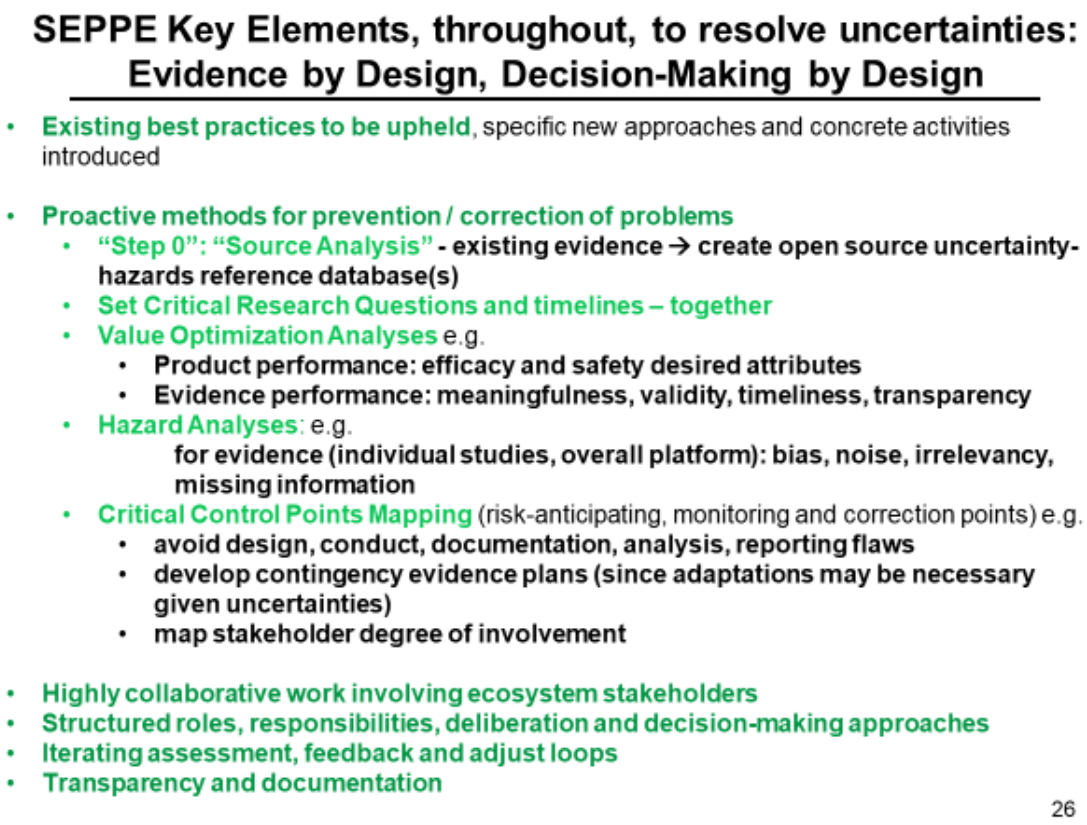
Regulatory viewpoint - Dr Robyn Lim, *Chief Scientific Advisor, Health Products and Food Branch, Health Canada*

Structured Evidence Planning, Production, and Evaluation (SEPPE) is a context-adaptable practice framework proposing that evidence be treated as something produced, much like manufactured goods, with global, built-in quality processes and proactive, iterative feedback from key decision-makers at critical, pre-identified control points (including decision points) in product R&D [1]. Explicit, specific approaches could narrow existing gaps between product and evidence needs and evidence and decision outcomes. This structured and predictable approach requires increased stakeholder collaborations and a shift to more comprehensive, built-in quality mindsets and procedures to avoid evidence quality defects and ensuing complications for decision-makers.

SEPPE consists of five main activity domains: understanding stakeholder product needs, understanding stakeholder evidence needs, planning evidence, producing evidence and evaluating the therapeutic product i.e. evidence performance, product performance and contexts. Cooperative risk anticipating, monitoring and corrective actions are built in along the way through multiple feedback loops, helping to avoid the avoidable problems, such as evidentiary uncertainties, and confront the unavoidable ones. A dedicated, long-term commitment to systemic transformation is critical for success.

SEPPE could provide a means to routinely and transparently align goals and incentives across stakeholder communities, improving health ecosystem connections and behaviours. For example, it gives patients, prescribers, and payers systematic opportunities, from earliest stages of product conception and evidence design and development, for their voices to be heard and actioned in evidence before it is too late in the development cycle. It could also integrate and streamline regulatory, HTA and payer efforts, as well as reduce development waste and costs for industry. For instance, establishment of open-source reference databases, cataloguing specific types of evidence uncertainties and their critical control points during product development, could provide an innovative, system-learning springboard for future R&D efforts

Although it is not possible to eliminate all evidence uncertainties under SEPPE, it could curtail moments where avoidable uncertainty becomes the issue tipping towards negative decisions. In addition, SEPPE could enable more careful handling of decision points for products not living up to their promise, potentially decreasing costly and resource-intensive negative licensing and reimbursement decisions. Lastly, SEPPE could inform strategic R&D choices, aligning these with health system priorities and needs above and beyond the level of individual products, by prompting decision-makers in R&D and policy development to collaboratively confront emerging issues and opportunities far upstream.



References:

[1] Lim R. et al (2018) Recognising that evidence is made, not born, *Clinical Pharmacology and Therapeutics,* 105(4), p844-856. Available at: **https://doi.org/10.1002/cpt.1317**

Are today's tools for addressing clinical uncertainties during development sufficient to meet the stakeholder's needs or are new approaches required to bridge the regulatory HTA gap?

HTA viewpoint – Dr Michael Kulig, *Head of Working Group Pharmaceuticals, Medical Consultancy Department, G-BA, Germany*

The aim of the G-BA is evidence-based optimal care at a reasonable price, even in the case of uncertainty. At the time of market access, G-BA carries out an initial benefit assessment to determine the extent of additional benefit compared to standard of care, which then informs pricing negotiations and a rebate after one year of access. A second additional benefit assessment is possible due to resolutions with time limits defined in the early assessment, and often with requirements for more data on safety i.e. late or rare adverse events, patient-relevant outcomes, and relative effectiveness. This may result in pricing re-negotiations, and in the case of orphan drugs, there is an obligatory additional price rebate if quantification of additional benefit is not possible.

As of September 2019, 92 orphan drugs had been assessed by G-BA. Although 73% of assessments included RCT data, there were still significant uncertainties related to long-term evidence i.e. study duration and follow-up, sample size, patient relevant outcomes, clinically relevant benefits and risk of bias. Interestingly, there seemed to be a difference in opinion on the relevance of primary endpoints (industry rated as patient-relevant in 92% of cases, whereas G-BA said the same in only 36% of cases).

The absence of an adequate control group is an issue for HTA assessments. External controls have major limitations including questions around validity, missing information regarding patients and disease characteristics, missing safety and quality of life outcomes and limited reporting quality. Early planning of additional evidence generation is important in managing uncertainty around external controls.

Early advice and dialogues (as early as possible) involving all stakeholders can provide tools for reducing uncertainty. 6/8 pharmaceutical companies reported to G-BA that they had made changes to their development plans following early dialogue. It may also be beneficial to estimate uncertainty using standard methods of evidence-based medicine or the international GRADE (Grading of Recommendations, Assessment, Development and Evaluations) approach.

Requirements for further evidence from HTA and regulatory bodies may be sufficient in managing or reducing uncertainty. However, generating relative effectiveness data after market access is very difficult as there is bias by indication, and at least in Germany, reimbursement of the new drug may limit the availability of controls. Germany is currently rolling out an obligatory IT rating system, which will inform physicians and their patients about evidence quality and uncertainties of new drugs.

Methods and tools sufficient for estimating and managing uncertainty?

During development until market access	Sufficient?
▪ Early scientific advice at national level	?
▪ Early dialogues at international level (e.g. EUnetHTA)	+
➢ relevant stakeholders involved? industry, regulatory, HTA, patients	++ Changes of study planning in ≈75%
➢ impact?	
▪ Relative effectiveness?	++
External control gruops if no RCT?	?
➢ Early planning of additional evidence generation (especially for external controls)	++
➢ Control treatment available and adequate (i.e. standard of care)	?
➢ Due to confounding only huge or dramatic effects acceptable	?
▪ Estimating uncertainty / bias of results	++
➢ Standard methods of evidence based medicine	
➢ International GRADE approach	

Gemeinsamer Bundesausschuss

Folie 9 | 9 Oct 2019 | Uncertainty – HTA viewpoint | Dr. Michael Kulig

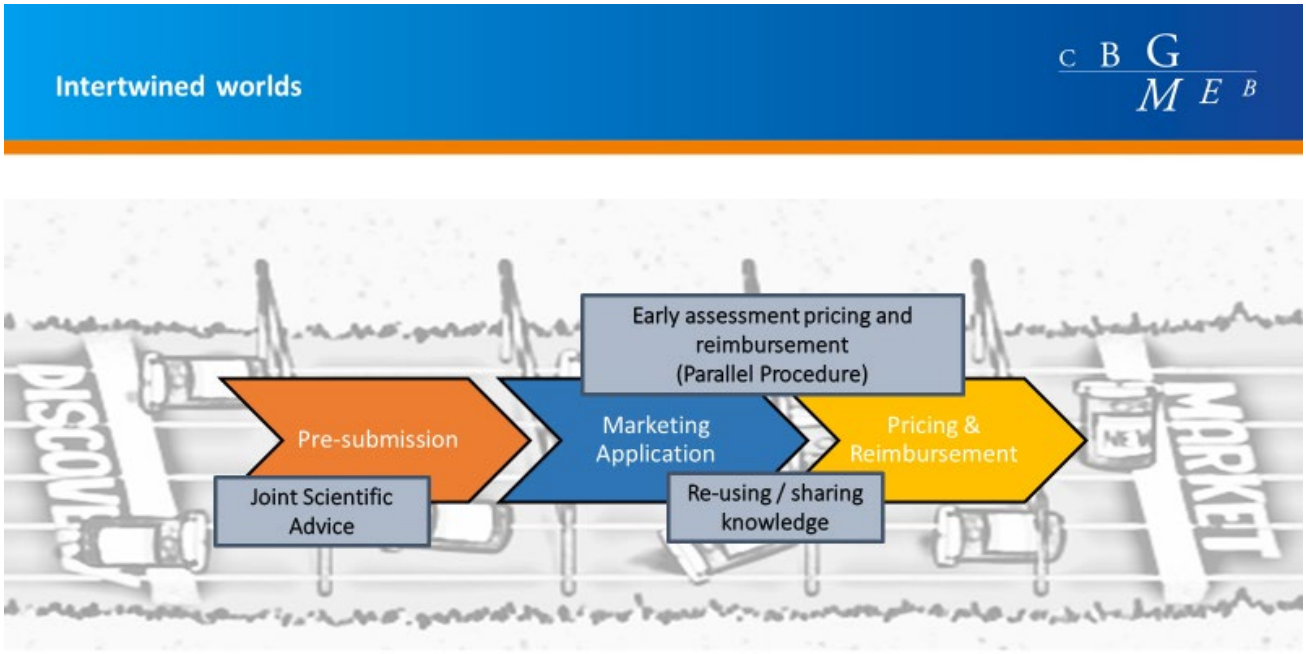
Regulatory viewpoint – Prof Anthonius de Boer, *Chair of the Medicines Evaluation Board (MEB), The Netherlands*

Marketing authorisation often does not translate into patient access. The average assessment time for reimbursement in the Netherlands is 88 days but it can take up to 262 days. Delay can be explained by a hold-up in submission to the National Healthcare Institute (ZiNL), but can also be linked to the different roles and evidentiary requirements for regulatory and HTA decision-making: benefit-risk and clinical effectiveness versus budget impact and cost-effectiveness. However, regulatory and HTA-decision making is becoming increasingly intertwined. Consequently, tools such as joint scientific advice and parallel procedures, are explored to close the regulatory and HTA gap and to streamline decision making.

In the Netherlands, Joint scientific advice with the MEB and ZiNL can be requested by 'the company' and usually takes place after phase I of clinical development. Depending on the questions being asked, patient organisations and the Central Committee on Research Involving Human Subjects (CCMO) may also be present. These collaborations have increased understanding and problem solving and helps to align study design requirements, which in turn could result in more relevant data for both registration and reimbursement.

The MEB and ZiNL are currently trialling a novel parallel procedure to facilitate early assessments of pricing and reimbursement. ZINL starts its assessment after Day 181 of the centralised marketing authorisation application procedure, Subsequently there is a meeting between MEB and ZiNL, with the aim to re-use gained knowledge on the disease and product, to provide context on the clinical studies performed and to avoid unnecessary duplication between procedures. This will allow the MEB and ZINL to streamline procedures and to increase patient access.

Joint scientific advice can help to meet stakeholder needs with regards to addressing clinical uncertainties during development for both market access as well for reimbursement. Benefits of the Netherlands' pilot parallel procedure include expedited patient access, more synergised procedures and increased sales revenue for the company. However, challenges remain such as pricing in the Netherlands, which is not listed as one of the 'first wave countries' for market introduction, and caution about the influence that regulators have on HTA decision making and *vice versa*.



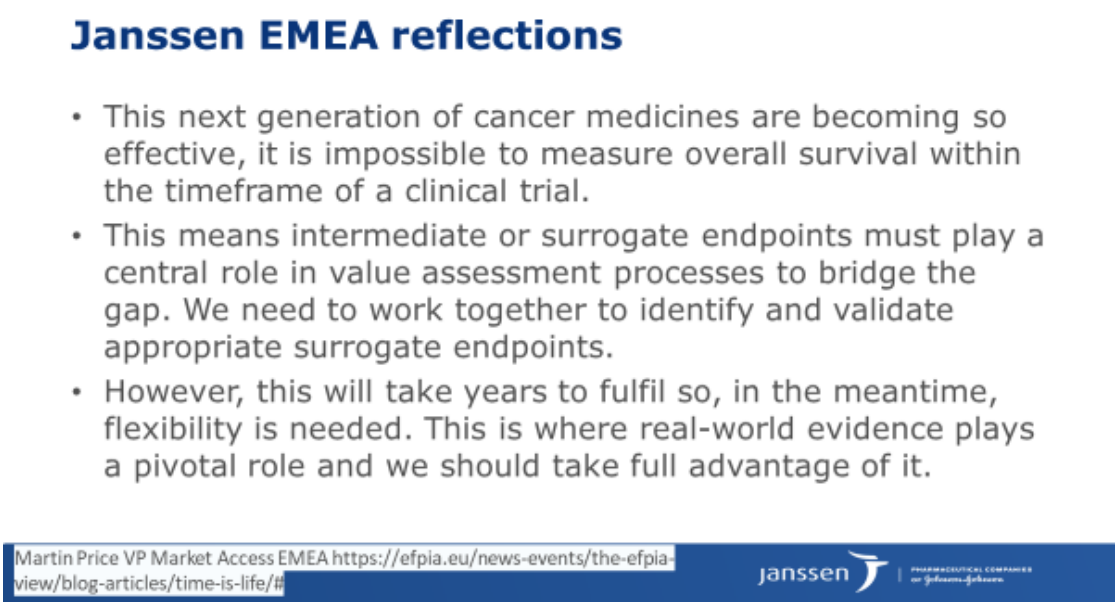
Company viewpoint – Shane Kavanagh, *Vice President, Health Economics, Janssen*

Cancer medicines are becoming so effective, it is impossible to measure overall survival within the timeframe of a clinical trial, which means that surrogate endpoints must play a central role in value-assessment processes [1]. However, it can take years to identify and validate appropriate surrogate endpoints, so flexibility is needed, and real-world evidence must play a pivotal role.

Janssen is a frequent user of early scientific advice across all the different available modalities. Key considerations for undertaking early HTA advice include cross functional effort, focus on product and indication, development phase, timings and timelines, confirmatory versus exploratory advice and range of different opinions across HTAs. Issues that can arise include the feasibility and performance of clinical outcomes assessment, the balance between evidence completion and burden, pre-qualification of patient-reported outcomes, cross-stakeholder perspectives and best use of scientific advice.

It is important to define uncertainty and understand different perspectives between regulators and HTA agencies. For example, within oncology, uncertainty related to overall survival data could be due to the direction of treatment effect, the strength of treatment effect, the quantification of treatment effect or data extrapolation. Collecting longer term trial data may help to reduce uncertainty but there are many ethical, operational and design issues to consider such as the effect on patient retention and changes in standards of care.

Finally, innovative payment models and outcomes-based risk-sharing approaches must become more widely accepted. Discussions should be started before new treatments are approved and involve all stakeholders, including payers, advocacy organisations and physicians, so that all options can be considered and access solutions co-created.



References:

[1] Price M. (2019) Time is life (Guest blog). [Blog] *The EFPIA View*. 3 October 2019. Available at: https://efpia.eu/news-events/the-efpia-view/blog-articles/time-is-life/# (Accessed 25 November 2019)

Utilising a life cycle approach as the way forward to manage uncertainties for early-access medicines: what are the practical considerations?

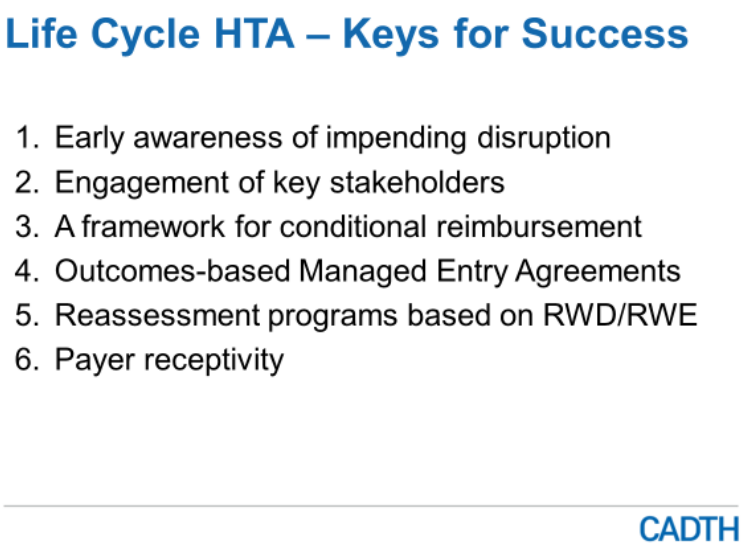
HTA viewpoint – Dr Brian O'Rourke, *President and CEO, Canadian Agency for Drugs and Technologies in Health (CADTH)*

Health systems around the world are facing a perfect storm of challenges in their ability to manage robust pipelines of promising and disruptive technologies. These include drugs with novel mechanisms of action, drugs for rare diseases, immunotherapies and other cancer drugs, and expensive drugs for common diseases. Increased demand for early and equitable access is accelerating the number of regulatory approvals, having a knock-on effect on the already limited capacity of healthcare systems and payers and resulting in an affordability crisis.

There needs to be a broader approach to HTA, shifting towards health technology management across the medical product life cycle. A good relationship with the national regulator, and meaningful engagement of patients and clinicians, are keys to facilitating evidence-informed implementation and for finding solutions for the delivery of new innovative technologies into care pathways. CADTH has recently started to embed its staff in health ministries and in hospitals to assist with decision-making and implementation around these technologies.

CADTH is starting to launch a reassessment programme based on real-world evidence, which has several benefits including facilitating conditional reimbursement and allowing early access for patients with the greatest need, supporting managed access and managed exit, allowing for expansion/contraction of the approved patient population, promoting appropriate prescribing and use, and fostering affordability. However major changes to recommendations could be challenging for payers, particularly if the recommendation becomes negative and there is a need to de-list a drug or further restrict prescribing.

A life cycle approach to HTA can facilitate the management of uncertainties for early-access medicines, but relies on several key elements and practical considerations (see below). To improve access while creating more predictability for payers and sponsors, there must be a shift beyond rebates to real risk sharing, such as performance-based agreements, risk pooling, and annuity-like payments. Payers need to be open to conditional reimbursement, managed entry and creative payment schemes e.g. Louisiana's subscription-based model for unlimited access to hepatitis C treatment [1].



References:

[1] Louisiana Department of Health (2019, June 26) Louisiana launches hepatitis C innovative payment model with Asegua Therapeutics, aiming to eliminate the disease. [Press release] Accessed from: http://ldh.la.gov/index.cfm/newsroom/detail/5181

How to manage uncertainty and mitigate risks identified at the time of approval and reimbursement using post-licensing evidence generation – what are the future opportunities and current barriers?

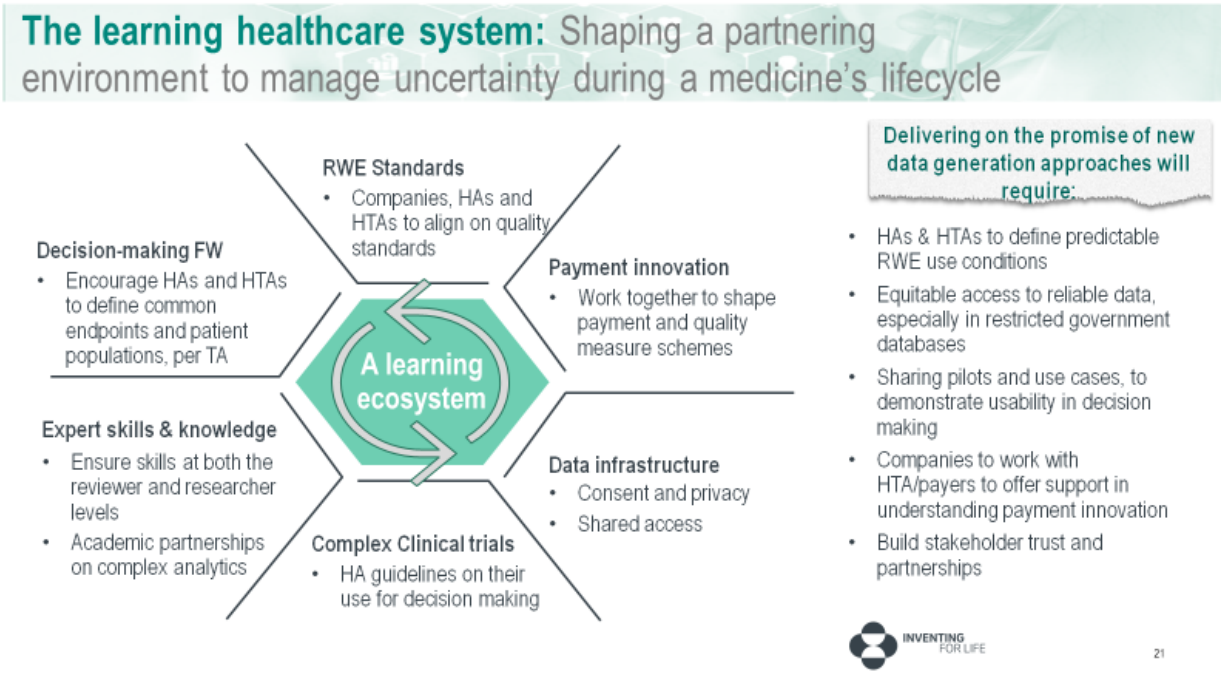
Company viewpoint – Dr Magdalini Papadaki, *Associate Director, Business Strategy & Operations, MSD, UK*

The benefit-risk (BR) profile of a new drug continues to evolve as evidence accumulates through real-world use and monitoring. How these data are used in assessment and decision making depends on the value drivers, purpose and views of key stakeholders, which are primarily regulators, HTA bodies and payers.

New regulatory pathways may allow for progressive build-up of a product's BR profile, using RWE and other approaches beyond RCTs. However, a lack of common evaluation standards in global HTA processes and differing assessment priorities among regulatory and HTA bodies can slow patient access to new therapies, requiring the submission of additional BR evidence after product approval. Although outcomes-based entry agreements and value-based contracting are promising tools for managing uncertainty, experience is still to be gathered in using RWE to design and implement these arrangements.

RWE can address some of the challenges of traditional RCTs, if stakeholders agree on data quality standards, evidence design principles and characteristics. Leveraging the promise of RWE and new trial designs calls for operational adaptations, new data-driven strategies, and an integrated partner ecosystem that captures high quality data, minimising gaps and allowing long-term follow up. Ultimately, new approaches to generate better BR information can enhance patient healthcare and outcomes, promote health system efficiencies and allow continued investment in innovation.

Pharmaceutical companies are already investing in new evidence-gathering approaches and systems, to complement the use of RCTs. However, to move forward with utilising different ways of managing uncertainty post-licensing and to ensure health systems benefit from the growing availability of RWE, innovator companies, regulators, HTA agencies and other stakeholders need to build capabilities and partnerships to understand and use RWE.



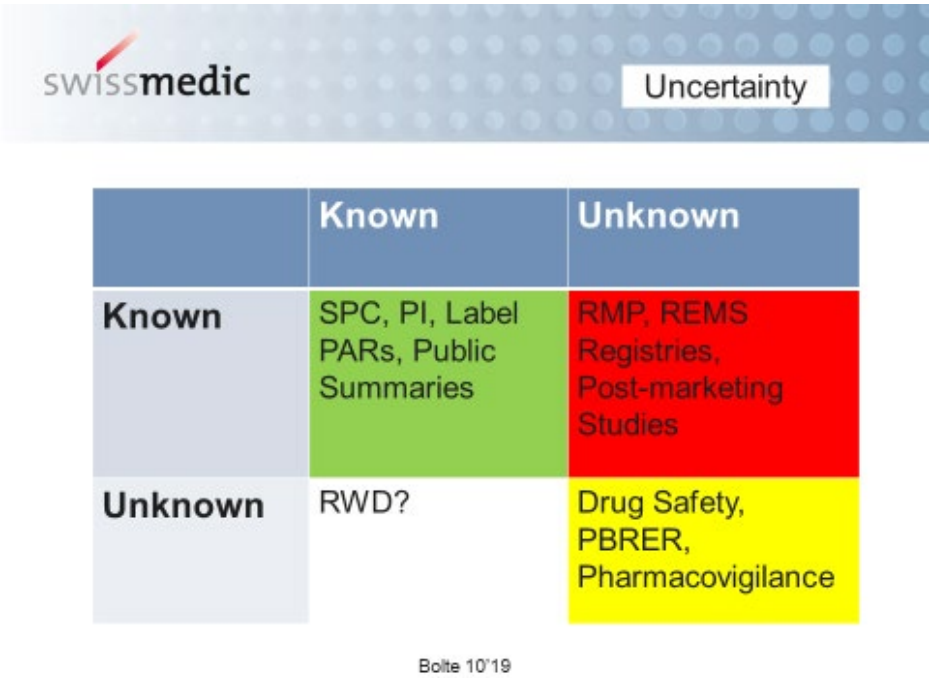
How should the level of known and unknown uncertainty and risk be communicated to key stakeholders at the time of product approval for early-access medicines?

Regulatory viewpoint - Dr Claus Bolte, *Head of Sector Marketing Authorisation, Swissmedic*

Uncertainties should be defined and described within the context given. They could be known knowns, known unknowns or unknown unknowns (as famously described by Donald Rumsfeld). Several tools exist to help stakeholders understand uncertainities, including Summaries of Product Characteristics (SPC), Prescribing Information (PI), Public Assessment Reports (PARs), Risk Management Plans (RMPs), Risk Evaluation and Mitigation Strategies (REMS), real-world data (RWD) and Periodic Benefit Risk Evaluation Reports (PBRERs) (see below).

In order to manage these uncertainties, we need to make decisions, so identifying, establishing and implementing best decision making practices is vital. CIRS has developed 10 Quality Decision-Making Practices that establish clear responsibilities, ensure decision quality, relevance and importance, consider decision alternatives and impact, and ensure decision transparency and communication [1]. To effectively communicate the basis of a decision, it is important to provide a record trail and explain the criteria and process used. Consistent application of these decision-making practices may help to reduce discrepancies between different regulators around drug indications.

Swissmedic provides active, passive and reactive information to its national and international stakeholders, including patients, healthcare professionals, professional societies and government colleagues. Communication approaches should involve your target audience and be tailored appropriately. For example, fact boxes are being considered to communicate quantitative evidence-based information about the benefits and harms of interventions to patients in Europe [2].



References:

[1] CIRS R&D Briefing 61 - Building Quality into Decision-Making Processes in Medicines' Development, Regulatory Review and Health Technology Assessment (2019). Available at: http://www.cirsci.org/wp-content/uploads/2019/09/CIRS-RD-Briefing-61-Decision-making-09092019.pdf

[2] Gigerenzer G., Kolpatzik K. (2017) How new fact boxes are explaining medical risk to millions. *BMJ,* 257: j2460. Available at: https://doi.org/10.1136/bmj.j2460

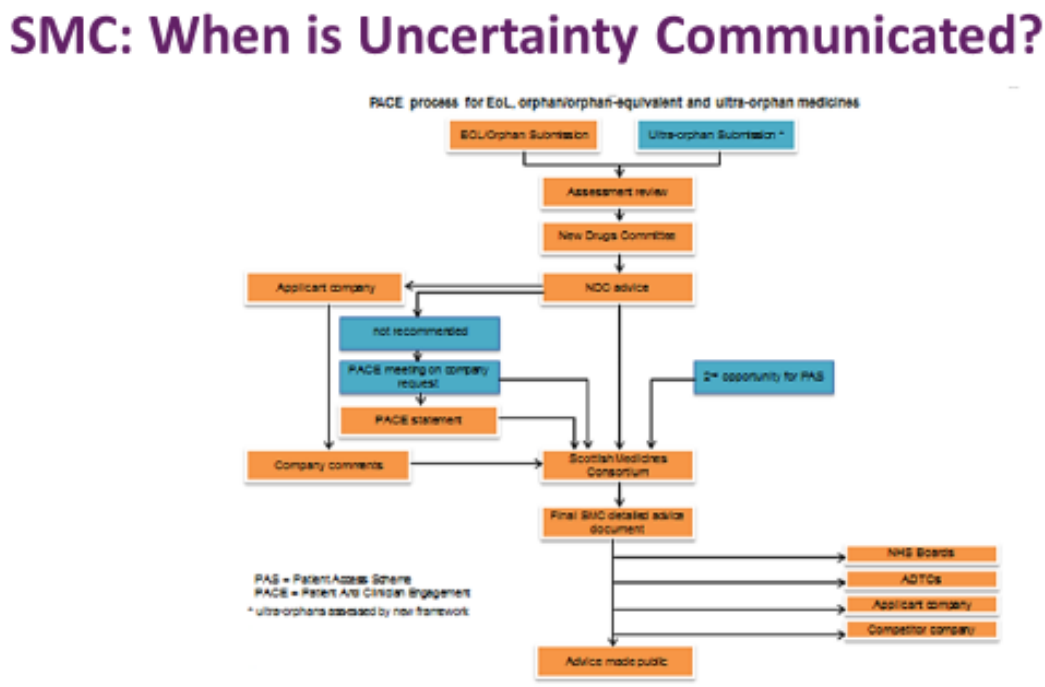
HTA viewpoint – Alan MacDonald, *Chairman, Scottish Medicines Consortium (SMC)*

The SMC needs to communicate with a range of stakeholders, including drugs and therapeutics committees from the 14 regional National Health Service (NHS) boards that make up NHS Scotland, submitting companies and their competitors, patient groups, patients and caregivers, government and parliamentarians, and the people of Scotland. From the point of submission, there is ongoing communication between SMC and the submitting company (see below). The SMC may request more data or further scenario analysis in order to address uncertainties in the submission. Once the decision-making committee has taken place, there is further dialogue with the submitting company to ensure the accuracy of advice statements that are ultimately to be made public.

When communicating decisions to the public, it is beneficial to be able to report key studies and up-to-date data in order to explain known and unknown uncertainties related to clinical effectiveness. Communicating the cost per QALY is helpful in terms of openness and transparency, however, it may not be possible to communicate overall QALY gains and there is inevitably going to be a lack of clarity around patient discounts.

SMC strategies to mitigate uncertainty can include complex Patient Access Schemes, an Interim Acceptance Option and the new Ultra-Orphan Pathway. The first step of the Ultra-Orphan Pathway is an initial assessment to validate the drug of interest as ultra-orphan. This is similar to a traditional SMC assessment, except that there is no requirement to come to a decision; if the drug is found to be ultra-orphan, reimbursement is granted for three years and during this time more evidence is generated. There has been considerable discussion about how evidence is collected, who does it and who pays for it. After the three-year period, SMC carries out a re-assessment and decides on routine use of the drug in NHS Scotland.

In summary, when communicating with key stakeholders, uncertainty should be embraced and not confused with a lack of rigour. Maximum possible transparency is critical to ensure public confidence when decisions are based on incomplete information. HTA has a key role in identifying uncertainties in evidence for early access medicines in a “coverage with evidence” setting e.g. a new Ultra-Orphan Pathway. Its role in directing how these gaps should be filled needs further thought.



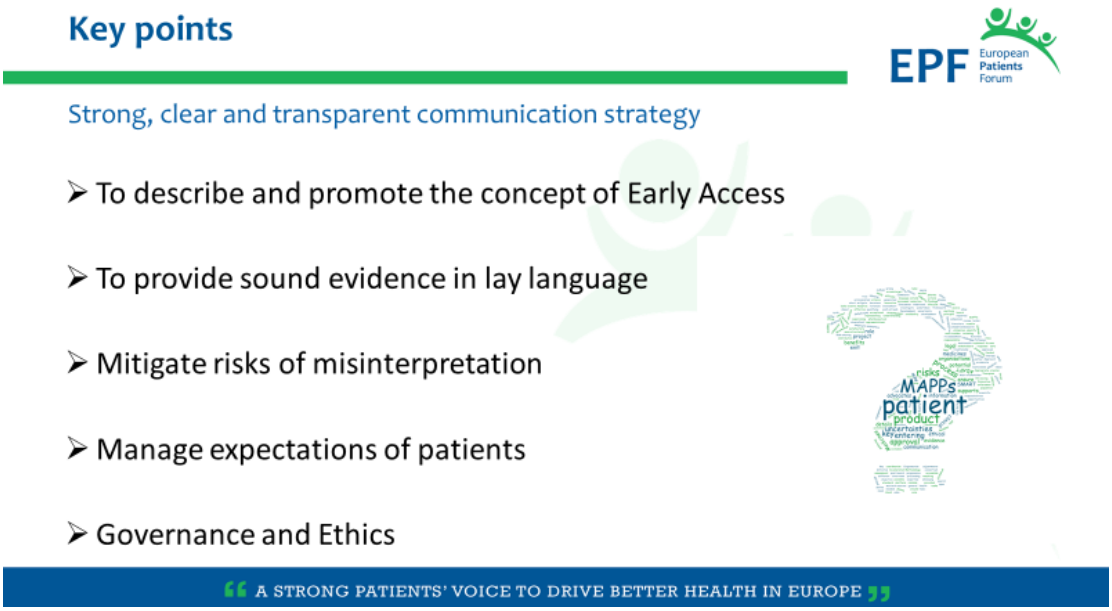
Patient viewpoint – Valentina Strammiello, *Programme Manager, European Patients' Forum (EPF), Belgium*

What matters to most patients is equity of access to high quality healthcare. Patient communities want to ensure investment is directed towards technologies that are safe, effective and improve quality of life. Access to such technologies should be timely and not dependent on where you live i.e. a postcode lottery.

There needs to be a clear governance and ethical approach to early access or adaptive pathways, with no compromise on safety and an exit strategy in case of withdrawal. Patient-facing materials should be in a lay language and aim to educate and empower patients, whilst being mindful of national and cultural differences. Patient organisations and advocates have a key role as information providers and resources like the European Patients' Academy on Therapeutic Innovation (EUPATI) can assist with patient engagement. For patients considering enrollment in early access or adaptive pathways, there needs to be strong communication about the tradeoff of benefits and risks, inclusion and exclusion criteria, operational and legal aspects, as well as clear guidelines for informed consent.

Clear and transparent messages are essential when communicating with the general public. There should be investment into a communication strategy to mitigate the risk of misunderstanding and misinterpretation and to better promote early access to innovative treatments by specifying the benefits for patients as well as costs for society. This should be an iterative process that communicates the evidence behind the innovative treatment and that there is a possibility to disinvest.

The level of uncertainty and risk should be communicated to patients using a clear and transparent communication strategy. This should describe and promote the concept of early access, provide sound evidence in lay language, mitigate risks of misinterpretation and manage the expectations of patients.



Managed entry schemes to manage uncertainty and ensure added value: is this the future for all new early-access medicines, what has been the experience and what should be the key considerations?

HTA viewpoint – Dr Wim Goettsch, *Associate Professor HTA, WHO Collaborating Centre for Pharmaceutical Policy, Utrecht University, The Netherlands*

Conditional marketing approvals (CMAs) are increasingly being granted in order to speed up patient access to medicines. However, HTA bodies in the Netherlands, Germany, France, England and Scotland have rarely given unrestricted positive recommendations to CMA products, irrespective of whether controlled data was included in the submissions [1].

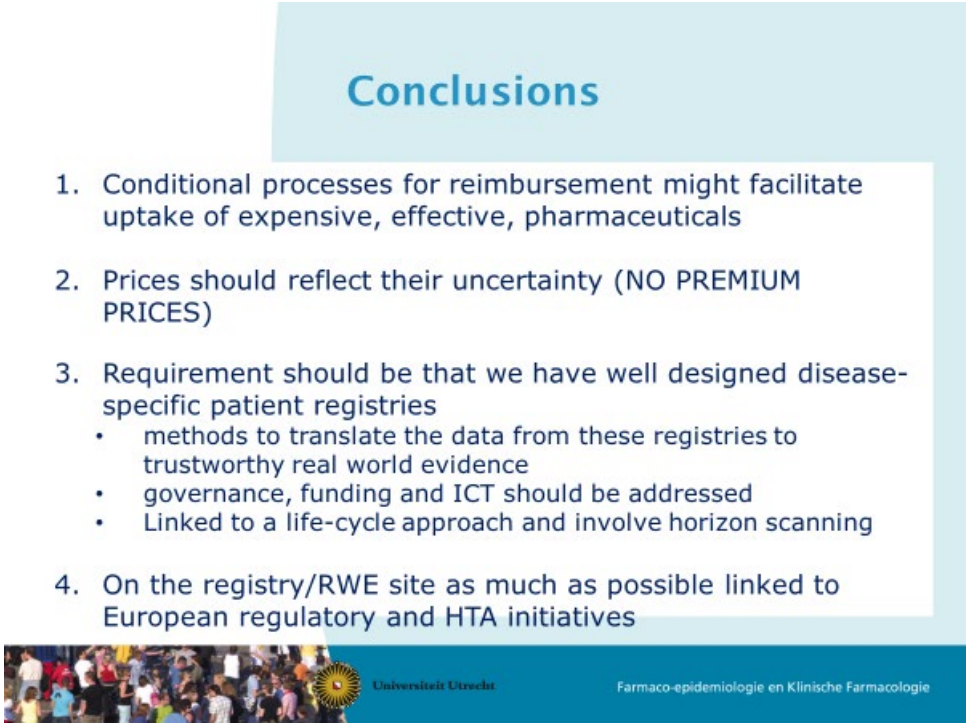
Conditional processes for reimbursement may facilitate uptake of expensive, effective, pharmaceuticals. For example, ZIN granted multiple sclerosis drug fampiridine a route of conditional reimbursement with additional data collection in 2015 (three years after issuing negative advice for the drug). However, upon reassessing rampiridine in 2017, ZIN again issued negative advice because the drug was not clinically relevant and had still not been compared to physiotherapy, which is a standard of care in the Netherlands. Finally, in 2019 (eight years after the CMA was granted), a third assessment led to positive advice for a severe subgroup of patients, with the condition that there should be more than 20% improvement in walking after two weeks of treatment.

Theoretically, conditional financing (CF) provides an option for quick but conditional access to high-cost drugs, however, a four-year pilot scheme in the Netherlands showed numerous shortcomings related to procedural, methodological and decision-making aspects of implementation [2]. Interviews with 30 stakeholders revealed that no one thought the CF scheme had achieved its perceived aims; half said it had only partially achieved its aims and the other half said not at all [3]. When asked about future perspectives, the majority felt that CF should be replaced with a new policy, such as adaptive pathways.

Experiences with previous experiments (such as in the Netherlands) should be taken into account in current policy, as well as prioritisation of disease areas and early identification of uncertainties. There is still a need for patient registries to obtain real-world evidence (RWE) on expensive medicines such as orphan drugs and CMA products, though more coordination is needed to improve the use of registries for HTA and decision making. As a starting point, an established minimal dataset and methodological toolbox to analyse RWE should be agreed.

Well-designed disease-specific patient registries should be a requirement for conditional reimbursement, including methods to translate the data from these registries to trustworthy real-world evidence; governance, funding and information and communication technology should be addressed, linked to a life-cycle approach including horizon scanning. It may be necessary to make participation in patient registries mandatory, though this raises a fundamental question about patient versus public rights. In addition, registries should be linked as much as possible to European regulatory and HTA initiatives e.g. European collaboration on patient registries of rare diseases.

To move forward with managed entry schemes for early access medicines, we should continue to pilot and learn from our mistakes. Well-designed registries are key, but we need to develop better structural governance/funding models and to solve ethical and technical issues such as who owns the data, and how to link different sources of data, respectively.



References:

[1] Goettsch WG et al (2019) Weighing of Evidence by Health Technology Assessment Bodies: Retrospective Study of Reimbursement Recommendations for Conditionally Approved Drugs, *Clinical Pharmacology and Therapeutics,* 105 (3): 684-691. Available at: https://doi.org/10.1002/cpt.1251

[2] Goettsch WG et al (2019) Implementing managed entry agreements in practice: The Dutch reality check, *Health Policy,* 123 (3): 267-274. Available at: https://doi.org/10.1016/j.healthpol.2018.09.016

[3] Goettsch WG et al (2019) Conditional financing of drugs in the Netherlands: past, present and future – results from stakeholder interviews, *Value in Health,* 22 (4): 399-407. Available at: https://doi.org/10.1016/j.jval.2018.11.016

Managed entry schemes to manage uncertainty and ensure added value: is this the future for all new early-access medicines, what has been the experience and what should be the key considerations?

Company viewpoint – Dr Vanessa Schaub, *Global Access Senior Health Systems Strategy Leader HTA & Reimbursement, F.Hoffmann-La Roche, Switzerland*

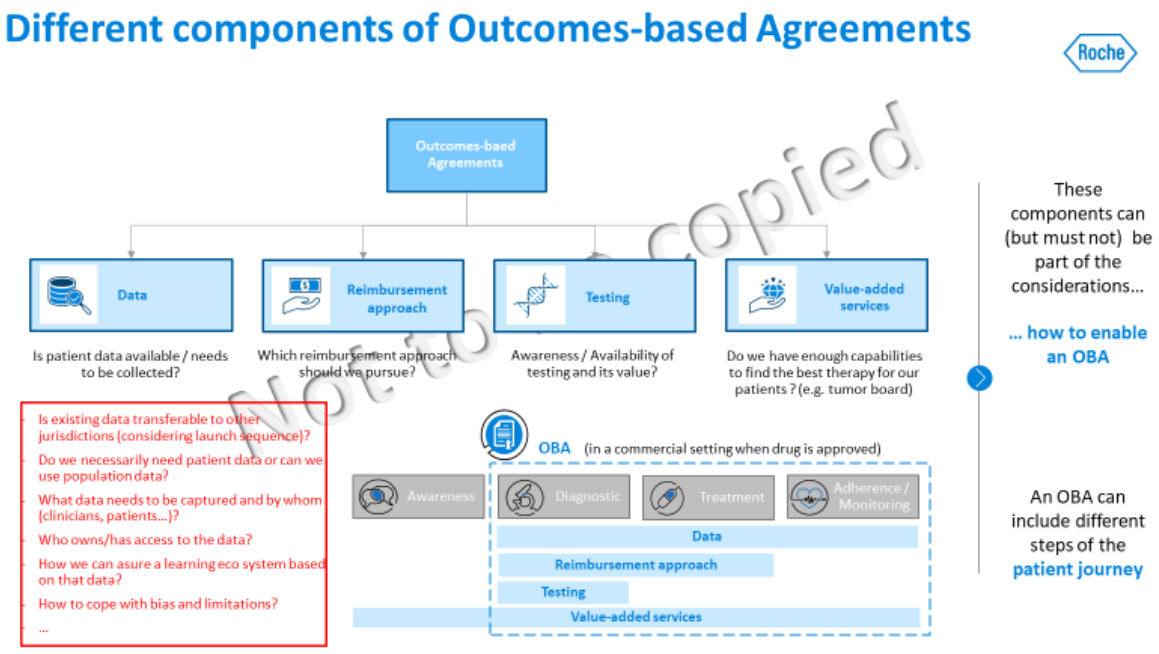
Payment schemes must be tailored to the uncertainty they are trying to address. For example, pay for performance schemes may be considered when there is ambiguity over the level of patient use, or cost capping/sharing if there are concerns over increasing costs. Outcome-based agreements address uncertainty based on clinical outcomes, not necessarily affordability concerns, which may occur in the context of ultra-rare diseases, small clinical datasets, basket trials, single arm trials, molecular-driven treatment options and tumour agnostic approaches.

Outcome-based agreements pay for the benefit a treatment delivers, rather than the treatment itself. Payment is made according to the level of clinical or health benefit (which can include budget and economic benefits) achieved. By capturing the outcomes that treatments deliver in clinical practice i.e. real-world data collection, the price paid for a medicine can be adjusted. Linking payment to outcomes can ensure that scarce healthcare resources are well spent on interventions proven to be effective.

Outcome-based agreements can cover multiple elements of companies' portfolios and should be applicable in all types of market (public, private, out-of-pocket) globally. They are set up as a co-creative approach or partnership with external stakeholders, as they require alignment on defined clinical outcomes, data gathering and monitoring, and expected/desired cut-offs.

Early alignment regarding outcome uncertainty and ways to close this gap is key and requires early multi-stakeholder dialogue. A multi-stakeholder approach is also needed to foster system-wide change and ready the necessary legal frameworks and IT infrastructure. Clarity on the limitations of data collection within outcomes-based agreements post-licensing and on their biases is crucial, as well as their implications for potential re-assessments.

In order to move forward with using managed entry schemes to improve patient access, we need to work together to start and pilot agreements that are truly based on clinical outcomes, keeping them as simple as possible. The overall aim should be to build a joint learning curve in implementing and evaluating outcome-based agreements.



Payer viewpoint – Vinciane Knappenberg, *Advisor (Directorate Pharmaceutical Policy), National Institute for Health and Disability Insurance (NIHDI), Belgium*

Managed entry agreements were introduced in Belgium in 2011 as a response to the new generation of pharmaceuticals addressing unmet medical needs but associated with very high price tags and a significant degree of clinical uncertainty. Their overall goal is to grant patients access to new promising therapies and grant pharmaceutical companies access to the Belgian market, while at the same time, manage clinical uncertainties and budgetary risk.

NIHDI classifies uncertainties into three groups:

- Uncertainties linked to the interaction between the therapy and the disease
  e.g. magnitude and relevance of treatment effect, impact on quality of life, uncertainties about long-term efficacy and safety, optimal dose, treatment duration etc.
- Uncertainties related to the disease itself
  e.g. the natural course of the disease, prognosis, the extent of unmet needs, incidence, prevalence.
- Uncertainties related to the healthcare ecosystem
  e.g. prescription pattern of NIHDI's providers and their capacity to work with the therapy, consequences of enlisting a drug in the healthcare system such as extra costs or cost offsets.

An obligation for companies to collect new evidence and budget compensation mechanisms are important parts of NIHDI's managed entry agreements. All managed entry agreements are negotiated by a working group, which tries to prioritise the uncertainties to avoid the collection of irrelevant data and reflect the voice of the patient. The working group also defines the data sources that will be used for evidence gathering.

Managed entry agreements can be financial or performance-based schemes. Financial schemes such as pre-specified budget caps, discounts or rebates, are usually used for medicines with very high budget impact or for medicines with an unfavourable value to cost ratio. In performance-based schemes, there is a relationship between the reimbursement rate of the product and the actual future performance with a pre-specified definition of the response. When negotiating managed entry agreements, it is crucial to come to an agreement on the timing and measurement of the clinical outcome and to address the high burden placed on registries i.e. financing, data ownership, data analysis. In Belgium, 77% of all managed entry negotiations have ended in convention and compensation mechanisms were usually 'percentage of turnover' based on a pay-for-performance rationale e.g. compensation for non-responders.

NIHDI is evolving towards patient-based outcomes schemes instead of purely financial schemes. These new types of schemes allow reimbursement that is clinically justified and focus on both value and budget control. Although they are subject to less political criticism, patient-based outcomes schemes can be difficult to conclude due to logistic and financial reasons such as timing restrictions, questions about the financing and ownership of data, as well as scientific reasons such as the definition of a response and non-response, and how and when responses are measured. Even if all these issues are resolved, there still remain questions around the value of a responder and whether reimbursement should cease for non-responders.

Rather than focus on one product at a time, NIHDI is moving towards managed entry agreements for therapeutic classes or indications. New methods for negotiation, new approaches to payment systems and horizon scanning are being considered, as well as participation in international collaborations to pool resources and increase negotiating power e.g. Beneluxa.

In summary, managed entry agreements are not a quick-fix solution to address the risk and uncertainty arising from the introduction of new therapies. To maximise their chance of success, strengths and opportunities should be evaluated against weaknesses and threats (see below).

Managed Entry Agreements

SWOT Belgian MEAs

Strengths

- **Transparent Decision Process with a clear Framework**
  - Legal certainties: NIHDI & applicant
  - Clear procedures
  - Timelines
  - Template of MEA
  - Intensive negotiation with headroom for creative and flexible solution seeking

Weaknesses

- **End of contract issues**

- **Timeframe**
  - Short term solution
  - Relevant New Evidence in short Time Frame?
  - Only observational studies are realistic → value of Information?

Managed Entry Agreements

SWOT Belgian MEAs

Opportunities

- **Best place in therapy**
  - Registries: Collecting evidence while drug is used in real-life
  - Optimizing the cost-efficacy of new therapies until clinical practice provides evidence about the best place in therapy

- **Improved use of resources**
  - Less political criticism for any loss of societal welfare if the product is later found cost effective; or for any misused resources if the product provides little or no benefit to patients

Threats

- **Feasibility** (workload 'new' MEA + evaluation 'old' MEA)
- **Decision of Reimbursement Commission could be undermined**
- **Discourage introducing new pharmaceuticals**
- **Confidentiality issues**

Addressing the expectations: how to manage the outcome of conditional approvals and reimbursement

Regulatory viewpoint – Dr Nithyanandan Nagercoil, *Medical Assessor, MHRA, UK*

With regards to early access medicines, the expectation from patients is to obtain early access to safe and efficacious medicines that have gone through a robust and reliable decision-making process. This is challenging as the benefit-risk assessment framework has not changed but making an early decision means having less data, which can lead to increased uncertainty in decision making. Regulators must therefore balance early access with decision uncertainty.

Conditional Marketing Authorisations (CMAs) are an early access route in the European Union for medicines that fulfil an unmet medical need and are only granted if the benefit of immediate availability for patients is greater than the risk of less comprehensive data than normally required. There is a commitment to generate comprehensive data post-authorisation to agreed timelines. Over the last five years, 13 CMAs were granted and only one was withdrawn based on post-authorisation evidence. This suggests that the EMA is generally conservative and cautious, tending to prioritise robust decision making over early access.

In 2014, the UK launched the Early Access to Medicines Scheme (EAMS), which, similarly to CMAs, applies to conditions with high unmet need and products that have a positive benefit-risk profile and are likely to offer significant benefits over existing treatment options. However, the applicant must be willing and able to supply the product free of cost until formal marketing authorisation is granted. EAMS has a quick turnaround time for assessments (within 75 or 90 days) and can be renewed on an annual basis. The scheme also presents companies with an opportunity to collect data on safety, effectiveness and quality of life in 'real world' settings, as well as to engage with NICE and NHS England at an early stage.

EAMS was envisioned to provide an opportunity for new medicines to be used in clinical practice in parallel with the later stages of regulatory process, however, companies appear to be applying to EAMS almost simultaneously with EMA submissions. Furthermore, access through EAMS was anticipated to be 12-18 months earlier than full marketing authorisation, but in practice, at least for the 24 expired EAMS products, access was on average only 4.5months earlier.

MHRA's benefit-risk assessment framework is based on a structured qualitative assessment, taking into account therapeutic context, favourable and unfavourable effects (and their importance/value) as well as uncertainties and limitations. With regards to CMAs, additional considerations include whether specific obligations or further comprehensive evidence can be generated and given in a timely manner, whether the evidence available is sufficient to conclude superiority over existing therapies and whether the product is for an orphan indication. In general, the evidence in a CMA is not comprehensive, so uncertainties exist in favourable and unfavourable effects, optimum dosing regimen/combination and the target population.

To manage outcomes of CMAs, MHRA strives to be clear in the communications particularly on the information in the product information including precise indication, succinct summary of the evidence to support benefit, known safety profile and adequate warnings on uncertainties and limitations. The European Public Assessment Report (EPAR) also provides more detail on the above aspects as well as describes how a positive benefit-risk conclusion was reached.

When post-approval evidence does not support a product's initial potential, it is important to clearly communicate the shortcomings through an update of the Summary of Product Characteristics & EPAR. In addition, a Dear Health Care Professional letter, an agreed Lines To Take document distributed to the different national competent authorities of the EU to ensure consistency in communication and in some circumstances, direct communication through the press may be necessary. It is challenging to withdraw a product based on a failure to confirm benefit, as there are likely to be many different opinions between physicians, patients and regulators. Potential exit strategies and disinvestment plans depends on the nature of the post-approval evidence and include:

- Stopping new patients from starting the medicine but maintaining supply to current patients, as long as it is considered necessary by their treating physician

- Stopping supply – but could continue on a case by case basis until existing stocks are used up
- Sort out supply logistics and reimbursement issues with relevant bodies
- Suspension of marketing, withdrawal of marketing authorisation and immediate product recall (usually only if unacceptable safety findings emerge)

In order to manage expectations and address unexpected findings, there must be early engagement between companies and regulatory agencies (both EMA and national competent authorities). Companies should form proactive and well-considered proposals that consider the relevant clinical and societal context and expectations of the specific target populations. Regulators must carry out prompt reviews and endorsements with/without modifications. Quick communication and implementation of agreed action plans should provide reassurance to patients and stakeholders, hopefully pre-empting issues.

In addition to new evidence on efficacy and safety in the post-approval setting of a CMA, there may be other emerging information with regard to a product, which will also need to be proactively managed. For example, an apparently different decision by another regulator in a different geographic region may necessitate additional review and communications for clarification and reassurance of the prescribers and patients.

Company viewpoint – Dr Jacqueline Brown, *Research Fellow, Health Outcomes, Eli Lilly and Company, UK*

Lartruvo (olaratumab) can be used as a case study for learning about decision making when post-approval evidence does not support a product's initial potential as well as the role of exit strategies and disinvestment plans. It was the first (and currently only) drug to be withdrawn following accelerated/conditional marketing approval.

Lartruvo was developed by Eli Lilly as a potential treatment for soft tissue sarcoma, a rare and heterogeneous group of cancers with limited treatment options and poor patient outcomes. Doxorubicin, either alone or in combination, has been a standard of care for advanced/metastatic soft tissue sarcoma since the 1970s. A randomised phase Ib/II study testing Lartruvo alongside doxorubicin met its predefined primary endpoint for progression-free survival and achieved a highly significant improvement of 11.8 months in median overall survival [1]. This led to conditional marketing authorisations being granted from the FDA and EMA in October and November 2016, respectively. In the subsequent two years, Latruvo gained additional, accelerated conditional and full approvals in over 40 countries worldwide. This demonstrates the regulatory confidence in the phase Ib/II data, despite uncertainty due to the small size of the study.

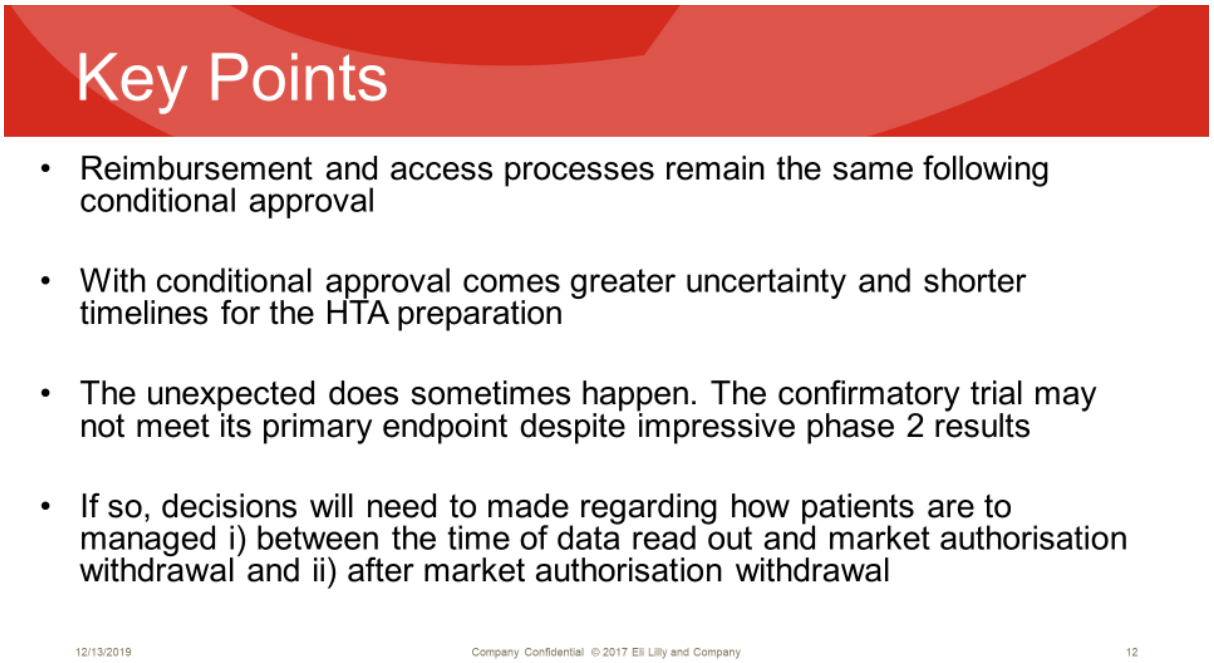
Regardless of whether a product has conditional approval, reimbursement and access processes remain the same. However, the timeline for HTA preparation inevitably gets shorter and there is greater uncertainty in submitted evidence. In the case of Lartruvo, the response from HTAs was largely positive. The drug received NICE approval in the UK via the Cancer Drugs Fund, an ideal process for products with conditional approval, and in Germany, the orphan status, limited treatment options and large overall survival improvement were key to receiving approval from G-BA. Nevertheless, not every country gave a positive response; some agencies had concerns over the uncertainties associated with the size and maturity of a phase Ib/II trial.

The phase 3 ANNOUNCE study testing Lartruvo was running at the time of HTA submissions. The expectation from HTAs was that this clinical data should be supplemented with real world data. This was challenging because of the short timescale in which to complete these studies to demonstrate any effectiveness outcomes, and the fact that soft tissue sarcoma is an orphan disease. At the time there were very few patients in any database, and it was difficult to find databases in Europe where these patients could be studied.

Despite being a well-controlled and conducted phase 3 study, ANNOUNCE failed to meet its overall survival primary endpoint and this was publicly announced by Eli Lilly in January 2019. Since the benefits seen in the phase Ib/II study had not been confirmed, the regulators and the company recommended that no new patients were to be started on Lartruvo. Eli Lilly engaged with regulators in approved markets to ensure that existing patients receiving benefit continued to have access to drug, despite withdrawal from the market. A Patient Access Programme was initiated for patients on Lartruvo in US, Canada and Italy, whilst in other countries there were programmes implemented in alignment with local agency guidance.

Whilst the termination of Lartruvo was hugely disappointing for patients and physicians, one positive outcome was that Eli Lilly's support had enabled physicians who often worked in isolation to make connections internationally. In addition, withdrawal of the drug involved multiple stakeholders and was carried out in an ethical, aligned and synchronised way.

Nevertheless, Lartruvo serves as an example to us all that the unexpected does sometimes happen; a confirmatory trial may not meet its primary endpoint despite very promising phase II results. This is the risk companies take when filing for conditional approval. What's most important is that patients are put first; stakeholders need to work together to make decisions about how patients are managed between the time of data read out and market authorisation withdrawal, and after market authorisation withdrawal.



References:

[1] Tap WD et al (2016) Olaratumab and doxorubicin versus doxorubicin alone for treatment of soft-tissue sarcoma: an open-label phase 1b and randomised phase 2 trial, *Lancet* 388(10043); p488-497. Available at: https://doi.org/10.1016/S0140-6736(16)30587-6

Payer viewpoint – Evert Jan van Lente, *Director EU Affairs, AOK-Bundesverband, Germany*

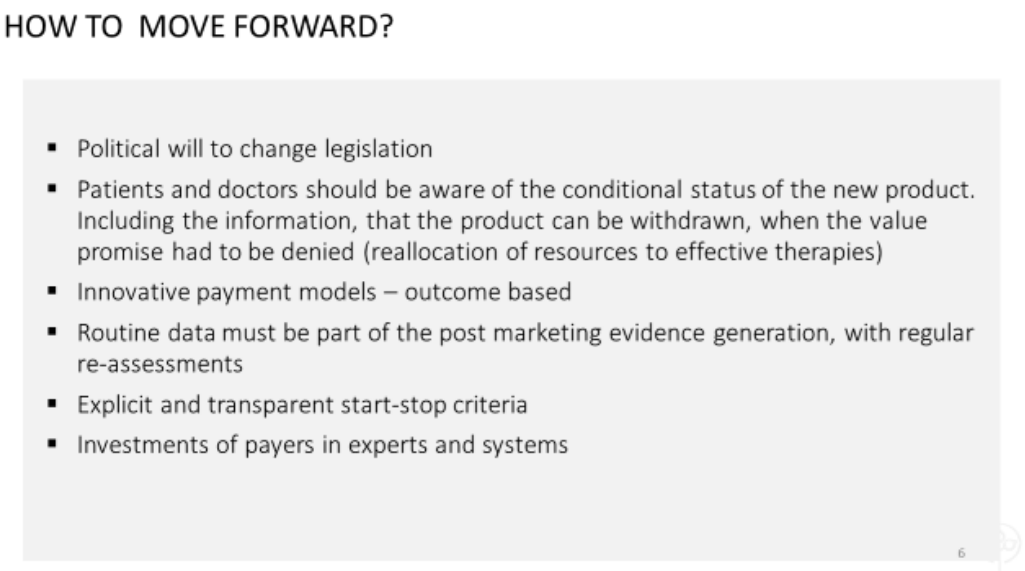
Payers aim to provide insured persons/eligible populations access to effective and efficient care by allocating limited financial resources in an optimal way. However, health systems are paying too much money for products with unknown effectiveness and safety, prescribing is often not rational and costs are challenging the sustainability of health systems. In addition, reimbursement and pricing practice is highly unsatisfactory and post marketing evidence generation is not approached in a structured way.

Cost-effectiveness and budget impact are important issues. Whilst payers can negotiate an adaptive price that reflects the level of uncertainty, there is currently no accepted algorithm for calculating the price of 100% certainty. Therefore, we must find or reach consensus on an anchor for pricing based on value, cost effectiveness, budget impact, willingness to pay and regional aspects such as German internal reference prices. This must also ensure an adequate return on investment for industry, though this may only be possible if there is a certain degree of transparency on cost components, including R&D. Payers and society want to incentivise research and development but should not be expected to pay a price based on potential savings only.

In Germany, legislation stipulates that all products with marketing authorisation are reimbursed by statutory health insurance; the role of HTA is to assess the product's added benefit, which serves as the basis for price negotiations. This is unlike other jurisdictions, where HTA assessments are used to decide whether a product should be reimbursed, taking into account uncertainty, cost effectiveness, budget impact, severity of the disease etc. There is considerable pressure on the decision-making authority to make new therapies available when there is a promise of better patient outcomes (even if uncertainty is very high).

Conditional reimbursement and adaptive pricing could be a potential solution but can't yet be implemented because of a lack of legislation, pricing methodology, satisfactory framework for methodological conditional approval and reimbursement, and payer expertise. In addition, high costs for post-marketing evidence generation and a lack of infrastructure can result in data of unknown quality.

To move forward with conditional reimbursement and adaptive pricing, we need political will to change legislation, innovative outcomes-based payment models, explicit start-stop therapy criteria, patient and doctor awareness of a therapy's conditional status (including potential withdrawal), payer resource investment and structured post-marketing evidence generation.



Section 3: Syndicate Discussions

Syndicate Discussion A

Managing the uncertainty in evidence development for regulators and health technology assessors for early-access medicines – can a list of areas of uncertainty be agreed by stakeholders for early-access medicines?	
Chair	**Dr Sean Tunis**, Senior Strategic Advisor, Center for Medical Technology Policy, USA
Rapporteur	**Dr Shalu Ramrakha**, Director, Global Regulatory Affairs, GlaxoSmithKline, UK

Background

Driven by complex requirements and divergent stakeholder needs, uncertainty is always present in the development, review and reimbursement of new medicines. Moreover, three types of uncertainty have been identified specifically related to early-access pathways: uncertainty resulting from unpredictable medical conditions, from the lack of available information and from the decision-making process, with each of these types requiring different approaches. However, understanding the degree of uncertainty and applying appropriate risk-mitigation strategies in either the pre- or post-approval space, may help to provide needed predictability to companies, regulators and health technology assessors in the generation of evidence for new treatments for diseases, especially those with inadequate or no treatments and which can benefit from early access schemes.

Regulatory uncertainty can be driven by human biologic variability, as clinical trials cannot provide full information about harm and effectiveness in real-world populations, cannot measure the effect during chronic use, nor determine the unknown or “unknown unknown” where data are missing or an event not studied. HTA uncertainty can be categorised around indirectness of extrapolation, imprecision underlying metrics, unavailability of evidence and systematic error or bias in value assumptions.

Companies use scientific advice to provide more aligned evidence for specific products, but this task is made more complex because of differing regulatory and HTA remits. Therefore, it needs to be determined if there are common lessons from both the HTA and regulatory spheres to help address the issues of potentially increased uncertainty for early-access medicines. Indeed, at a CIRS/Utrecht joint meeting in 2018 it was recommended by a syndicate group that an important piece of research would involve mapping the main drivers of uncertainty for each group of stakeholders. From an understanding of the groupings and differences among stakeholders that would emerge, it may be possible to determine the evidence that would satisfy the uncertainties of those groups.

The question for this syndicate group is in trying to manage regulatory and HTA uncertainty in the evidence development for early access medicines, can a list or areas of known or potential clinical (safety, efficacy and effectiveness) uncertainties be mapped, which of these could be resolved by better evidence generation and which ones are unlikely to be resolved during development.

Objectives

1. Map the main drivers of clinical uncertainty for each group of stakeholders (regulators, HTAs and the company) and develop a list or areas of known or potential clinical uncertainties that can be identified that may occur during the development of early access medicines
2. Discuss which of these can be considered resolvable in the development space by better evidence or are unlikely to be resolved during development
3. Make two or three recommendations as to the way forward for this topic.

Discussion results

Uncertainties are viewed very differently by each stakeholder with different questions being asked. For example, regulators ask if there is a positive benefit-risk, HTAs/payers ask what the value of outcomes are and patients ask about the impact on quality/quantity of life. This leads to differences in the level of uncertainty acceptability between stakeholders. Uncertainties can be resolved pre- or post-approval but the confidence and degree of uncertainty each stakeholder is willing to accept depends on the decision and its potential consequences.

In general, the greater confidence an HTA or payer has in clinical outcomes or an uncertainty being addressed, the more likely they are to be amenable to pricing and reimbursment discussions. Clinical uncertainty is not necessarily a driver for the HTA decision, but rather resource use consequences e.g. avoid/decrease in hospitalisations or use of other drugs. The patient population considered by HTA/payers is often broader than the population studied in the clinical trial to obtain regulatory approval.

There is often a difference in how stakeholders approach clinical uncertainties. For example, regulators will compare a product against a comparator, placebo or natural history control, however, HTA agencies need to compare across all available products in an indication as well as comparing clinical benefits across different therapeutic areas. There can also be differences in the translation of endpoints to the label claim and the impact on quality and quantity of life.

Conditional marketing authorisations have different consequences for regulators and HTAs. Regulators are concerned with benefit-risk and can withdraw a licence if this is not maintained. In contrast, it is difficult for HTAs to delist a medicine if its value is not maintained or proven but patients are still deriving benefit from it, especially if there are no alternatives available.

Other critical issues included the applicability of global clinical data e.g. efficacy, dose, in Asian populations and the recognition that patients may be willing to accept a greater risk than the regulator, HTA or payer. From a company perspective, uncertainty in how HTAs assess early access medicines can potentially impact on the global company product development plan, and when those medicines will be accessible in other countries and other markets.

This syndicate agreed on a list of clinical questions considered by stakeholders:

- What is the duration of effect?
- What is the relevance of the clinical endpoint to the clinical outcome?
  - Use of validated endpoints
  - Early access medicines likely to have more conservative endpoints – different impact on each stakeholder
- Use of surrogate endpoints and biomarkers
  - Real world evidence needs to show clinical outcome predicted by biomarker is obtained
  - Sample size for randomisation/single arm study being compared to natural history
- Evidence required to enable extrapolation of results to population and value proposition
- Definition of patient population:
  - Indication identified by biomarker, mutation etc.
  - Confidence in biomarker definition
  - Does biomarker have equal importance in e.g. all solid tumours
  - Reliability of clinical diagnostic testing
- Long term safety in broader population with potential drug-drug interactions

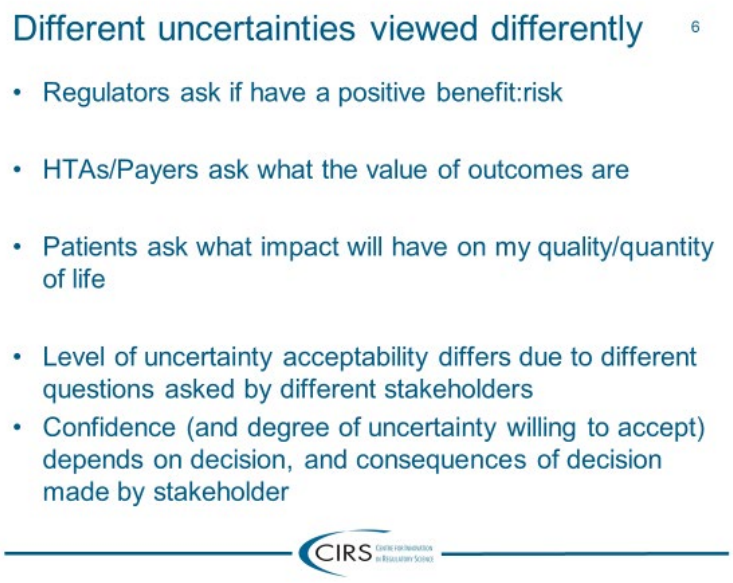
The syndicate also agreed a list of more systemic questions considered by stakeholders:

- Ease and time to collect data requested post approval
  - Will these answer uncertainties
  - What is the relevance of the outcome to the patient and caregiver burden?
- Impact of new medicine on other medicines in same indication?
  - If new medicine given as e.g. 1L treatment how will it impact current 2L therapies

  - Supply to global markets
- Novel products – unknown long-term impact of technology/science
- Pace of innovation – adaptive statistics, surrogate endpoints, clinical development etc.

Recommendations

- Apply learning from one therapeutic area to another to understand uncertainties to be addressed regarding unexpected safety concerns.
- Develop a regulators' risk management programme to potentially address HTA uncertainties including post-launch scientific advice (EUnetHTA/EMA) and phase 3 designs to address both HTA/regulator needs and that accommodates the level of uncertainty in development pathway at timing of interaction.
- Develop global standardisation of surrogate endpoints, biomarkers and historical controls.
- Create incentives for Wave 2+ regions so that they can access early access products and ensure regulatory oversight; include recommendations for sharing risk management programmes.
- Improve quality of real world evidence and standardised medical data collection and develop a methodology to extrapolate real world evidence into clinical outcomes.
- Develop HTA frameworks to manage early access programme uncertainties.



Syndicate Discussion B

Can we develop a high-level framework to systemically identify and calibrate the type or degree of uncertainty?	
Chair	**Dr Thomas Lönngren**, Independent Strategy Advisor, PharmaExec Consulting, Sweden
Rapporteur	**Anders Blaedel Lassen**, Senior Director & Head of Patient Insights, Lundbeck, Denmark

Background

Driven by complex requirements and divergent stakeholder needs, uncertainty is always present in the development, review and reimbursement of new medicines. However, understanding the degree of uncertainty and applying appropriate risk-mitigation strategies in either the pre- or post-approval space may help to provide needed predictability to companies, regulators, and health technology assessors in the generation of evidence for new treatments for diseases, especially those with inadequate or no treatments and benefitting from an early access scheme.

Regulatory uncertainty can be driven by human biologic variability, as clinical trials cannot provide full information about harm and effectiveness in real-world populations, cannot measure the effect during chronic use, nor determine the unknown or “unknown unknown” where data are missing or an event not studied. HTA uncertainty can be categorised around indirectness of extrapolation, imprecision underlying metrics, unavailability of evidence and systematic error or bias in value assumptions.

Although companies use scientific advice to provide more aligned evidence for specific products, this task is made more complex because of differing regulatory and HTA remits. In addition, HTA decisions rely on estimating the extent of differences among comparators and on assumptions, analysis and modelling beyond the clinical evidence available to the regulators. Indeed, for both regulatory and HTA a number of frameworks have been established on both sides to aid decision making, from benefit risk assessments to evidence generation. It needs to be determined, therefore, if there are common lessons from both the HTA and regulatory spheres to help address the issues of potentially increased uncertainty for early-access medicines.

Although uncertainty needs to be evaluated on a case-by-case basis, the question is would a general framework which can systematically identify, characterise and calibrate different forms of uncertainty across the stakeholders be of value for early access medicines? This may help in dealing with uncertainties both systematically and more explicitly. Such a framework could include items such as the degree of unmet need, legal, social, scientific or product-related uncertainties.

Objectives

1. Discuss what areas should be considered for a framework or an approach which will underpin the systematic identification and calibration of the type or degree of uncertainty on early access medicines
2. Identify how such a framework could be utilised by companies, HTA and regulatory agencies to aid in evidence generation decisions as well as the review and reimbursement decision
3. Make two or three recommendations as to the way forward for this topic.

Discussion results

While scoping out the objectives, this syndicate noted that the current approach to uncertainty is rooted in evolving parallel scientific advice, which aims to bring different stakeholders together. However, no specific methodology for identifying uncertainty has been developed from this approach.

Although the instructed focus for discussion was on medicines with high unmet need or early access medicines, this syndicate acknowledged that uncertainties have broader healthcare system implications. The group also discussed the definition of a framework and concluded that it relates to ideas of how to manage uncertainties.

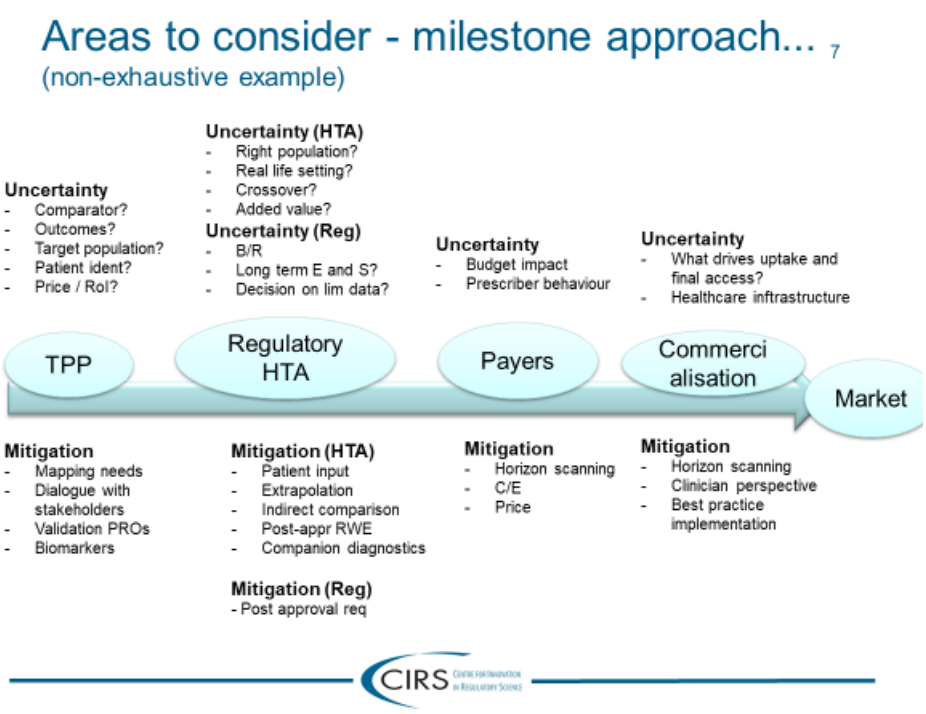
This syndicate agreed that existing frameworks could be used or adapted for the purpose of handing overall uncertainty. The European Risk Management Plan is one example that provides an already well-established framework for discussing how to identify risks, how to understand them, how to potentially prevent them, and how they can be studied further. It might be possible to broaden this framework for an overall evidence generation perspective, though there are globally accepted standards for drug safety but not for other types of evidence. A critical issue will be how to assess broader uncertainties across stakeholders and regions. In addition, it must be ensured that the selected/adapted framework fits with other existing tools developed by different stakeholders e.g. company evidence plans, HTA Core Model® developed by EUnetHTA.

This syndicate proposed the creation of an Integrated Uncertainty Management Plan (IUMP), a framework that can be used over the medical product life cycle with a clinical development focus. This 'living' plan would be produced by the company and discussed in context of regulatory and HTA advice, including relevant stakeholders, and should:

- identify uncertainties in relation to key aspects of medicine development towards market
- propose how to mitigate these uncertainties, including perspectives and preferences from patients and prescribers
- provide a mechanism for continuous reporting / updating as development progresses.

In order to work towards an IUMP, there are several key questions that need answering, such as whether it is possible to develop a standard list of uncertainties that need mitigation. The group proposed a milestone approach as a starting point for listing uncertainties (see below). It will also be essential to know how stakeholders are currently working with and addressing uncertainties, and whether there might be alignment across these perspectives. In addition, it will be important to consider variation across disease areas and whether an IUMP could/should be a one-size-fits-all approach.

Another key area of discussion was related to whether regulators, HTA bodies, payers and companies can make use of the same framework. It will be important to know how current regulatory and HTA pathways and guidance frameworks are linked to the issue of uncertainties, and how the same baseline understanding of handling mitigation of uncertainties can be created. In addition, it may be important to consider the likelihood that uncertainties change over time and are addressed at different time points.



Recommendations

In the short term, carry out a mapping exercise on current context, in order to inform an IUMP framework:

- Map existing activities / models across current stakeholders (industry, regulators, HTA, payer) with view to understand potential for optimising use or combining in the context of an IUMP framework.
- Map different payer / HTA systems for better understanding of potential ‘global’ approach to IUMP.
- Map existing advice pathways to understand timing and purpose in relation to the development timeline and which type of uncertainties are in scope.

In the longer term, discuss and refine IUMP scope and methodology:

- Recommend on structured methodology for assessing and aligning on uncertainties and mitigation activities.
- Re-visit current advice / interaction framework with recommendation on potential need for changes, including patient and prescriber perspectives.
- Assess and address gaps in incentives for data collection (uncertainties mitigation) in relation to IUMP framework.

Syndicate Discussion C

Utilising a life cycle approach for early access medicines to manage uncertainties – what are the considerations?	
Chair	**Dr Luc Boileau**, President and CEO, INESSS, Canada
Rapporteur	**Lourens Bloem**, Pharmacovigilance Assessor & PhD candidate, Dutch Medicines Evaluation & Utrecht University, The Netherlands

Background

Driven by complex requirements and divergent stakeholder needs, uncertainty is always present in the development, review and reimbursement of new medicines. Moreover, three types of uncertainty have been identified specifically related to early-access pathways: uncertainty resulting from unpredictable medical conditions, from the lack of available information and from the decision-making process, with each of these types requiring different approaches. However, understanding the degree of uncertainty and applying appropriate risk-mitigation strategies in either the pre- or post-approval space, may help to provide needed predictability to companies, regulators and health technology assessors in the generation of evidence for new treatments for diseases, especially those with inadequate or no treatments and which can benefit from early access schemes.

For early access medicines a number of these will have either been approved through facilitated development and regulatory pathways; however, at the time of HTA evaluation, either the perceived value of the new medicines is not seen or the instigation of Coverage with Evidence Development (CED) occurs or a managed entry agreement is put in place. The former outcome shows a misalignment between regulatory pathways to meet unmet need with the value seen by HTA to meet the specific jurisdictional health care needs. As many of these divergent decisions are made because of issues around uncertainty, these approaches may require the commitment from agencies for the company to undertake further studies in the post-approval stage where, as new information becomes available, the perceived value seen in the development space can be tested.

This, therefore begs the question, should the utilisation of a lifecycle approach be common practice for early access medicines. Indeed CADTH (not just for early access medicines), has made the adoption of a lifecycle approach one of its strategic priorities. The key components of such an approach include premarket dialogue, managed entry agreements, active post-marketing surveillance and the evaluation of appropriate use, as well as clear articulation of managed exit or disinvestment strategies. The question for this syndicate group is, many organisations are already applying elements of a lifecycle approach to their products. Of the experiences to date, what elements appear to work well, which require further refinement, and which are not yet addressed in a holistic manner?

Objectives

1. Discuss the use of a lifecycle approach for early access medicines and what the key considerations need to be.
2. Identify the key components that would make up a life-cycle approach and how these could be utilised for early access medicines to manage uncertainty.
3. Make two or three recommendations as to the way forward for this topic.

Discussion results

While scoping out the objectives, this syndicate discussed the context of the 'perfect storm' that is the constantly changing environment in the drug life cycle and the need for proactivity and flexibility. They discussed whether a life cycle approach should focus on specific disease area(s) and/or from a public health impact point of view and agreed that multi-stakeholder evidence requirements should be prospective and gathered pre-approval.

Common data, evidence and assessment standards should be considered and allowed to evolve over time as new methods and insights emerge. In addition, the effect of disruption, concurrent/sequential competitors, potential channelling in interpreting data and evidence, and divergences across regions e.g. impact of tiered US system should be considered. It would be useful to develop case studies to understand what approach, evidence considerations etc work or don't work, and to allow continuous learning to be implemented.

This syndicate agreed that a life cycle approach should contain several key elements:

- Prospective multi-stakeholder evidence discussions, including patient involvement
- Linking benefit-risk assessment to multi-stakeholder discussions e.g. regulatory health technology management
- Incentives for companies to create evidence e.g. outcomes-based Managed Entry Agreements
- Ways of evidence generation and acceptability, including
    - Patient Reported Outcomes (PROs) vs. patient-important data
    - RCTs vs. observational studies
    - Disease registries (who owns, uses, funds etc)
    - Digital patient health information e.g. social media, wearables
- Continuous adaptation and exit / disengagement strategy if needed
- Systematic learning environment - learn from barriers, successes, failures

Recommendations

- **Now:** All stakeholders should choose a champion to take part in a coalition to continue discussing and moving the topic forward.
- **Within 1 year:** Jointly agree on a framework for common data collection across jurisdictions. Important considerations include:
    - Making it fit-for-purpose, ensuring quality/consistency and a governance model acceptable to all stakeholders.
    - Feasibility and acceptability should be informed by a multi-stakeholder survey, potentially through CIRS.
    - Results should be published / publicly available and aligned with/informed by other initiatives e.g. EMA registry (qualification) initiative.
    - Multiple data sources are needed for different purposes (not all have to adhere to RCT gold standard).
    - Determine who is going to pay for real-world data collection.
- **After 1 year:** Ensure multi-stakeholder prospective life cycle planning through adaptive and flexible risk management plan-like document/agreement. Make use of existing concepts but involve all key aspects relevant to all stakeholders.

  Key consideration: what is the research question and with which data must/should/can we address it?

APPENDIX: WORKSHOP ATTENDEES

Health technology assessment agencies		
Dr Luc Boileau	President and CEO	Institut national d'excellence en santé et en services sociaux (INESSS), Canada
Niklas Hedberg	Chief Pharmacist	TLV, Sweden
Dr Michael Kulig	Head of Working Group Pharmaceuticals, Medical Consultancy Department	G-BA (Federal Joint Committee), Germany
Jeanette Kusel	Director for Scientific Advice	NICE, UK
Andrew Mitchell	Strategic Adviser, Evaluation	Department of Health, Australia
Dr Brian O'Rourke	President and CEO	CADTH, Canada
Adj Asst Prof Fiona Pearce	Senior Lead Specialist (Drug & Vaccine Evaluation)	Agency for Care Effectiveness (ACE), Ministry of Health, Singapore
Patient groups		
Dr Jenny Sharpe	Research Communications Manager	Muscular Dystrophy UK
Valentina Strammiello	Senior Programme Manager	European Patients' Forum, Belgium
Payers		
Dr Michael Ermisch	Specialist	GKV-Spitzenverband, National Association of Statutory Health Insurance Funds, Germany
Vinciane Knappenberg	Advisor, Directorate Pharmaceutical Policy	National Institute for Health & Disability Insurance (NIHDI), Belgium
Evert Jan van Lente	Director EU-Affairs	AOK-Bundesverband, Germany
Pharmaceutical companies and associations		
Simon Bennett	Director, EU Regulatory Policy	Biogen Ltd, UK
Dr Matt Bradley	VP and Head, Regional Regulatory Affairs, TA Head, Value Evidence & Outcomes	GlaxoSmithKline, UK
Dr Patrick Brady	Vice President, Head of Regulatory Policy and Intelligence	Bayer AG, Germany
Dr Jacqueline Brown	Research Fellow, Health Outcomes	Eli Lilly and Company, UK
Scott Doyle	Senior Director, TA Head Specialty – Global Health Outcomes	Astellas, UK
Dr Helen Fitton	VP and Head, Regional Regulatory Affairs	GlaxoSmithKline, UK
Dr Bruno Flamion	VP, Head Strategic Development	Idorsia Pharmaceuticals, Switzerland
Ruth Flynn	Interim Therapy Area Head, Oncology/GRS – WE Regulatory Affairs	AbbVie, UK
Dr Louise Gill	Regulatory Brexit Implementation Head	GlaxoSmithKline, UK
Sharon Gorman	Director, EU and International Regulatory Policy	Pfizer, UK
Dr Alicia Granados	Head of Global HTA Scientific Strategy	Sanofi, Spain
Angus Gunn	Access and Evidence Strategy Lead, Global Clinical Development	UCB Celltech, UK

Dr Olivier Günther	Senior Director, Global EVD Therapeutic Area Head	Merck Healthcare KGaA, Germany
Ian Hawkins	VP, Global Regulatory Affairs	Vertex Pharmaceuticals, UK
Adam Heathfield	Senior Director, Patient and Health Impact	Pfizer, UK
Dr Estenban Herrero-Martinez	Director, Regulatory Policy and Intelligence	AbbVie, UK
Dr Claire Hill-Venning	Senior Director, Regulatory Policy	Janssen, UK
Fred Ivanow	Head of Global Regulatory Intelligence & policy	Astellas PharmaEurope B.V, The Netherlands
David Kane	Senior Director	Vertex Pharmaceuticals, UK
Gabriele Kapfer	Market Access Policy	Bayer AG, Germany
Shane Kavanagh	Vice President, Health Economics	Janssen, Belgium
Dr Maren Koban	Associate Director, Global Regulatory and Scientific Policy	Merck Healthcare KGaA, Germany
Dr Maria Kubin	Head of MACS TA Cardiovascular	Bayer AG, Germany
Anders Blaedel Lassen	Senior Director and Head of Patient Insights	Lundbeck, Denmark
Agathe Le Lay	Senior Director and Head of Value Evidence	Lundbeck, Denmark
Gavin Lewis	VP, Europe Value, Access & Policy	Amgen (Europe) GmbH, Switzerland
Dr Thomas Lönngren	Independent Strategy Advisor	PharmaExec Consulting Filial SE, Sweden
William Malbecq	Distinguished Scientist	MSD, Belgium
Laura Montanari	Associate Director, Regulatory Affairs	Takeda, UK
Dr Magdalini Papadaki	Associate Director, Business Strategy & Operations	MSD, UK
Dr Shalu Ramrakha	Director, Global Regulatory Affairs	GlaxoSmithKline, UK
Graeme Roberts	Director, HEOR	Idorsia Pharmaceuticals Ltd, Switzerland
Dr Simon Rothwell	Senior Manager Global Market Access	Eisai, UK
Carolina Santos	Vice-President, International Access & Reimbursement	Vertex Pharmaceuticals Europe, UK
Claudine Sapede	Director, Global HTA Policy	Novartis International AG, Switzerland
Dr Vanessa Schaub	Global Access Senior Health Systems Strategy Leader HTA & Reimbursement	F.Hoffmann-La Roche, Switzerland
Dr Stefan Schwoch	Senior Director	Eli Lilly and Company, UK
Cyndy Simon	Market Access Director	Eisai Limited, UK
Dr Isabelle Stoeckert	Head Regulatory Affairs EMEA	Bayer AG, Germany
Robin Thompson	Director	Biogen, Switzerland
Regulatory agencies		
Lourens Bloem	Pharmacovigilance Assessor & PhD candidate	Dutch Medicines Evaluation Board & Utrecht University, The Netherlands
Prof Anthonius de Boer	Chair	Medicines Evaluation Board, The Netherlands
Dr Claus Bolte	Head of Sector Marketing Authorization and Board Member	Swissmedic
Prof Hans-Georg Eichler	Senior Medical Officer	European Medicines Agency, The Netherlands

Dr Robyn Lim	Senior Scientific Advisor	Health Products and Food Branch, Health Canada
Dr Tomas Salmonson	Former Chair, CHMP Partner	EMA Consilium Salmonson & Hemmings, Sweden
Dr John Patrick Stewart	Director General, Therapeutic Products Directorate	Health Canada
Universities and non-profit organisations		
Dr Helga Gardarsdottir	Assistant Professor, Drug Regulatory Sciences	Utrecht University, The Netherlands
Dr Wim Goettsch	Associate Professor HTA, WHO Collaborating Centre for Pharmaceutical Policy	Utrecht University, The Netherlands
Prof Finn Boerlum Kristensen	Professor, Faculty of Health Sciences	University of Southern Denmark, Denmark
Prof Sam Salek	Professor of Pharmacoepidemiology; Head – Public Health & Patient Safety Research Group	University of Hertfordshire, UK
Prof Adrian Towse	Emeritus Director and Senior Research Fellow	Office of Health Economics, UK
Prof Art Tucker	Professor	Barts Health NHS Trust, UK
Centre for Innovation in Regulatory Science		
Dr Magda Bujar	Manager, Strategic Development	
Dr Jesmine Cai	Senior Research Analyst	
Dr Lawrence Liberti	Head, Regulatory Collaborations	
Dr Neil McAuslane	Director	
Dr Jamie Munro	Executive Director	
Prisha Patel	Manager, Global Development Programme	
Dr Céline Rodier	Senior Research Analyst	
Professor Stuart Walker	Founder	
Tina Wang	Manager, HTA Programme	