Uncertainty in the development of new medicines:

How should clinical development, regulatory and HTA uncertainties be managed, or mitigated?

22–23rd June 2023

Workshop Report

CIRS Centre for Innovation in Regulatory Science

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About CIRS

The Centre for Innovation in Regulatory Science (CIRS) is a neutral, independent UK-based subsidiary of Clarivate plc. CIRS' mission is to maintain a leadership role in identifying and applying scientific principles for the purpose of advancing regulatory and Health Technology Assessment (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. It is governed and operated by Clarivate for the sole support of its members' activities. The organisation has its own dedicated management and advisory boards, and its funding is derived from membership dues, related activities and grants.

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Section 1: Executive Summary

Background to the workshop

Over the last decade and during the COVID-19 pandemic, medicines development has seen a tremendous increase in innovation, not just in the conduct of clinical trials, evidence generations techniques and new types of products, but also an increased use of facilitated regulatory pathways. Like most companies, regulators and health technology assessment (HTA) bodies now have robust frameworks for assessing potential benefit and risk. However, uncertainty and how to manage it has emerged as a major challenge in the development, review and reimbursement of new medicines.

Factors driving uncertainty include:

- Patient expectations of earlier access based on smaller regulatory data sets, including from smaller populations
- Use of biomarkers/surrogate endpoints resulting in part from the use of priority/accelerate and conditional/provisional pathways
- Desire for intervention at earlier stages of disease progression – preventative/curative therapies e.g., for cancer or dementia
- Extrapolation of clinical trial population to the real world leading to uncertainty over how the medicine will perform in populations that are broader in scope than the original clinical trial population – i.e., the gap between efficacy and effectiveness
- New technologies (e.g., advanced therapy medicinal products [ATMPs]) which do not lend themselves to traditional development models
- Paucity of HTA and payment models and lack of agreement between industry and HTA bodies on HTA and payment models that in the view of both groups can adequately cope with uncertainty.

In CIRS workshops conducted in the UK and the Netherlands between 2017 and 2019, aspects of identification of regulatory and reimbursement uncertainty were discussed[1,2]. These meetings identified a need to better understand the types of uncertainty facing different stakeholders so that they can be managed or mitigated, either during development or post approval and how best to meet different stakeholder needs. It is important to have a clear understanding or map of the main drivers of uncertainty for each group of stakeholders, based on the medicine's development review and reimbursement pathways. But once this understanding is obtained, the critical issue is development and application of better approaches to manage and mitigate uncertainty through medicines development. This should facilitate decision-making approaches and reduce expensive wasted investment by companies but hopefully enable more promising medicines to be brought to market with a greater consensus on how uncertainty will be managed.

This workshop brought together companies and agencies (HTA and Regulatory) to discuss the sources of uncertainty that are being built in, by the way medicines development has evolved and how these are being assessed, graded and viewed by both HTA and regulators. The meeting also discussed the key strategies that are being or can be employed to resolve uncertainties or mitigation strategies that are in place to provide confidence to decision makers and patients.

Workshop objectives

- Identify the source and drivers of clinical, regulatory and HTA uncertainties
- Identify what strategies, tools, criteria are utilised to assess and reduce uncertainties within drug development, review and reimbursement
- Recommend new approaches to manage uncertainty in regulatory and HTA decision making for innovative medicines and how to these can be managed or mitigated pre- or post-approval.

Venue

The workshop took place at the Hyatt Regency Hotel at Tyson's Corner, Virginia, USA, commencing at 09:00 on 22nd June and finishing at 15:20 on 23rd June 2023.

1. Flexible regulatory/ access pathways: Are we there yet? CIRS workshop 2017: https://www.cirsci.org/publications/2017-workshop-report-flexible-regulatory-access-pathways/

2. Identifying and understanding regulatory and reimbursement uncertainty during development: How can this improve predictability of regulatory and HTA outcomes? CIRS workshop 2019: https://www.cirsci.org/publications/2019-workshop-report-identifying-and-understanding-uncertainty-during-development/

Workshop Programme

Affiliations are stated as they were at the time of the meeting (22–23rd June 2023).

SESSION 1: UNCERTAINTY – WHAT ARE THE MAIN DRIVERS AND HOW BEST TO MANAGE OR MITIGATE?
CIRS welcome – Dr Neil McAuslane, Scientific Director, CIRS
Chair's welcome and introduction – Dr Supriya Sharma, Chief Medical Advisor**,** Health Canada
Managing uncertainty in a changing medicines development landscape – What are the drivers/types of uncertainty that are keeping regulators and HTA agencies up at night? **Regulatory perspective – Adjunct Prof John Skerritt,** University of Sydney, Australia **HTA perspective – Heather Logan,** Vice President of Strategic Relationships and Initiatives, Canada's Drug and Health Technology Agency (CADTH) **Company perspective – Jeffrey Francer,** Vice President, Head of Global Regulatory Policy & Strategy, Eli Lilly & Company, USA
SESSION 2: MAPPING UNCERTAINTY DURING CLINICAL DEVELOPMENT – WHAT ARE PRACTICAL TOOLS/STRATEGIES AND ACTIVITIES FOR COMPANIES AND AGENCIES?
Mapping clinical efficacy uncertainties in the evidence generation during development – How can it be applied in a practical manner to inform company decision making? **Company perspective – Jacques Mascaro,** Senior Vice President, Oncology Regulatory Science, Strategy and Excellence, AstraZeneca, USA
Can duplication of regulatory and HTA analysis of efficacy, safety and uncertainty be avoided – What approaches during development could regulators and HTA adapt to address a common issue of uncertainty? **Regulatory perspective – Dr Steffen Thirstrup,** Chief Medical Officer, EMA **HTA perspective – Dr Nick Crabb,** Programme Director, Scientific Affairs, NICE
Are current company/agency interactions during development an effective approach to identify and resolve uncertainties that are of concern to regulators and HTA agencies? **Irwin Tran,** Global Access Evidence Enabler, Roche, USA
SESSION 3: DECISION MAKING UNDER UNCERTAINTY – WHAT APPROACHES ARE HTA AND REGULATORY AGENCIES TAKING AT THE TIME OF ASSESSEMENT?
Chair's introduction - Dr David Jefferys, Senior Vice President, Global Regulatory, Government Relations, Public Affairs and European Product Safety, Eisai, UK
Consideration of uncertainty within FDA's benefit-risk framework **Dr Leila Lackey,** Program Lead, Decision Support Service, Center for Drug Evaluation and Research (CDER), FDA, USA
Grading uncertainty at the time of decision making – Is this of value to decision makers and does it enable communication of uncertainty across stakeholders? **Dr Jon Campbell,** Senior Vice President for Health Economics, Institute for Clinical and Economic Review (ICER), USA

Do commonly used regulatory tools to manage efficacy and safety uncertainty work?

Agency perspective – Dr Peter Marks, Director, Center for Biologics Evaluation and Research (CBER), FDA, USA

Company perspective – Dr Álmath Spooner, Director, Regulatory Policy and Intelligence, AbbVie, Ireland

Are current HTA agency tools for managing uncertainty fit for purpose? If not, why not and what needs to change?

HTA perspective – Mélanie Caron, Assistant Director of Evaluation of Medication and Technology, Institut national d'excellence en santé et en services sociaux (INESSS), Canada

Company perspective – Dr Indranil Bagchi, VP, Global Pricing and Market Access Head, GlaxoSmithKline, USA

SESSION 4: SYNDICATE SESSIONS

Breakout A: How can particular aspects of uncertainty around drugs that go through an accelerated/priority or provisional/conditional approval be managed or mitigated?

Chair: Prof John Lim, Executive Director, Centre of Regulatory Excellence (CoRE), Duke-NUS Medical School, Singapore

Rapporteur: Nina Barchha, Senior Director, Group Lead Regulatory Affairs – Oncology, Astellas, USA

Breakout B: How can uncertainty for drugs trialled in small populations (e.g., orphan drugs, rare diseases), "single shot" cell, gene and tissue therapies or potentially curative or preventative therapies be managed or mitigated?

Chair: Prof Steffen Thirstrup, Chief Medical Officer, EMA

Rapporteur: Sana Hussain, Director, US Regulatory Policy, GlaxoSmithKline, USA

Breakout C: Differences between drug efficacy observed in clinical trials and real-world effectiveness gap have commonly been found, especially for patients with co-morbidities or groups poorly represented in the clinical trials. How should uncertainty in the real world be managed or mitigated?

Chair: Dr Murray Lumpkin, Deputy Director – Integrated Development / Lead for Global Regulatory Systems Initiatives, Bill and Melinda Gates Foundation, USA

Rapporteur: Aideen McGee, Associate Director, HTA Strategy, AbbVie, USA

SESSION 5: SYNDICATE SESSIONS FEEDBACK

Chair's introduction - Adjunct Prof John Skerritt, University of Sydney, Australia

Feedback of syndicate discussions and participants' viewpoints

Panel discussion: Managing uncertainty – reflections on what should be future considerations and next steps

Regulatory perspective – Dr Supriya Sharma, Chief Medical Advisor, Health Canada

Company perspective – Dr Felipe Dolz, Global Regulatory Affairs Innovation Lead, Sanofi, USA

Payer perspective – Dr Detlev Parow, Former Head, Department of Medicines, Medical Remedies and Selective Contracts, DAK – Gesundheit, Germany

SESSION 6: COMMUNICATION OF UNCERTAINTY – CAN THIS IMPROVE TRUST AND CONFIDENCE IN REGULATORY AND HTA DECISIONS?
Chair's introduction - Dr Claus Bolte, Deputy Chief Executive and Head of Sector Marketing Authorisation, Swissmedic
Building confidence in agency decision making – Do public reports (regulatory and HTA) provide clarity on source and agencies' perspective of uncertainty surrounding the decision and how identified uncertainties both real and potential will be resolved? **Regulatory agency viewpoint – Karen Reynolds,** Director General, Pharmaceutical Drugs Directorate, Health Canada **HTA agency viewpoint – Pauline McGuire,** Principal Pharmacist, Scottish Medicines Consortium
Communicating uncertainty – What are good practices in communicating uncertainty and risk to key stakeholders at the time of product approval/recommendation? **Patient perspective – Dr Bellinda King-Kallimanis,** Director of Patient-Focused Research, LUNGevity Foundation, USA **Communicating regulatory outcomes – Dr Finnuala Lonsdale,** Director Human Product Authorisation and Registration, Health Products Regulatory Authority, Ireland **Communicating HTA outcomes – Dr Gowri Raman,** Associate Director, Patient-Centered Outcomes Research Institute, USA
Chairman summary and close of meeting

Key points from presentations

Please note that the following presentation summaries represent the views of the individual presenter and do not necessarily represent the position of the organisation with which they are affiliated. Affiliations are stated as they were at the time of the meeting.

Session 1: Uncertainty – what are the main drivers and how best to manage or mitigate?

Prof John Skerritt, *University of Sydney, Australia and Chair, Scientific Advisory Council, CIRS,* gave an overview of managing uncertainty in a changing medicines development landscape from a regulatory perspective. It is critical for all stakeholders to distinguish between uncertainty and risk or harms. Regulatory uncertainty has increased in recent years with new types of therapies, smaller clinical trial designs and facilitated access pathways. Efforts should be made to try to identify sources of uncertainty, although many cannot be removed pre-market. Post-approval commitments and other post-marketing tools are used to manage uncertainty but there have been challenges in implementation. Regulatory public assessment reports should communicate uncertainty but be clear that the uncertainty is described at a particular point of time.

Heather Logan, *Vice President of Strategic Relationships and Initiatives, Canada's Drug and Health Technology Agency (CADTH),* gave an HTA perspective on uncertainty management and mitigation. HTA agencies need to be agile and willing to learn and unlearn as new innovations emerge. The current unprecedented pace of change, evolving stakeholder expectations and emergence of real-world evidence are common challenges for HTA agencies. Early upstream discussion together with regulators, payers and patients can help to identify uncertainty and agree on some of the solutions in a multi-stakeholder fashion going forward.

Jeffrey Francer, *Vice President, Head of Global Regulatory Policy & Strategy, Eli Lilly & Company, USA,* gave a company perspective on uncertainty management and mitigation. Key sources of regulatory uncertainty include clinical, methodological and evidentiary requirement uncertainty. From a company perspective, regulators can help mitigate uncertainty by using processes that are science and rules based, predictable and collaborative. Planning and coordination prior to the submission of marketing applications can reduce uncertainty. The more that can be done upfront to ensure that the right evidence is generated, the better the outcome for all stakeholders, including patients.

Session 2: Mapping uncertainty during clinical development - what are practical tools/strategies and activities for companies and agencies?

Jacques Mascaro, *Senior Vice President, Oncology Regulatory Science, Strategy and Excellence, AstraZeneca, USA,* spoke about how mapping uncertainty during clinical development can be applied in a practical manner to inform company decision making. There are challenges that increase complexity and uncertainty during clinical evidence generation including diversity in clinical trial populations, focus on dose optimisation, advancing accelerated approvals, endpoint evaluation and scientific advice from regulatory and HTA bodies. A Probability of Technical and Regulatory Success assessment evaluation framework was shared. Digital transformation of R&D is set to transform R&D productivity over the next 10 years. Moving from document to data exchange could dramatically change the regulatory ecosystem.

Dr Steffen Thirstrup, *Chief Medical Officer, European Medicines Agency (EMA),* spoke about approaches during medicines development that regulators and HTA agencies could adapt to address a common issue of uncertainty. In Europe, conditional marketing authorisation provides an example of how regulators distinguish uncertainties from risks. The aim of European collaboration between regulators and HTA bodies is to build synergies between regulatory evaluation and HTA along the medicine lifecycle. The new HTA Regulation in Europe recognises the value of such collaboration. There will be touch points for engagement between regulators and HTA bodies and the opportunity to reduce duplication of work.

Dr Nick Crabb, *Programme Director, Scientific Affairs, NICE,* gave an overview of how regulators and HTA agencies could address a common issue of uncertainty from the HTA perspective, noting that there may not be a common regulatory and HTA issue of uncertainty, but that collaboration can still help. Regulators are increasingly efficient and timely in identifying new medicines with a positive benefit/risk profile; however, evidence on which to base HTA may be limited at the time of marketing authorisation. Potential solutions include interim funding approaches, managed access approaches, price negotiations that ensure opportunity cost is manageable at the agreed price despite uncertainties, and innovative payment models.

Irwin Tran, *Global Access Evidence Enabler, Roche Products Ltd USA,* spoke about the effectiveness of company/agency interactions during development to identify and resolve uncertainties that are of concern to regulators and HTA agencies. Company/agency interactions are effective but only if stakeholders are aligned on the uncertainties. Regulatory and HTA uncertainties are not always coordinated, and so companies need to consider how to prioritise advice that they receive. There is a risk that not all uncertainties for every agency can or will be addressed. Further alignment between regulatory, HTA and industry may help prioritise the uncertainties that need to be addressed, resulting in a better evidence package.

Session 3: Decision making under uncertainty - what approaches are HTA and regulatory agencies taking at the time of assessment?

Dr Leila Lackey, *Decision Support Service Program Lead, Decision Support and Analysis Staff, CDER/FDA, USA*, spoke about consideration of uncertainty within the FDA's benefit-risk framework. FDA's benefit-risk assessment is a case specific assessment of science and medicine that considers evidence submitted, therapeutic context, uncertainties and regulatory options. Structured benefit-risk planning is a purposeful activity carried out by the sponsor to incorporate consideration of the product's benefit-risk assessment throughout the drug development life cycle. It can be used to strengthen the evidence generated by a development programme thus reducing uncertainty and informing the final benefit-risk assessment.

Dr Jon Campbell, *Senior Vice President for Health Economics, Institute for Clinical and Economic Review (ICER), USA,* spoke about grading uncertainty at the time of decision making. ICER's evidence-based medicine rating matrix was summarised, which rates comparative clinical effectiveness based on two main dimensions: net health benefit (including risk and safety) and level of certainty in the evidence, which are distilled into ordered categorical grades.

Dr Peter Marks*, Director, Center for Biologics Evaluation and Research (CBER), FDA, USA,* spoke about commonly used regulatory tools to manage efficacy and safety uncertainty from the agency perspective. The FDA does have post-market commitments, but they do not help significantly with managing uncertainty because frequently they are not for key issues. Also managing safety uncertainty is different to managing efficacy uncertainty. For cell and gene therapies, managing

efficacy uncertainty may pose challenges because increasingly, enzyme levels, protein levels and surrogate markers are required to confirm an accelerated approval and this may increase the risk of a negative confirmatory trial.

Dr Álmath Spooner, *Director, Regulatory Policy and Intelligence, AbbVie, Ireland*, spoke about commonly used regulatory tools to manage efficacy and safety uncertainty from a company perspective. Regulators are leveraging new approaches to evidence generation to address the access evidence trade-off to best meet and serve patient needs. Dialogue opportunities and early engagement are critical facilitators, particularly to allow multi-stakeholder alignment, but recognising that the evidence package is informed by the decision-making context. As various stakeholders in the health data ecosystem increase their capacity, it is going to become even more critical to build alignment on the fitness of data sources, methodologies, and analytical approaches and to view these in their global context.

Mélanie Caron, *Assistant Director of Evaluation of Medication and Technology, Institut national d'excellence en santé et en services sociaux (INESSS), Canada*, addressed whether tools for managing uncertainty are fit for purpose from an HTA perspective. HTA scientific professionals must appreciate uncertainty in various forms efficiently, in a timely manner and be able to translate it simply. Improvements to manage uncertainty have been made in Quebec but many changes are on the radar for 2024. INESSS plans to have open dialogue and conversation with regulators and manufacturers. Economic scenarios are going to be changing and require an openness to enable discussions, analyses and negotiations of these new scenarios to take place.

Dr Indranil Bagchi, *VP, Global Pricing and Market Access Head, GlaxoSmithKline, USA,* addressed whether tools for managing uncertainty are fit for purpose from a company perspective. Regulator and HTA/payer data needs are different. Data uncertainty can be addressed with real-world evidence (RWE) post-launch. However, there needs to be ways to address uncertainty in the interim. There are a wide range of preferred mitigation strategies observed across stakeholders and uncertainties. Joint Health Technology Assessment International (HTAi) and Drug Information Association (DIA) guidance may foster timely dialogue on mitigation strategies across stakeholders, as well as improve consistency and transparency. Whilst remit may be different, all stakeholders can explore the same or similar frameworks to enable faster patient access to life saving medicines.

Session 5: Syndicate sessions feedback

Participants were divided into three syndicate groups to discuss management and mitigation of uncertainty in the context of 1) drugs that go through an accelerated/priority or provisional/conditional approval, 2) drugs trialled in small populations (e.g., orphan drugs, rare diseases), 'single shot' cell, gene and tissue therapies or potentially curative or preventative therapies and 3) drugs where differences between efficacy observed in clinical trials and real world effectiveness are commonly found (i.e., patients with co-morbidities or groups poorly represented in clinical trials).

Summary of recommendations: *How can particular aspects of uncertainty around drugs that go through an accelerated/priority or provisional/conditional approval be managed or mitigated?*

All stakeholders (both short and long term)	• Recognition that all stakeholders have a shared purpose in reducing uncertainty. • Proactive establishing of multistakeholder platforms and strengthening existing platforms to improve dialogue and progress actions to reduce uncertainty.
All stakeholders (both short and long term)	• Acknowledgment of evidence gap depending on timepoint of development (pre-approval or post-approval). • Alignment on the best approach to fill the gap i.e., utilisation of sandbox. For example, pre-approval this could be an additional study or amendment of studies.
CIRS with support from all stakeholders (short term)	• CIRS to investigate successes with commercial arrangements (risk sharing/time limits around reimbursement conditions) for drugs that have received accelerated/priority or provisional/conditional approval. • Learnings need to be translated across disease states and regions.
CIRS with support of all stakeholders (short term)	• CIRS to conduct a deeper dive into which uncertainties are avoidable/unavoidable, and discuss planning tools around avoidable ones.

Summary of recommendations: *How can uncertainty for drugs trialled in small populations (e.g., orphan drugs, rare diseases), 'single shot' cell, gene and tissue therapies or potentially curative or preventative therapies be managed or mitigated?*

All stakeholders	*Knowledge sharing and collaboration to identify uncertainties*: • Leverage existing infrastructure (e.g., Centers of Excellence for rare diseases, patient advocacy groups, RWE) • Enhance education and awareness of efforts among stakeholders • Develop further infrastructures to be able to identify rare disease areas and therapies where uncertainties can be shared among stakeholders • Early stakeholder engagement • Develop opportunities for cross-learnings • Next steps - CIRS workshop to drill this down further
Regulator, company, HTA	*Co-construction approach to uncertainty assessment* - post-approval as the first step (ultimately including pre-approval).
All stakeholders	*Knowledge sharing in a global forum* – discussions on how to develop therapies for rare diseases and how they arrive to the patients.
All stakeholders	*Evaluation of existing tools* used by multiple stakeholders - ensure they are being used in a meaningful way.

Summary of recommendations: *Drugs where there are differences between efficacy observed in clinical trials and real-world effectiveness gap have commonly been found, especially for patients with co-morbidities or groups poorly represented in the clinical trials. How should uncertainty in the real world be managed or mitigated?*

Regulator, company	•Economic incentives and commitments to include under-served patient populations in trials or in post marketing studies.
Regulator, HTA, company	•Early scientific advice includes questions on patient population, patient reported outcomes and how best to approach uncertainty.
Regulator	•Ethics committee to review the diversity of the population included in trials.

In a concluding panel discussion, representatives from regulatory, industry and payers provided reflections on future considerations for managing uncertainty and next steps.

Dr Supriya Sharma, *Chief Medical Advisor, Health Canada*, presented a regulatory perspective and spoke about the advances made since the last CIRS workshop on uncertainty, including increased use of RWE, more crosstalk between regulators and HTA assessors and innovations in clinical trial design. Industry and regulators have continued to work together on developing guidance documents. For regulators, there is a greater sense of being part of an ecosystem and a willingness to consider uncertainty. Further work is needed to effect change for patients and to ensure equality, diversity and inclusion in discussions.

Dr Felipe Dolz, *Global Regulatory Affairs Innovation Lead, Sanofi, USA*, gave a company perspective and spoke of growing uncertainty because of increasingly complex science/technology, along with increasing societal expectations. There is an incentive to align and streamline processes; opportunities should be garnered to initiate conversations with all stakeholders early on regarding trial endpoint selection, enrolment criteria and patient needs and diversity. International work-sharing opportunities such as Project Orbis provide a path forward to different thinking and collective knowledge. How patient data is collected to optimise trial management and outputs should be explored.

Dr Detlev Parow, *Former Head, Department of Medicines, Medical Remedies and Selective Contracts, DAK – Gesundheit, Germany,* spoke about what uncertainty means for payers, including the quantity and speed at which EMA-approved drugs are reimbursed and available to patients in Germany, and particularly in an era of increasing conditional approvals and early access. Payers can feel underrepresented with limited influence on the chain of medicines development beyond reimbursement decisions and pricing structures. Learnings from previous assessments does not provide certainty regarding future assessments.

Session 6: Communication of uncertainty – can this improve trust and confidence in regulatory and HTA decisions?

Karen Reynolds, *Director General, Pharmaceutical Drugs Directorate, Health Products and Food Branch, Health Canada*, spoke about the importance of rigorous documentation and transparency in decision making when communicating uncertainty. Some of Health Canada's key transparency initiatives include the Summary Basis of Decision (SBD), which describes the scientific and benefit-risk analysis that factored into the decision to approve a novel product, and the Regulatory Decision Summary, which summarises the purpose of the submission and why the decision was issued. Health Canada's approach to uncertainty is dynamic and will continue to evolve and adapt with learnings from experience. Challenges continue to exist, but transparency and regulatory initiatives are evolving in the right direction.

Pauline McGuire, *Principal Pharmacist, Scottish Medicines Consortium (SMC), UK*, spoke about how the SMC's public reports are vital and clearly describe uncertainty in decision making. The SMC provides advice to NHS Scotland about the value of newly licensed medicines and incorporates patient group and clinical expert involvement during the process. As policy direction to increase access to new medicines is adding uncertainty in decision making, thoughts on how to address this are required. RWE provides exciting opportunities to add context to these uncertain decisions.

Dr Bellinda King-Kallimanis, *Director of Patient-Focused Research, LUNGevity Foundation, USA*, addressed communicating uncertainty from a patient perspective, considering two major inflection points for patients: clinical trial participation and standard treatment planning. Individual factors influence how people hear uncertainty. These may include expertise, attitudes/optimism, numeracy skills/education and personal goals and preferences. We need to use these models of uncertainty and realise that patient centricity is much more than engaging with certain patients/patient groups at certain points in drug development. This may require multiple tools to communicate the benefits and risks of new treatments to patients when they are making their treatment choices.

Dr Finnuala Lonsdale, *Director, Human Product Authorisation and Registration, Health Products Regulatory Authority, Ireland*, spoke about communicating regulatory outcomes. Communicating risk and uncertainty needs to be approached from the perspective of improving decision making by identifying desired outcomes, learning from experts and communicating as a team effort between health system partners. There is a need to set an expectation that for regulators now, stakeholder engagement, partnerships and communication skills are a fundamental part of the job. Agility is key. This means thinking about recruitment and retainment to develop regulators with these competencies.

Dr Gowri Raman, *Associate Director, New Technology, Engagement, Patient Centered Outcomes Research Institute (PCORI), USA*, spoke about communicating HTA outcomes. PCORI utilises a multi-stakeholder engagement process to elicit uncertainty in health outcomes for emerging interventions, in addition to available data. PCORI descriptively communicates uncertainty in outcomes through reports and issue briefs and has future opportunities in using visualisation tools, which might be more audience friendly.

Section 2: Presentations

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Session 1: Uncertainty – what are the main drivers and how best to manage or mitigate?

Managing uncertainty in a changing medicines development landscape – what are the drivers/types of uncertainty that are keeping regulators and HTA agencies up at night?

Regulator perspective

Adjunct Prof John Skerritt, *University of Sydney, Australia*

Background

Identifying and addressing uncertainty is important because uncertainty is often confused with hazard or risk and can lead regulators to deny approvals. If uncertainty can be correctly identified and managed there are many positive outcomes for companies, regulators, HTA/payers and patients.

Regulatory uncertainty has increased in recent years. While uncertainty about how a medicine will perform in populations that are broader in scope than a clinical trial has been around for years, uncertainty now also arises due to expectation that patients can get earlier access to new drugs, greater use of facilitated (conditional and provisional approval) pathways by regulators, more drugs for smaller orphan populations (often evaluated through observational trials), interest in interventions for earlier stages of diseases (and potentially for preventive and curative therapies) and more gene and cell therapies being developed that are not amenable to classical trial designs (and uncertainty about the durability of therapeutic effect).

Types of uncertainty and their impact

There are several major types of uncertainty that need to be considered by decision makers:

- From lack of predictability e.g., drugs with an inconsistent patient-to-patient response or lack of confidence in translating outcomes between populations – **stochastic uncertainty**
- Relating to clinical trial design/ population – **methodological uncertainty**
- **Relating to data** – not enough data, unreliable/irrelevant or conflicting data
- Uncertainty that can be reduced as the available information is increased – larger / confirmatory trials, real world evidence – **epistemic uncertainty**
- Uncertainty when there is all the available information but there are both clear benefits and risks and it is unclear to how value a drug – **decision uncertainty**
- Uncertainty relating to the **impact of the drug on the disease**, or the disease itself
- Uncertainty as to **how the new treatment would fit into the health system**

Clinical trials are inherently about uncertainty and here we must improve patient communications. Indeed, clinical equipoise, i.e., the assumption that there is not one 'better' intervention (control vs experimental group) during the design of a randomised controlled trial (RCT) is crucial as it supports the ethical basis for random assignment of patients to treatment arms and enables objective measurement of outcome. This type of uncertainty in trials, where outcomes cannot be predicted, should be maintained through to unblinding. While uncertainty is an essential part of clinical trials it can also stop patients from enrolling, due to concerns about being assigned a placebo or an experimental drug that doesn't work, uncertainties about side effects of a new drug and concerns about being given a treatment of last resort.

Further, within clinical trials there is uncertainty around the efficacy-effectiveness gap. Trial participants may not be representative (for example when those with comorbidities are excluded) and loss of participants can add uncertainty and skew trial conclusions. Statistical uncertainty and bias are other potential sources. It may be possible to mitigate these uncertainties in a structured way, for example, by enforcing timely post-authorisation commitments, reconsidering trial exclusion criteria (including those with co-morbidities) and making greater use of real-world evidence (RWE) in label extension submissions. However, uncertainty from rare, unpredictable safety events (e.g., AstraZeneca COVID 19 vaccine related thrombosis with thrombocytopenia syndrome) will remain a challenge.

In terms of the impact on regulatory decision making, uncertainty comes at various stages. This includes pre-clinical, especially if basic pharmacology/mechanism of action is unclear (noting that animal models may not be effective predictors of human toxicology) and uncertainties in chemistry, manufacturing, and controls (CMC) and quality (e.g., scale up and shelf life of ATMPs and movement between sites). Uncertain clinical efficacy is a major focus for regulators and can arise from small trial sizes, observational trials, case series, situations where a placebo is inappropriate or blinding not possible, clinical trial durations for drugs for chronic conditions, drugs only efficacious in a percentage of trial participants (but where no marker has identified that subpopulation) and uncertainty around dose, populations and durability of therapeutic effect. Off-label use is particularly controversial when it comes to the discussion on uncertainty, particularly if extensive off-label use is predicted. Is it appropriate to consider uncertainty about off-label use or should it be mitigated by very clear labelling? What are the potential financial implications of off-label use?

Reducing uncertainty

While it is important to identify the sources of uncertainty, it may be naïve to consider that it can be eliminated. If one takes the view that all uncertainty must be removed, drugs may never get to market.

Suggestions to reduce uncertainty prior to regulatory approval are as follows:

- Scientific dialogue and pre-submission meetings with regulators to be clear about data requirements.
    - Be systematic in identifying different types of uncertainty.
    - Establish whether post-marketing requirements will be needed.
- Establish whether the aim is to reduce or manage uncertainty - would more pre-market data reduce uncertainty?
- Early clarity on the desired efficacy, effectiveness and safety attributes of the drug and where will it potentially fit in therapy.
    - Regulators to publish clearer guidance on trial design, sources of information that build evidence in clinical development and endpoint requirements.

    - Determine whether we approach uncertainty differently for first versus second/third line therapies; and for first in class versus me-too drugs.
- Avoid duplication between regulatory and HTA requirements through joint dialogue with companies to agree what is needed to reduce or manage uncertainty.

Much work has been done post-approval, including black triangle schemes and black box warnings, risk management plans, post-approval commitments and conditional and provisional approvals, although post-approval commitments are not always met. Greater enforcement of post-market commitments is coming in the United States (US) via the US Food and Drug Omnibus Reform Act (FDORA). Where post-approval commitments are met but the confirmatory trials are negative, it can be very hard to take drugs out of the system, especially once reimbursed. There are also examples of drugs that were approved under significant initial uncertainty that have gone on to be very successful and useful (venetoclax was provided as an example: initially an orphan drug, it was the first haematology-oncology drug converted from provisional or conditional approval to full approval in Australia).

Even when conditional and provisional approvals are in place, are current HTA/payment tools suitable when there is high uncertainty? Industry and payers can be very nervous regarding drugs with conditional approval. Many payment models exist but may not be being implemented in a way that enables access to drugs in an environment of uncertainty.

Regulators must play a role in public communication of uncertainty, because sometimes patients and prescribers don't distinguish between risk and uncertainty. Uncertainty can also spark significant ethical debates. Is it ethical for the system/regulators to deny a seriously ill person a drug due to uncertainty even if there are no alternatives? One approach is to publicly communicate uncertainty, acknowledging that there are uncertainties about how well a drug works, that it is being monitored, and this will require data every 6 or 12 months as part of a binding commitment, but that it can be used.

Summary

It is important to distinguish the difference between uncertainty and risk and not to try to eliminate all sources of uncertainty. It is helpful to try to identify the sources of uncertainty, but many cannot be removed pre-market. Post-approval commitments and other post-market tools are used to manage uncertainty, but there have been challenges in implementation. Regulatory public assessment reports should communicate uncertainty but be clear that the uncertainty is described at a particular point of time. Finally, HTA tools to manage uncertainty exist, but more policy work is needed.

Conclusions

- Critical for all stakeholders to **distinguish between uncertainty and risk or harms**
- Positive outcomes for companies, regulators, HTA/payers and patients **if uncertainty can be identified and managed**
- **Regulatory uncertainty has increased in recent years** with new types of therapies, smaller clinical trial designs and facilitated access pathways
- Try to identify the **sources of uncertainty**, but many cannot be removed pre-market
- **Post approval commitments** and other postmarket tools used to manage uncertainty, but there have been challenges in implementation
- Regulatory **public assessment reports should communicate uncertainty**, but be clear the uncertainty is described at a particular point of time
- **HTA tools to manage uncertainty** exist, but more policy work is needed

Managing uncertainty in a changing medicines development landscape – what are the drivers/types of uncertainty that are keeping regulators and HTA agencies up at night?

HTA perspective

Heather Logan, Vice President of Strategic Relationships and Initiatives, Canadian Agency for Drugs and Technologies in Health (CADTH)

Introduction to CADTH

The organisational purpose of CADTH is to power evidence-informed drug and health technology decisions for sustainable, world-class healthcare for all. Thinking about uncertainty and how HTA organisations respond, everything that CADTH does is designed with the end user in mind, taking patient perspectives, clinicians, and industry stakeholders into account. Agility, and a willingness to change in response to environmental changes or new innovations, is required, taking learnings from others around the world. Focus must also be maintained on equity, diversity, inclusion and accessibility (including indigenous populations and work on reconciliation and engagement) and finally, transparency.

CADTH operates under three strategic pillars which all relate to uncertainty in the environment: anticipate (enable future-ready care), innovate (unleashing the value of health technology across its lifespan and transform (catalyse health system change).

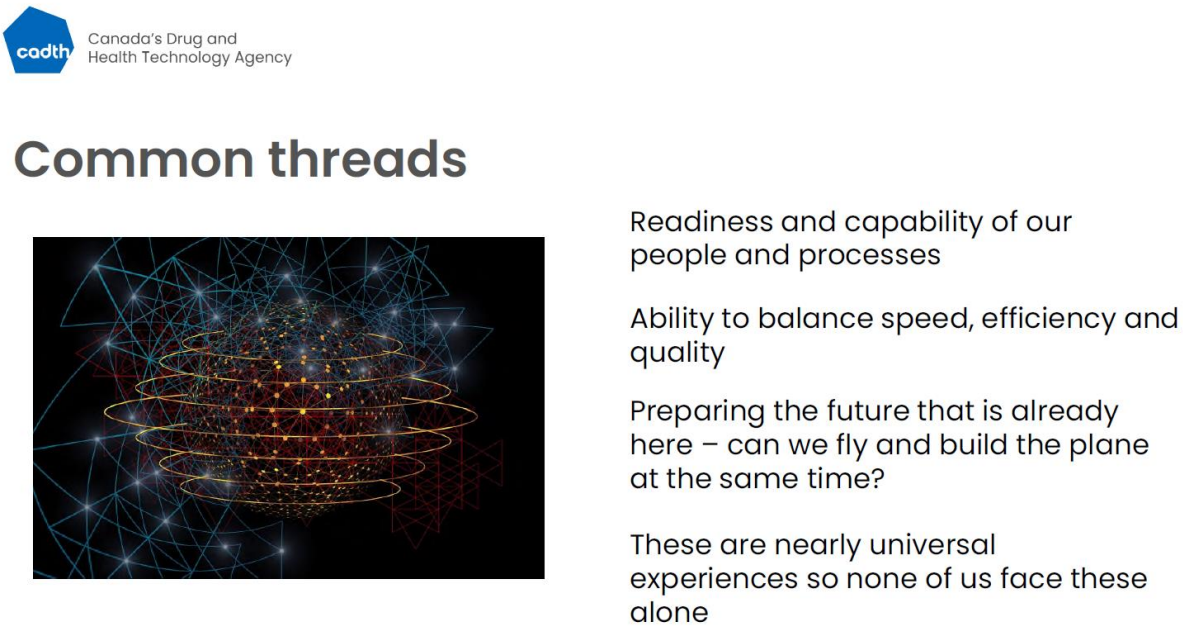
A common set of issues

There are a common set of issues across HTA organisations that relate to uncertainty:

1. *The unprecedented pace of change.* The combination of information being readily available and that ‘anybody can be an expert’ makes the risk of misinformation increasingly important and both threatens and elevates the role of HTA organisations and the role of evidence.
2. *Stakeholder engagement.* Patient perspective is important; however, the degree of variation in the patient experience is hard to capture and increasingly so for rare diseases. We are moving to hearing from people individually, finding ways to hear their voice, including diversity across populations, and to a position of less consultation and more co-creation. This makes things more uncertain from a deliberation perspective, but more important. This is an area that will become increasingly important as science and understanding of disease moves towards less common, smaller populations.
3. *Methods and data, including RWE*. More than 90% of rare diseases have no effective drug treatment, and so these uncertainties will continue going forward. Canada has announced a national rare disease strategy, though how to collect data with small populations is something that still needs to be resolved. CADTH has released a report recently looking at guidance for reporting RWE and how to integrate that into the HTA process systematically[1] but notes that this is the start of the process.
4. *Relevance of HTA organisations*. Evidence provision should be when required, not when desired, and should be designed with the end user in mind. Speed and rigour are important.
5. *The ubiquitous access to data and the risk of misinformation*.

For regulatory and HTA, the pressures and expectations of working quickly are increasing. Canada has an aligned review process that a manufacturer can consent to, but the number of manufacturers that are participating in this process is declining. There is frustration over the pace of negotiations, but in a space where there is uncertainty, jurisdictions need to understand how to build that into the pricing models that they are investing in. Regarding submission requirements and information exchange, more could be done to reduce that uncertainty, including better communication; however, harmonising regulatory/HTA requirements will continue to be a challenge. Finally, the stakeholder engagement expectations between regulatory and HTA will not be the same, but how best to leverage the patient experience back to the regulator in the post-market space is important.

There are common threads across regulators and HTA organisations across the world, and their experience dealing with payers (see below).



Summary

Dealing with uncertainty in terms of mitigating risks means being agile, being able to listen and being able to learn and unlearn things as the pace of change accelerates. Early upstream discussion together with regulators, payers and patients can help us to identify uncertainty and agree on some of the solutions in a multi-stakeholder fashion going forward. Collaborative working is beneficial, particularly in the rare disease space where protocols and approaches to increase our understanding and confidence of the risk-benefit profile can be shared.

References

1. CADTH Methods and Guidelines. Guidance for Reporting Real-World Evidence. May 2023. Available at: https://www.cadth.ca/guidance-reporting-real-world-evidence

Managing uncertainty in a changing medicines development landscape – what are the drivers/types of uncertainty that are keeping regulators and HTA agencies up at night?

Company perspective

Jeffrey Francer, Vice President, Head of Global Regulatory Policy & Strategy, Eli Lilly & Company, USA

Background

Sources of regulatory uncertainty include clinical uncertainty, methodological uncertainty and evidentiary requirement uncertainty. Continued progress has been made on the latter on the regulatory side over the years. However, we continue to see evidentiary requirement uncertainty on the HTA side, where more work needs to be done.

From the company perspective, regulators (and sponsors) can help mitigate uncertainty. Companies advocate for a style of regulation that is science based, rules based and predictable, collaborative and engaged. In practice, this means standards that are set out in advance that are clearly science based, but that regulators are also iterating with sponsors and speaking about amongst themselves. Reliance and harmonisation are important to enable patients to be able to access innovation as quickly and efficiently as possible.

The Prescription Drug User Fee Act – mitigating uncertainty in the US

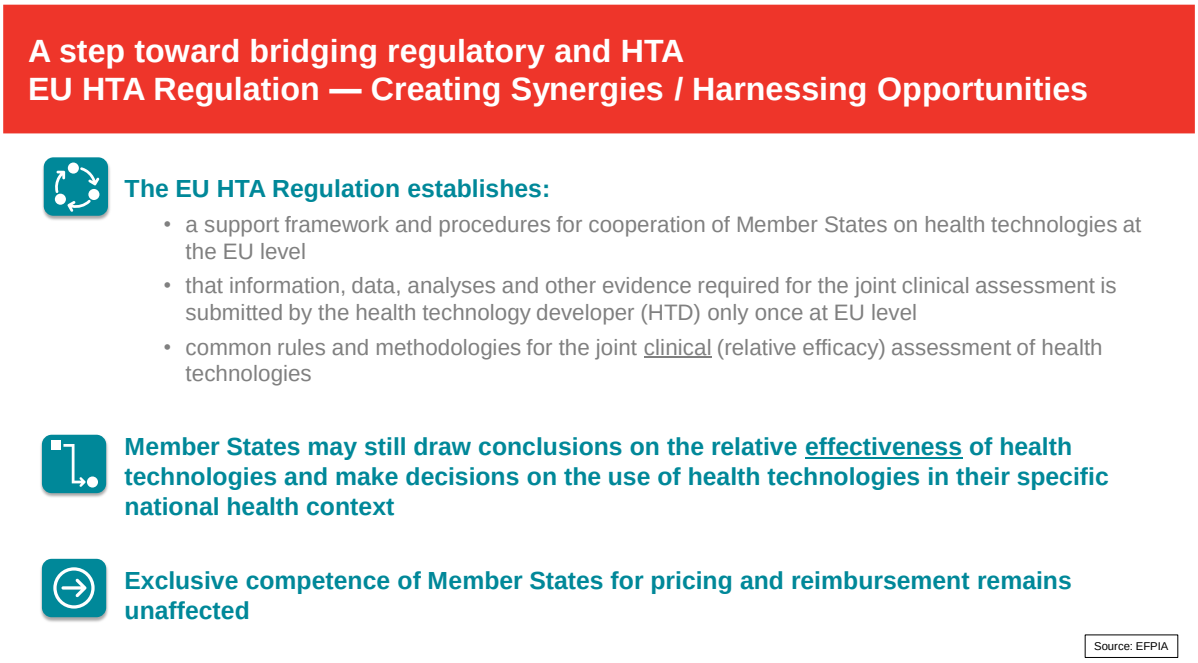
The Prescription Drug User Fee Act (PDFUA) has developed significantly over the past few decades and has helped to mitigate regulatory uncertainty in the US. Companies pay for applications and in exchange, the industry gets together with the US Food and Drug Administration (FDA) every five years and renegotiates standards. One of the principal ways of trying to ensure that evidentiary uncertainty can be mitigated is that the company meets with the FDA at different times in the development pathway. There is a shared interest between the FDA and sponsors in eliminating uncertainty and trying to make sure that there is early planning and agreement on the type of evidence that is going to be required. However, there has been a recent divergence in the US between the evidence that the FDA required in a specific class of drugs (anti-amyloid treatment for Alzheimer's Disease), and what the Centers for Medicare & Medicaid Services (CMS) is requiring to cover the drugs. This is a historic situation but demonstrates uncertainty in the US's own form of HTA (CMS coverage).

Evidentiary requirement uncertainty in Europe

While Europe operates a different system to the US there is a common theme in trying to mitigate regulatory evidence uncertainty. The European Medicines Agency (EMA) has taken strides by allowing more of an iterative framework to address evidence generation, having a multi-stakeholder process, and beginning to think about the coordination between regulators and payers. While there is no one-size-fits-all solution between countries with different forms of governments, different budgets, and different regulators, there is some convergence in the fact that early planning and coordination can help improve the process.

On the one hand, there is a growing amount of regulatory flexibility and nimbleness. However, there are some tensions in Europe between EMA requirements, regulatory approval, and divergent requests for additional evidence after approval.

There are more types of expedited pathways and questions regarding how scientific breakthroughs will be treated in the future, including what the future of evidence generation is going to look like in Europe. At the same time, member states that will continue to have their own questions about HTA evidence, and we see many divergent requests for additional information, even after marketing authorisation. One way that the European system has attempted to bridge this gap is by trying to have more coordination. The EU recently passed the HTA Regulation, which is intended to improve coordination of the member states and create common rules and methodologies. At the same time the rule recognises that member states can still drive their own conclusions on the relative effectiveness of different health technologies, and they can still pose their own questions to sponsors. There is more collaboration, joint scientific consultations, horizon scanning, and voluntary cooperation, specifically at the HTA level, but questions remain.



Summary

Planning and coordination prior to the submission of marketing applications can reduce uncertainty. We all want to reduce unexpected obstacles at the end of the regulatory approval process, and we are beginning to see more progress in Europe in terms of early planning. Greater flexibility and iteration throughout the approval process is desired by all. The more that can be done upfront to ensure that the right evidence is generated, the better the outcome for all stakeholders, including patients.

Session 2: Mapping uncertainty during clinical development - what are practical tools/strategies and activities for companies and agencies?

Mapping clinical efficacy uncertainties in the evidence generation during development – How can it be applied in a practical manner to inform company decision making?

Company perspective

Dr Jacques Mascaro, Senior Vice President, Oncology Regulatory Science, Strategy and Excellence, AstraZeneca

Background

From a company perspective (and particularly in oncology), challenges that increase complexity and uncertainty during clinical evidence generation were identified as: the need to increase the diversity of clinical trial populations; an increased focus on dose optimisation; FDA's Project FrontRunner - advancing accelerated approvals to earlier cancer treatment; endpoint evolution; and scientific advice from regulatory authorities and HTA bodies.

Diversity in clinical trials

It is important that the data being generated in clinical trials are applicable to the populations who will use the treatments. Indeed, in accordance with FDA and EMA guidelines, AstraZeneca anticipates that by 2025, clinical trial participants will mirror the characteristics of disease populations. AstraZeneca operates under three strategic pillars to achieve trial diversity: data-driven continuous improvement; innovative solutions; and effective external engagement and collaboration.

Dose optimisation

This is particularly important given Project Optimus that the FDA has been implementing. Maximum tolerated dose or dose limiting toxicity are no longer principal considerations in oncology; therefore, dose optimisation should be considered very early in the process. In oncology particularly, where there may not be efficacy in monotherapy, but there may be biological plausibility to combine treatments, the issue of dose can be even more important.

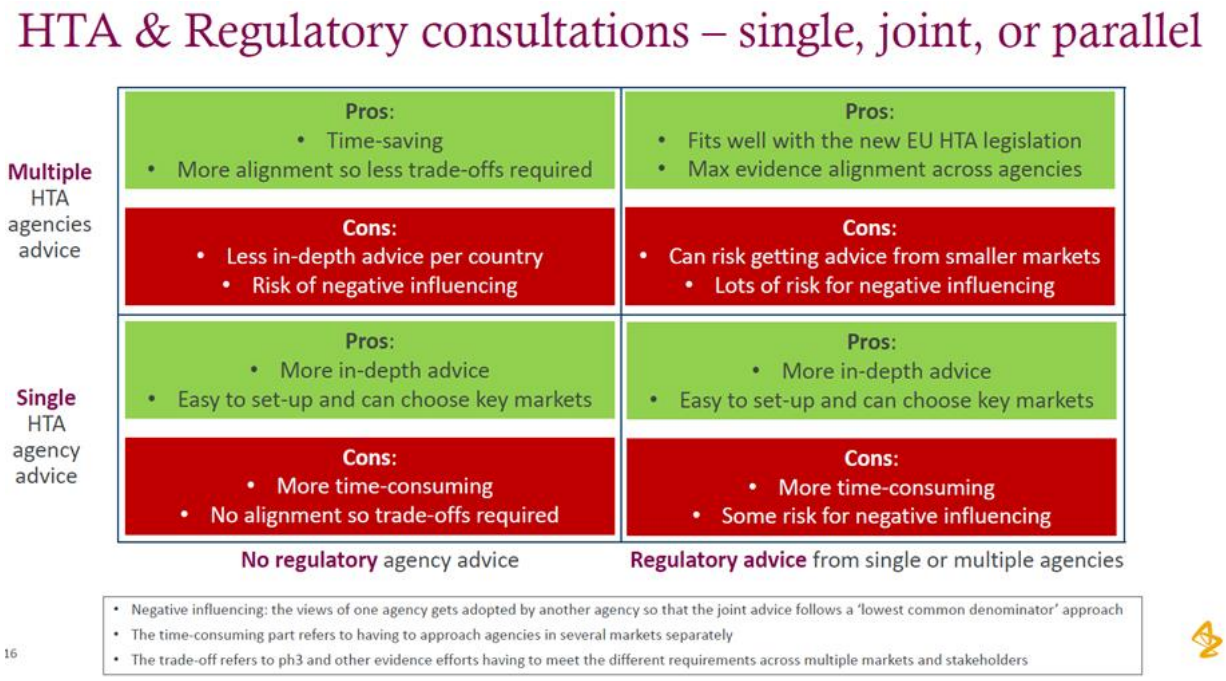
The FDA-based initiative, Project FrontRunner, aims to accelerate the study of therapies in earlier settings, while improving the quality of data to inform the initial risk/benefit decision (i.e., randomised data). Friends of Cancer Research has published a white paper that discusses the elements that need to be considered to make decisions on accelerated approvals of new therapies in earlier metastatic treatment settings, and what design and strategy should apply in agreement with the agency[1].

Endpoint evaluation

Treatments are improving in oncology meaning that it can take a longer time to obtain overall survival data. In recent years regulators have shown some flexibility in accepting new early endpoints in their decision making for early-stage cancer treatments and in sharing their thinking on how novel endpoints could be used in drug development. For example, circulating tumour DNA is being examined as a potential early or surrogate endpoint in early-stage solid tumour drug development.

Scientific advice between regulators and HTA

While collaboration is welcome, there are complexities in that regulatory agencies can choose to liaise with several HTA agencies together or separately, which has various pros and cons (see below).



Technical success

AstraZeneca has developed an automated tool looking into the clinical design with the probability of technical success (PTS) and the probability of regulatory success (PRS). These are separate tools developed based on accumulated data (including CIRS benchmarking data and publicly available data). The PTS of the clinical program is multiplied by the PRS to obtain the probability of technical and regulatory success (PTRS), a critical factor in project and portfolio evaluations.

Digital transformation in R&D

How to exchange data and how to make decisions via good consultation between different stakeholders is challenging and there are opportunities with digital transformation to see greater convergence between agencies. Projects such as Orbis and Access have helped to make progress in this area. However, there is a lot of exchange of documents (which are built on other documents), and this is another element of uncertainty. Stakeholders should look over the next 10 years on how they can start exchanging *data* to continue this progress.

Summary

We are at the crossroads of big change in the pharmaceutical and biotech sectors and while this will bring new elements of uncertainty, it also brings opportunities to decrease these uncertainties. Access to treatment remains a complex issue requiring more partnership between stakeholders. Finally, moving from document to data exchange could change the regulatory ecosystem dramatically in the next 5 to 10 years.

References

1. Friends of Cancer Research. Accelerating investigation of new therapies in earlier metastatic treatment settings. 2022. https://friendsofcancerresearch.org/wp-content/uploads/Accelerating_Investigation_Therapies_Earlier_Metastatic_Treatment_Settings.pdf

Can duplication of regulatory and HTA analysis of efficacy, safety and uncertainty be avoided - What approaches during development could regulators and HTA adapt to address a common issue of uncertainty?

Regulatory perspective

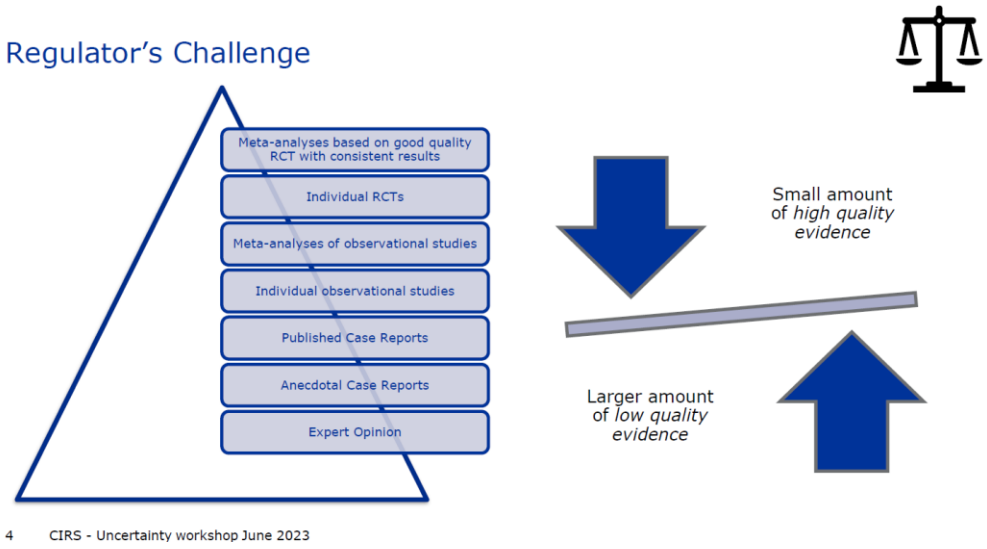
Dr Steffen Thirstrup, Chief Medical Officer, EMA

Background

For a product to be approved, regulatory authorities need to see sufficient and satisfactory documentation for quality, efficacy and safety. However, what is 'sufficient and satisfactory'? And what is the risk-benefit balance? For regulatory decision making, pricing and reimbursement is not key. Generating evidence for quality, efficacy and safety, comes with a lot of gaps. The challenge for regulators regarding uncertainty is the balance between having a small amount of high-quality evidence versus having large amounts of lower-quality evidence (see below).

The regulator's challenge

Balancing this challenge in the right way is key as there are numerous factors, such as cost of development, time and availability of patients (for rare conditions) etc. From a European perspective, the conditional marketing authorisation provides an example of how to distinguish uncertainties from risks. This is because people outside of regulatory can associate conditional approval with having a risky product on the market (which is not the case). To obtain a conditional marketing authorisation, the condition being treated must be a serious, life-threatening condition. There must also be a positive benefit-risk balance. This is not the same as saying that everything is known about the product, but at the time of authorisation there should be greater benefits than harms in terms of what is known. Intermediate endpoints can be helpful, but it is important that to address uncertainty, the applicant can provide comprehensive data post-approval. Regulators need to be reassured that whatever is planned as confirmatory is up and running and not influenced by putting the product on the market.



European collaboration between regulators and HTA

A new HTA regulation has come into force in Europe (grace period until January 2025 when it will become mandatory for oncology products and for advanced therapies initially). This builds on a long collaboration between the HTA bodies in Europe (EUnetHTA collaboration). There have been 60 procedures in parallel consultation (between regulators and HTA bodies regarding the scientific advice on the development). There have been publications on post-approval evidence generation or post-licensing evidence generation. A method of sharing the unredacted Committee for Medicinal Products for Human Use assessment report in a confidentiality agreement between the HTA bodies and the EMA has been established.

Governance of HTA cooperation under the new regulation

The Members States Coordination Group on HTA has been established. It includes representatives from all 27 EU member states who work in four different subgroups. There will be joint scientific consultations, some horizon scanning and a methodology working party that will develop guidance. In addition, there will be touch points for engagement between regulators and HTA bodies.

It is important to note a change in terminology: ‘joint’ refers to collaborative work amongst HTA bodies, while work between regulators and HTA bodies is now termed ‘parallel’.

Summary

In the context of the EU HTA Regulation, there will be opportunities to reduce the duplication of work, with certain touch points between EMA and HTA bodies. However, the details for how exactly this will be implemented in Europe are not yet known.

Can duplication of regulatory and HTA analysis of efficacy, safety and uncertainty be avoided - What approaches during development could regulators and HTA adapt to address a common issue of uncertainty?

HTA perspective

Dr Nick Crabb, Programme Director, Scientific Affairs, NICE

HTA analysis of efficacy

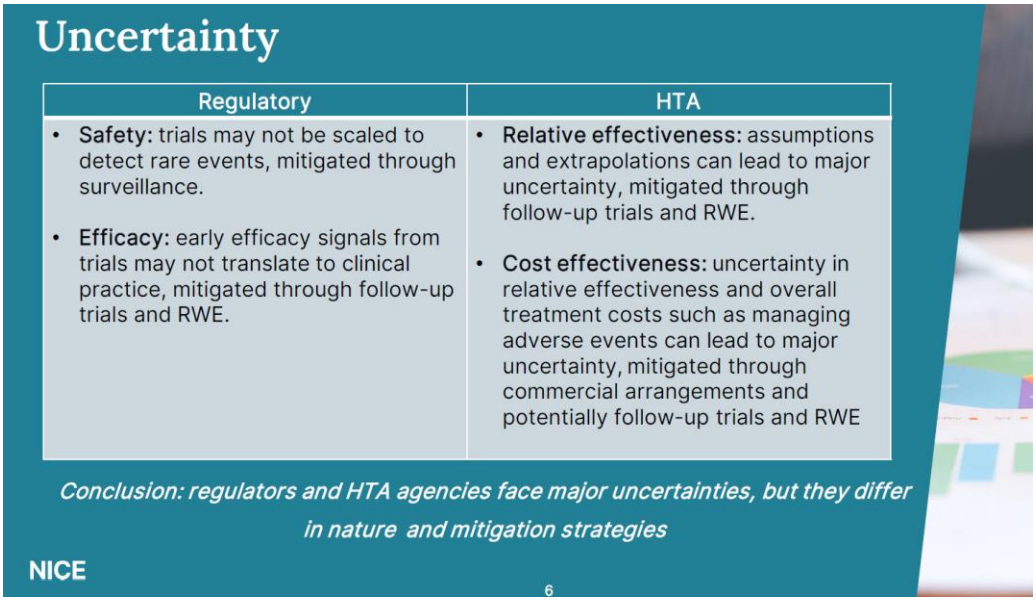
Randomised control trial (RCT) efficacy data plays a pivotal role in the HTA of new medicines and indications. Duplication of regulatory and HTA analysis is not necessarily an issue, as different analyses are needed to answer different questions from each stakeholder. However, for HTA, efficacy data may be limited in several ways at the time of product launch. This may include use of surrogate outcomes in clinical trials. In addition, periods where trial participants are randomised between treatment and control arms in crossover studies can be short, and the control-arm treatments, which could be active or placebo, may not reflect the most relevant comparators in the relative effectiveness assessments. Also, comparators may be different in different jurisdictions. While clinical trial designs are rightly designed to detect benefit-risk signals as efficiently as possible, this leaves much additional consideration at the HTA stage, including, potentially, indirect comparisons (network meta-analyses), extrapolation from surrogate endpoints to those needed to estimate impacts on length/quality of life and extrapolation from short randomisation periods in clinical trials to estimate long-term outcomes.

HTA analysis of safety

In HTA, the explicit consideration of safety is not normally done as this is addressed by the regulators. One caveat would be where there is a known safety issue that impacts some patients and that obviously then impacts the length and quality of life. That is then taken into account in the assessment of relative effectiveness and also in quantitative health economic models. Overall, there is not duplication as such.

HTA and uncertainty

There is a high degree of uncertainty in relative effectiveness and cost effectiveness as summarised below. Follow-up trials and real-world evidence (RWE) can help to mitigate both. Indeed, with the NICE Cancer Drugs Fund, RWE does not necessarily help with efficacy, but has proven valuable in helping to establish the real costs of treatment etc.



Approaches to address common regulatory and HTA issues of uncertainty

There are not really any common regulatory and HTA issues of uncertainty; instead, there may be a range of uncertainties that impact regulators and HTA agencies in different ways. Collaboration between regulators and HTA agencies can still help, i.e., joint scientific advice and other engagements with companies to ensure that evidence requirements for regulation and HTA are progressed in parallel (including if there is going to be post-launch relevant evidence development), discussions and agreement of most relevant active comparators where feasible and development of a common understanding of the downstream impacts on HTA agencies and payers of licensing based on immature evidence.

Reframing the problem – an issue of alignment

Through advancements in regulatory science and international collaboration, regulators are increasingly efficient and timely in identifying new medicines with a positive benefit/risk profile and issuing marketing authorisations accordingly. However, at the time of marketing authorisations, the evidence on which to base HTA may be very limited. Furthermore, healthcare systems across the world are under major pressures and HTA and the consideration of opportunity cost is more important now than ever before.

While cooperation between regulators and HTA agencies is important and generally working well, full alignment is not feasible given the different remits and uncertainties to manage. Solutions are likely to require collaboration across industry, regulators, HTA agencies and payers with significant focus on pricing and commercial arrangements.

Potential solutions could be:

- Interim funding that is not dependent on HTA, with HTA conducted later to inform long term pricing (e.g., the system in Germany).
- Interim funding based on ‘light touch’ HTA with full HTA conducted later to inform long term pricing (such a policy could potentially include ‘correction’ of pricing during the interim funding period when the full HTA is available). This could be applied to all medicines, or to a subset of medicines addressing high unmet need.

- Managed access approaches with data collection for new medicines with high promise and immature evidence (e.g., Cancer Drugs Fund / Innovative Medicines Fund in England and arrangements in Italy).
- Price negotiations such that despite the uncertainty, the decision risk (opportunity cost) is manageable at the agreed price.
- Innovative payment models where needed to manage decision risk.

Facilitators of these potential solutions include responsible pricing, continued innovation to improve the efficiency of product R&D leading to financially sustainable new medicines and continued innovation in regulatory and HTA science.

Summary

While there may not be a common regulatory and HTA issue of uncertainty, collaboration between regulators and HTA bodies can still help. Regulators are increasingly efficient and timely in identifying new medicines with a positive benefit/risk profile; however, evidence on which to base HTA may be limited at the time of marketing authorisation. Potential solutions include interim funding approaches, managed access approaches, price negotiations that ensure opportunity cost is manageable at the agreed price despite uncertainties and innovative payment models.

Are current company/agency interactions during development an effective approach to identify and resolve uncertainties that are of concern to regulators and HTA agencies?

Irwin Tran, Global Access Evidence Enabler, Roche, USA

What are the opportunities for interactions between industry and regulatory/HTA?

From a high-level perspective, there are formal scientific advice meetings where industry can go directly to agencies to discuss specific issues related to a trial, evidence, or other aspects of a medicine's approval. There are also ad hoc consultation advice meetings. For example, NICE has an Office of Market Access, which is an opportunity to consult on the potential gaps or activities that could be done to ensure that the company is taking the correct approach with their HTA submissions. There are also advisory committees, for example, with the FDA. On an annual basis, there are many topics being discussed at these advisory committees, and they provide an opportunity for manufacturers to interact with regulators. At the point of submission there is another opportunity to interact with agencies to talk about the evidence package, the value propositions, and how to get patients access to the medicines.

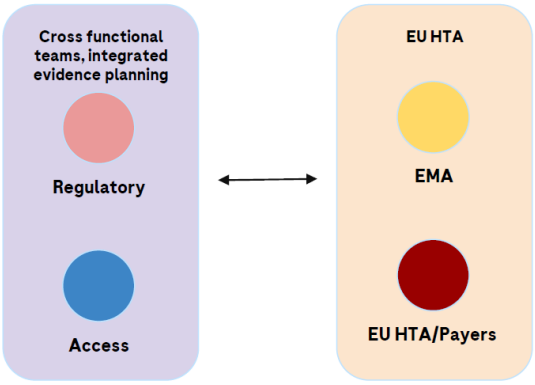
Are these interactions working?

Overall, the manufacturer and agency interactions are working. If following formal or informal consultation the regulatory and HTA agencies are aligned on what uncertainties are present, it becomes very difficult for manufacturers to ignore addressing those uncertainties. However, in most instances, regulatory and HTA agency uncertainties are not always coordinated. The regulatory agencies tend to focus more on safety, whereas HTA agencies tend to focus more on population, comparative effectiveness and outcomes. There can also be differing uncertainties *across* the agencies in different localities.

Differing incentives between agencies plays a role and impacts the advice that a company receives. Companies can receive different advice regarding what the uncertainties are and how to address them, and this creates a lot of noise that impacts manufacturer decision making. Internally, for the manufacturer, the question is how best to process all of the advice, which then creates internal tensions within an organisation to determine the final evidence package (regulatory department vs HTA vs biostats vs commercial vs clinical operations vs real world data departments etc. as each advocate for their stakeholders). This results in a risk that not all agency uncertainties will be addressed, and the possibility of a suboptimal evidence package being produced.

However, there are initiatives to try to coordinate regulators, HTA agencies and industry across the lifecycle of a product. Roche and Genentech for example use integrated evidence planning to ensure that different departments are aligned as to what evidence gaps are and what the trade-offs and implications would be if certain evidence were not produced, or certain types of uncertainty were not addressed.

There are current initiatives to promote alignment between agencies and within companies



Summary

Company/agency interactions are effective but only if stakeholders are aligned on the uncertainties. Regulatory and HTA uncertainties are not always coordinated, and so manufacturers need to consider how to prioritise advice that they receive. There is a risk that not all uncertainties for every agency can or will be addressed. Further alignment between regulatory, HTA and industry may help prioritise the uncertainties that need to be addressed, resulting in a better evidence package.

Session 3: Decision making under uncertainty - what approaches are HTA and regulatory agencies taking at the time of assessment?

Consideration of uncertainty within FDA's benefit-risk framework

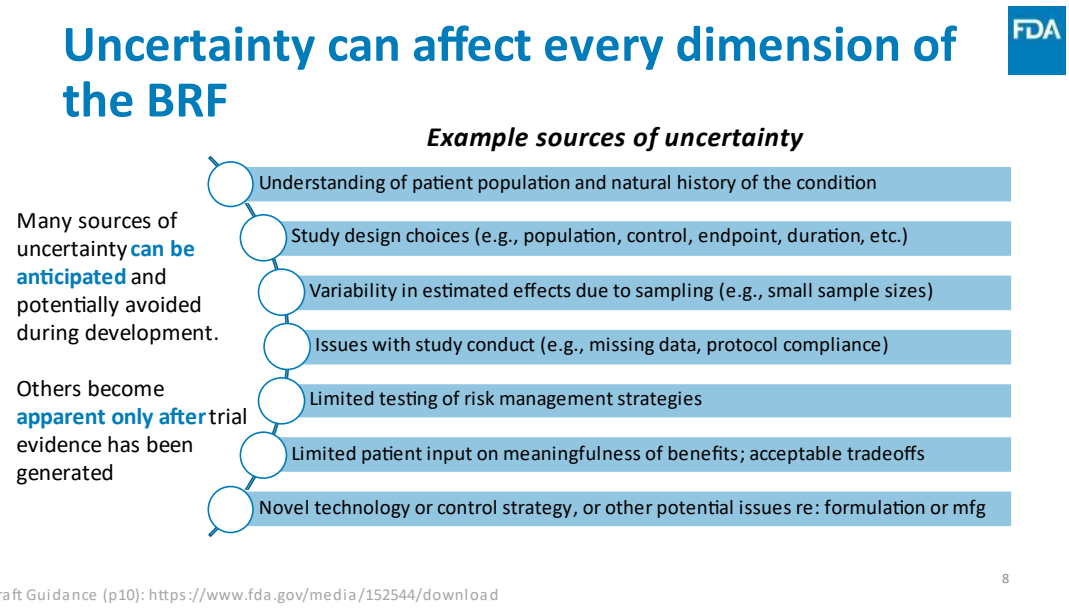
Dr Leila Lackey, Program Lead, Decision Support Service, Center for Drug Evaluation and Research (CDER), FDA, USA

The FDA benefit-risk framework

FDA's benefit-risk assessment is a case specific assessment of science and medicine that considers evidence, therapeutic context, uncertainties and regulatory options. It is a vehicle that the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) use for conducting and communicating benefit-risk assessments. It can provide a structured, qualitative approach for identifying, assessing, and communicating important considerations, such as analysis of the condition, current treatment options (therapeutic context), benefit and risk and risk management (product-specific assessment of the available evidence).

The FDA guidance lays out some of the key considerations that the agency has when evaluating benefit-risk for a product[1]. First is therapeutic context, for which intended use and unmet need, patient populations, the most relevant aspects of the condition and available therapies, are considered. The second consideration is benefit: strength and limitations of the evidence, the relationship between the endpoints measured and the outcomes of importance, generalisability and characteristics of the drug are considered. Third is risk and risk management, which also considers the strength and limitations of the evidence as well as the level of certainty about any causal associations, differences between clinical trials and post-marketing setting (relationship to risk and the effectiveness of proposed risk mitigation strategies, which may or may not have been tested in the clinical trials). In concluding, the framework looks at the strength of evidence overall, how the therapeutic context affects the assessment and the relative importance of the benefits and the risks. Underlying all these facets is patient input which can be potentially informative for all these considerations as well as for uncertainty.

Uncertainty can affect every dimension of the benefit-risk framework (see examples below). Uncertainties can be anticipated and addressable, anticipated and unaddressable, or unanticipated. While unaddressable and unanticipated uncertainties require scientific and clinical judgements, many sources can be anticipated and potentially be avoided or mitigated through decisions made in development. Other uncertainties become apparent only after the development is underway or after a pivotal trial is completed.



Structured risk planning

Given all these uncertainties, one concept in the FDA guidance is structured benefit-risk planning. The guidance defines this as a purposeful activity that is carried out by the sponsor to incorporate considerations of the product's benefit-risk assessment throughout the drug development life cycle. The goal is to reduce the important uncertainties that will be important factors when the agency considers the benefit-risk profile at the time of reviewing the new drug application or the biologics licence application. The building blocks of benefit-risk planning include defining the target patient population and the unmet medical need, as well as looking to identify the most important benefits and risks as early as possible. This then allows the development programme to focus on minimising uncertainties related to those critical factors. Some of the most basic tools include value trees, effects tables, and forest plots.

Another tool that is discussed in the guidance is additional benefit-risk analysis which builds on the review of evidence from all the disciplines as well as the structured benefit-risk assessment tools. Three approaches in the guidance for additional analysis include estimation of clinically important benefit or risk outcomes that were not directly measured, modelling of benefit and risk outcomes in a real-world setting and integrating benefits and risk in a combined analysis.

Summary

Benefit-risk planning can be used to help strengthen the evidence generated by a development programme. The goal is to reduce uncertainty and inform the final benefit-risk assessment. Additional tools such as value trees and effects tables, as well as more complex tools such as patient preference information and additional analysis can be used to help inform aspects of the overall benefit-risk assessment and address uncertainties within the development programme. While not perfect, these tools promote critical thinking. Tools should be pre-specified, and they should complement but not replace the integrated assessment in the benefit-risk framework.

References

1. FDA, Benefit-Risk Assessment for New Drug and Biological Products Guidance for Industry (final guidance). 2023. https://www.fda.gov/media/152544/download

Grading uncertainty at the time of decision making – is this of value to decision makers and does it enable communication of uncertainty across stakeholders?

Dr Jon Campbell, Senior Vice President for Health Economics, Institute for Clinical and Economic Review (ICER), USA

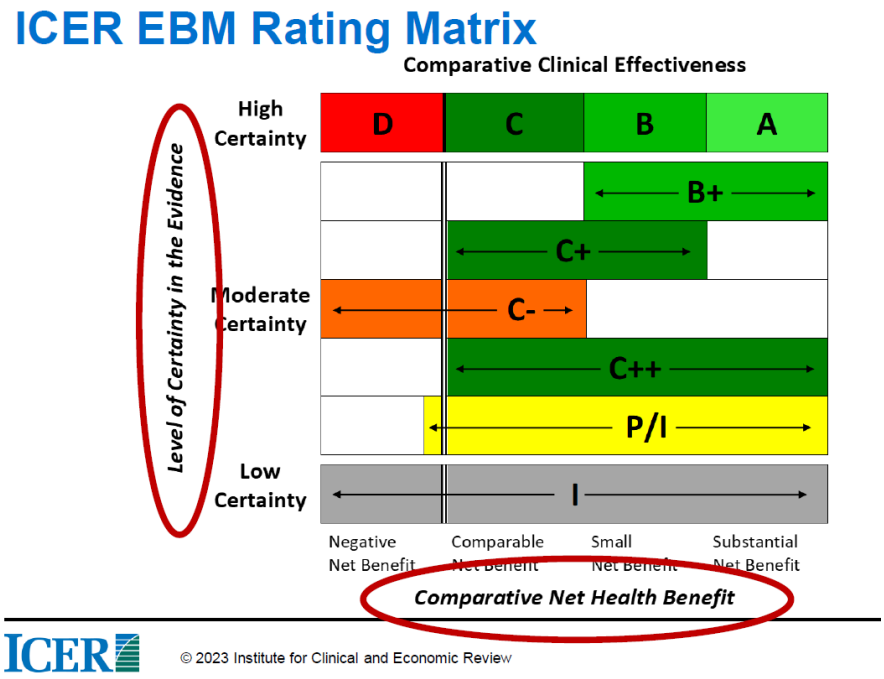
Background

ICER is an independent nonprofit research institute whose mission is to bring multiple stakeholders together and help the US health care system to achieve fair pricing, fair access, and future innovation. It does this by producing publicly available value assessment reports, which have several pillars within them including incorporating the patient voice, comparative clinical effectiveness and cost-effectiveness. Evidence reports that review evidence on one or more health interventions are shared in a public forum, and deliberated upon by an independent appraisal committee that votes on the net health benefit of the intervention(s).

ICER is predominantly funded by nonprofit foundations, with some support from health plans, manufacturers and ICER analytics subscribers. The ICER Value Framework's purpose is to shed light on and increase transparency of how value is conceived and evaluated. It takes a population perspective as opposed to trying to serve as a shared decision-making tool to be used by individual patients and their clinicians.

Comparative clinical effectiveness

ICER's work in comparative clinical effectiveness is predominantly at the study level (not generating new evidence). This involves systematically reviewing evidence that is available at the time of the assessment work (direct comparisons or indirect comparisons through network meta-analysis). ICER engages with manufacturers and other stakeholders to understand evidence that may not be in the public domain, but for the most part, published data is relied upon. There is also an examination of subgroups and heterogeneity of treatment effects. Together, this work results in an understanding of the ICER Evidence Based Medicine (EBM) Rating Matrix which presents ratings of comparative clinical effectiveness. There are two main dimensions: net health benefit (including risk and safety) and level of certainty in the evidence, which are distilled into ordered categorical grades (see below).



Cost-effectiveness analysis

ICER anchors value assessment using two health measures: quality-adjusted life years (QALY) and equal-value life years (evLY). The difference between the evLY and QALY is that for evLY, if an intervention extends life beyond that of the comparator it adds life years on average and that added life year is assigned the same quality of life weight irrespective of the population characteristics or the quality of life of those individuals.

Is there a relationship between comparative clinical effectiveness and modelled health gains (QALYs)?

To address this question, ICER used data from ICER's Evidence Compendium and corresponding reports. Eligibility required a lifetime time horizon for the model and published reports between 1/1/2017 and 9/1/2021 (N=83). For each pairwise treatment comparison that was included, their respective Evidence Ratings, and incremental QALY findings were extracted. ICER collapsed the evidence ratings into three categories based on estimated net health benefit: superior (including A, B, B+; N=65), comparable or better (including C+, C++; N=7), and uncertain (including P/I, I; N=11) and assessed the QALY gains across those three levels. On average, the superior evidence-graded treatments added 2.5 QALYs. For the comparable or better category, health gains were 1.0 QALY on average. For uncertain, there were health gains, but closer to 0.4 QALYs on average.

Policy considerations regarding uncertainty

Recommendations from the ICER Accelerated Approval Considerations 2021 White Paper[1] included:

- Increase mandatory federal rebate levels until the time of full approval.
- Full market pricing at launch reverts to marginal cost pricing if confirmatory trials are not completed in a reasonable timeframe or do not support value for money.
- Accelerated approval therapies require outcomes-based contracts.

Summary

ICER makes judgment calls in its work in order to have an impact in the health ecosystem. Those interpretations and judgments should be balanced alongside findings that are signalled in ICER's work around uncertainty. This includes deliberative processes and votes on comparative clinical effectiveness and long-term value, sensitivity and scenario analyses in cost-effectiveness analyses, and combining findings from modelling work with conservative and optimistic analyses (important for some gene therapies or one-time therapies).

References

1. ICER white paper explores policy options to improve accelerated approval pathway. PharmacoEcon Outcomes News 877, 31 (2021). https://doi.org/10.1007/s40274-021-7680-5

Do commonly used regulatory tools to manage efficacy and safety uncertainty work?

Agency perspective

Dr Peter Marks, Director, Center for Biologics Evaluation and Research (CBER), FDA, USA

Background

In the US there are no conditional approval pathways. All approvals (unless in an emergency use authorisation, for example), must meet an approval standard that requires information from adequate and well-controlled trials. There must be substantial evidence of effectiveness, including for accelerated approvals. The difference between traditional and accelerated approval is the level of uncertainty.

But what does 'substantial evidence of effectiveness' mean? There is some room for interpretation. While for some therapies it is very clear, even with low patient numbers, for other approvals it is much more challenging to assess. For example, accelerated approval makes use of biomarkers or intermediate endpoints reasonably likely to predict enzyme levels or structural protein levels. This is almost always associated with increased residual uncertainty compared with traditional approvals. Unlike in Europe, the FDA does not have an essential payer's system or HTA system to be able to help balance.

Managing residual uncertainty in the US

Residual uncertainty is a real challenge. In the US it is managed through statutory authority (what can be done forcibly as a post-marketing requirement). The FDA can require sponsors to demonstrate clinical benefit for drugs approved under the accelerated approval requirements. It can also manage uncertainty by requiring sponsors to do pediatric studies, or safety studies if a safety signal is observed. The FDA can also ask sponsors to complete studies if an approval is under the Animal Efficacy Rule. The FDA Reform Act of 2022 gave the FDA more latitude to make sponsors do studies, and the agency does now more frequently ensure that clinical studies are completed in a timely manner.

Summary

The FDA does have post-market commitments, but they do not help significantly with managing uncertainty because frequently, they are not for key issues. Also managing safety uncertainty is different to managing efficacy uncertainty. For cell and gene therapies, managing safety uncertainty may be less challenging than managing efficacy uncertainty because increasingly, enzyme levels, protein levels and surrogate markers may be required to approve gene therapies. Ultimately this may increase the risk of a negative confirmatory trial (which could be negative because there is truly no activity of the product or simply because the results were not demonstratable based on the clinical trial design).

Managing Uncertainty

- Post-Marketing Requirements (Enforceable)
  - Demonstrate clinical benefit for drugs approved under the accelerated approval requirements
  - Deferred pediatric studies when studies are required under the Pediatric Research Equity Act (PREA)
  - Studies or clinical trials to demonstrate safety and efficacy in humans that must be conducted at the time of use of products approved under the Animal Efficacy Rule
  - Assess a known serious risk, signal of serious risk, or potential of serious risk related to the use of the drug

Do commonly used regulatory tools to manage efficacy and safety uncertainty work?

Company perspective

Dr Álmath Spooner, Director, Regulatory Policy and Intelligence, AbbVie, Ireland

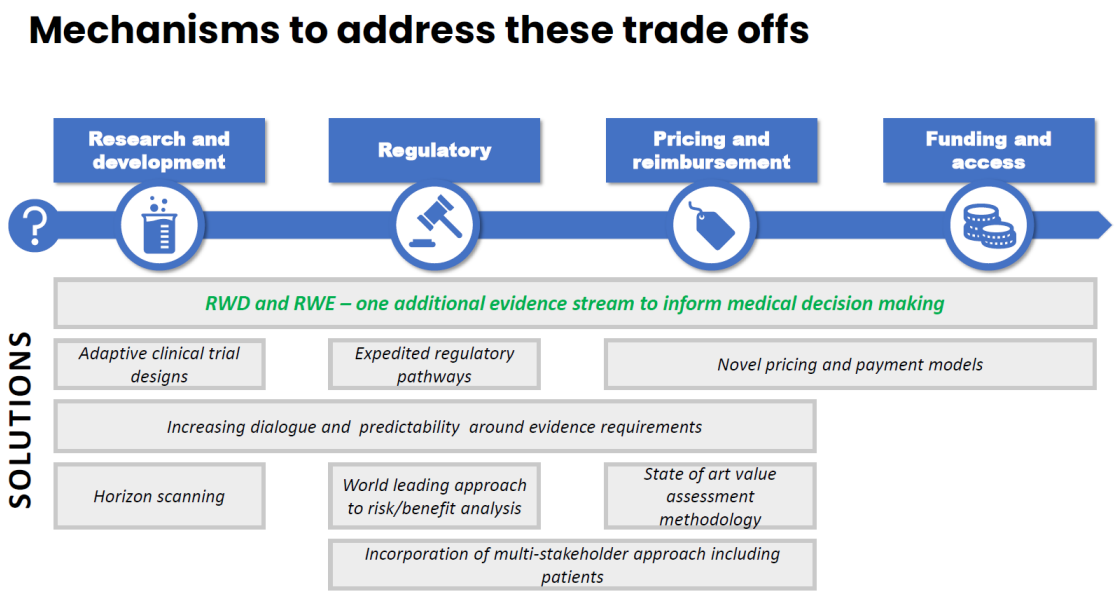
Background

It should be acknowledged that 1) trade-offs exist between speed of access, evidence and increasing certainty; 2) the research question and the decision context guide the selection of the evidence stream and the methodological approach; and 3) predictability of evidence requirements, supported by iterative dialogue opportunities, guidance and a learning environment, are key enablers.

Clinical uncertainty

Managing clinical uncertainty is predominantly about managing the trade-off between access, evidence and certainty. There are questions that can only be answered with large population exposure and/or experience from real-world use. In addition to the long experience with safety and risk, the field is now moving to think more broadly about uncertainty in the context of benefit-risk.

Managing trade-offs is a multi-stakeholder effort:



RWE case studies and learnings

- COVID-19 highlighted the need to embrace the totality of evidence, to accelerate epidemiological understanding of disease and the value of existing and new preventative and therapeutic interventions. Several COVID-19 mRNA vaccines were evaluated in the real-world setting using electronic health records and vaccination data. This RWE provided a timely mechanism to address uncertainties for more clinical trials in specific subpopulations. The COVID-19 pandemic also highlighted the many challenges for RWE generation, including variation in access and standards and the importance of data quality.

- Use of an external control arm to establish the magnitude of benefits. The key learning that emerged was the value of early engagement with the EMA through PRIME, a scheme to enhance support for the development of medicines that target an unmet medical need.
- A case where RWD was used to accelerate assessment. The key takeaway was that RWD in combination with a single-arm clinical trial can accelerate regulatory approval in situations where a disease is rare, prognosis is very poor and there are limited therapeutic options available.

Fit-for-purpose RWE is changing drug development

RWE policies and frameworks continue to evolve, which is very encouraging. However, a proliferation of documentation and recommendations will make the RWE environment increasingly difficult to navigate both for medicine developers and for decision makers in terms of what should be expected and what is good practice in a particular situation. International alignment and harmonisation will help to drive efficiencies. Efforts towards international collaboration will improve consistency in study quality and evaluation and ultimately, support timely delivery of innovative medicines. To de-risk the use of RWE and development programmes, there needs to be alignment at a high level amongst stakeholders (particularly downstream from approval) on the role of RWE in clinical evidence generation.

Use of RWE has evolved through decades of experience and is contributing to faster, better decision making through product development. However, to facilitate more consistent uptake, there needs to be greater predictability for sponsors on whether RWE is fit for purpose in a particular decision-making context. There is experience that can be leveraged in developing guidance and defining use cases where RWE will be suitable. Earlier approvals have been enabled by RWE, with expedited pathways facilitated through increased capacity for RWE generation, substantial exploration of the use of RWE external control arms, and clinical research becoming more longitudinal with increasing regulatory focus on longer-term follow-up. RWE is facilitating a more patient-centred approach towards evidence generation.

Summary

Regulators are leveraging new approaches to evidence generation to address the access evidence trade-off to best meet and serve patient needs. Dialogue opportunities and early engagement are critical facilitators, particularly to allow multi-stakeholder alignment, but recognising that the evidence package is informed by the decision-making context. As various stakeholders in the health data ecosystem increase their capacity, it is going to become even more critical to build alignment on the fitness of data sources, methodologies, and analytical approaches and to view these in their global context.

Are current HTA agency tools for managing uncertainty fit for purpose? If not, why not and what needs to change?

HTA perspective

Mélanie Caron, Assistant Director of Evaluation of Medication and Technology, Institut national d'excellence en santé et en services sociaux (INESSS), Canada

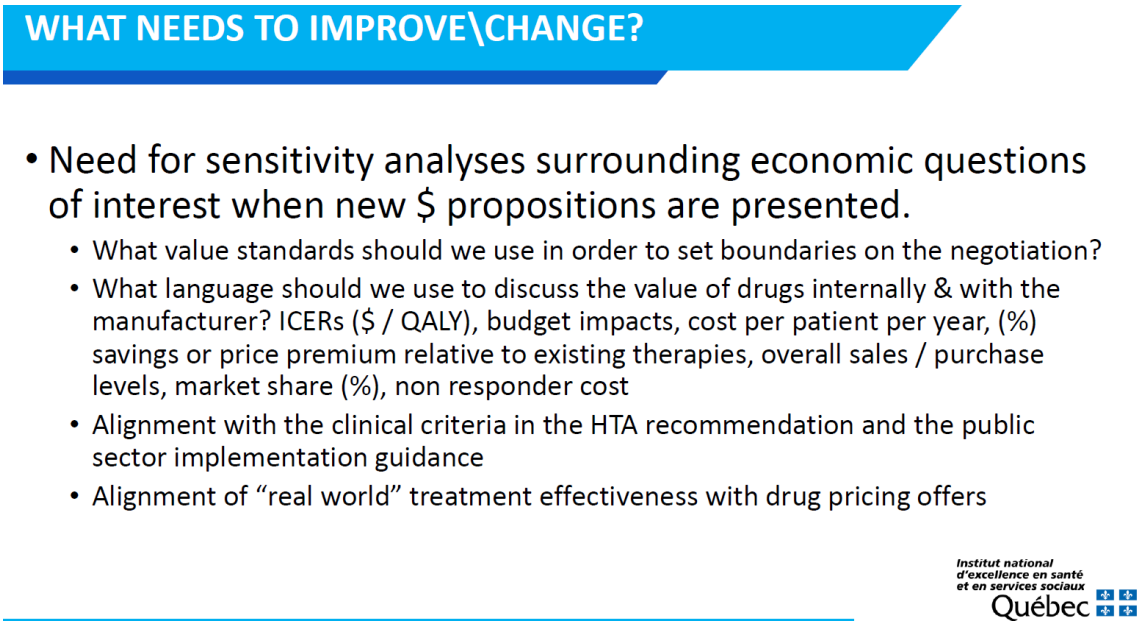
Background

INESSS is the HTA agency for the province of Quebec, the only jurisdiction in Canada that has a public universal drug plan. INESSS has a very close relationship with the Ministry of Health because the agency's recommendations go directly to the Minister. If INESSS considers that the therapeutic value of a drug has been demonstrated, it sends its recommendation to the Minister after evaluating the following: fairness of the price, cost effectiveness of the medication, consequences of adding the drug to the medication list on the health of the population and on other components of the health and social services system, and the advisability of including the medication on the list with regard to the purpose of the basic prescription drug insurance plan.

INESSS has input from ethicists, economists, clinical experts, patients, citizens and doctors (but no one from the government). Deliberations consider five dimensions to produce an overall value assessment: clinical, population, organisational, sociocultural and economic dimensions.

Managing uncertainty - what needs to improve/change?

HTA scientific professionals must appreciate uncertainty in various forms efficiently, in a timely manner and must be able to translate it simply to the derivative committee. Further, the HTA agency must be able to discuss the level of uncertainty considered acceptable in specific contexts with the regulator. Pharmacoeconomists need to develop/adapt/modernise their modelling to translate uncertainty into cost effectiveness and budget impact analysis. Indeed, INESSS has upgraded their team of economists. They partner with academics to give courses on advanced economic modelling and collaborate with clinicians to discuss indirect comparison studies.



Once professionals are evaluating a clinical study and the economic teams put forward the effectiveness into one paper, the deliberative committee must be in a position to fully appreciate the data, properly document arguments, recommend further real-world data (RWD) when needed and be certain of the possibility of re-evaluation. Manufacturers need to propose scenarios where degrees of unmet needs and evidence of clinical benefit can be put forward, explored, or refined. This is necessary, particularly because INESSS has access to public databases as all patients are covered.

HTA agencies need to put in place solid reassessment steps including interpretation of RWD. This can be challenging if not yet published. Use of artificial intelligence is also likely to become a more significant component of HTA. Regulators and HTA also need to reinforce knowledge transfer activities to enable healthcare professionals and clinicians to understand where evidence is coming from and the uncertainty gap. For example, how do we inform patients that there may be a disinvestment at some point in time?

Health system organisational issues are a problem in Quebec. For example, the Quebec provincial lab is struggling with the high increase in biomarkers that are necessary to prescribe newer therapies; therefore, HTA must consider not only the cost, but also add other economic considerations into the equation.

Summary

Improvements to manage uncertainty have been made in Quebec but many changes are on the radar for 2024. INESSS plans to have open dialogue and conversation with regulators and manufacturers. Economic scenarios are going to be changing and require an openness to enable discussions, analyses and negotiations of these new scenarios to take place.

Are current HTA agency tools for managing uncertainty fit for purpose? If not, why not and what needs to change?

Company perspective

Dr Indranil Bagchi, VP, Global Pricing and Market Access Head, GlaxoSmithKline, USA

DIA-HTAi working group on uncertainty

While regulator and HTA/payer data needs are different, the divergence of decisions can often come down to tolerance for uncertainty. The Drug Information Association Health Technology Assessment International (DIA-HTAi) framework seeks to address this. Its objectives are to:

- Clarify broader stakeholder considerations on uncertainty in the interface.
- Understand what contributes to uncertainty.
- Identify management strategies.
- Produce a peer-reviewed article on mapping stakeholder views to address uncertainty.

The DIA-HTAi working group has good representation from industry and multiple different payer and HTA agencies and also receives advice from the European Medicines Agency (EMA) and other regulatory agencies. Following initial working group calls, there was a roundtable held at DIA Europe in Brussels in March 2022, a panel discussion at HTAi in Utrecht in June 2022 and further discussion at DIA Europe in Basel in March 2023. This has culminated in a recent publication in the *International Journal for Technology Assessment in Health Care*[1].

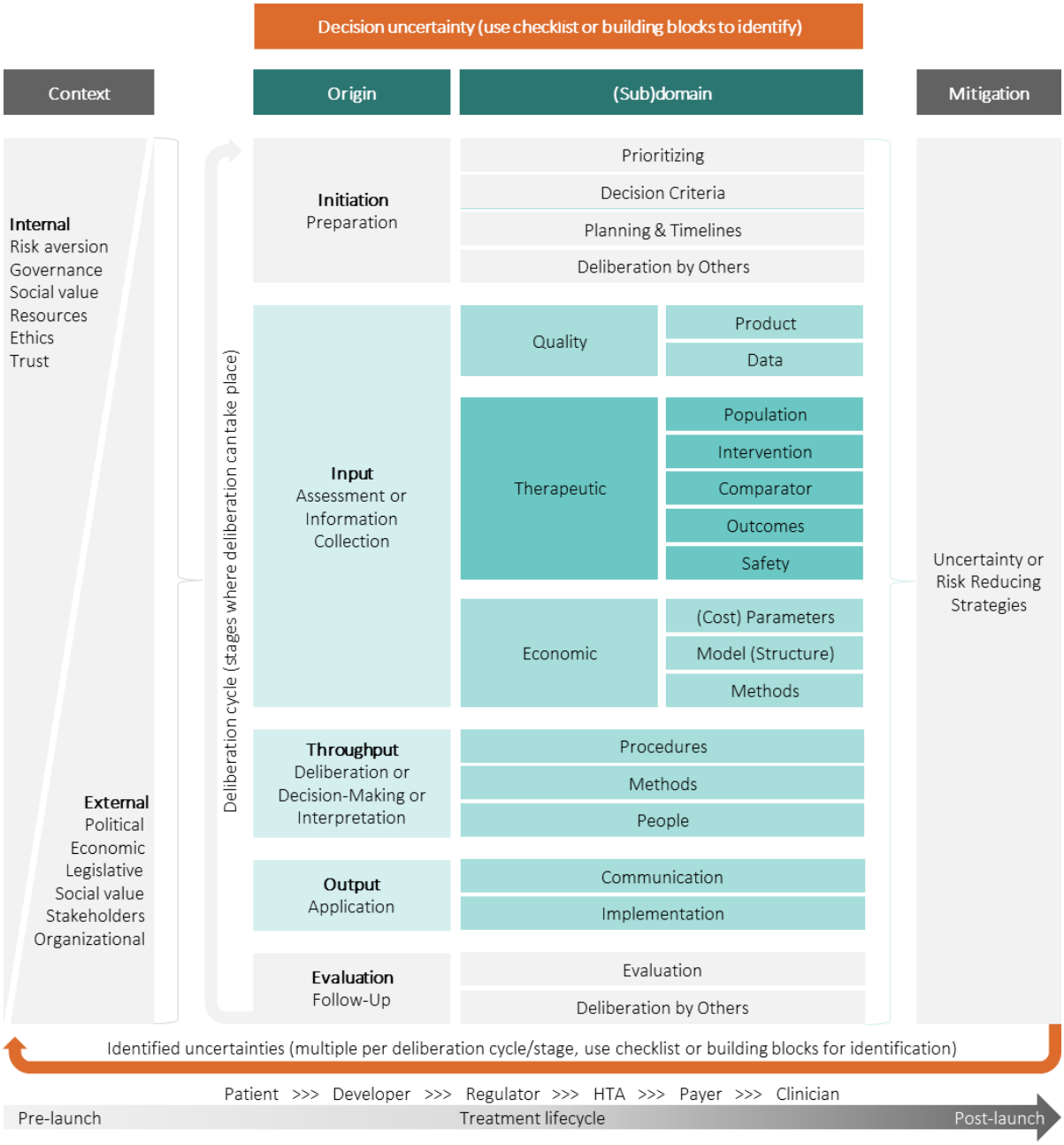
Identifying and mapping uncertainty

The DIA-HTAi working group looked to define and identify uncertainty. For example, is information unavailable, inaccurate, conflicting or non-understandable? Ultimately, the goal is to try to predict the future and there are impacts and risks from these predictions. In turn, what is the relevance to the decision maker? What is the context of the decision?

The group has devised a framework to look at the input, the throughput, and the output, and question at every stage whether the information available is sufficient to make a given decision. If it is not, where is the uncertainty and what are the potential mitigation strategies?

An uncertainty map was also constructed based on the input-throughput-output framework (see below)[1]. This acknowledges that there will be internal factors, many of which can be controlled, as well as external factors, many of which will be beyond control within the context of a decision-making process.

The goal of the framework is to help decision makers to identify what they are comfortable with versus where there may be uncertainty that needs to be addressed. Case studies have demonstrated how to utilise the framework to identify and mitigate uncertainty, for example, in the event that a new gold standard treatment enters the market during a clinical trial[1].



Summary

Differences between regulatory approval and patient access can often be attributed to tolerance for uncertainty. Data uncertainty can be addressed with real-world evidence post launch; however, there needs to be ways to address uncertainty in the interim. There are a wide range of preferred mitigation strategies observed across stakeholders. HTAi-DIA guidance may foster timely dialogue on mitigation strategies across stakeholders, as well as improve consistency and transparency. Whilst remit may be different, all stakeholders can explore the same or similar frameworks to enable faster patient access to life saving medicines.

References

1. Hogervorst MA, Vreman R, Heikkinen I, et al. Uncertainty management in regulatory and health technology assessment decision-making on drugs: guidance of the HTAi-DIA Working Group.

International Journal of Technology Assessment in Health Care. 2023;39(1):e40. doi:10.1017/S0266462323000375. Available at: https://doi.org/10.1017/S0266462323000375

Session 4: Syndicate sessions

In this session participants were divided into three syndicate groups to discuss management and mitigation of uncertainty in the context of:

a) drugs that go through an accelerated/priority or provisional/conditional approval
b) drugs trialled in small populations (e.g., orphan drugs, rare diseases), 'single shot' cell, gene and tissue therapies or potentially curative or preventative therapies
c) drugs where differences between efficacy observed in clinical trials and real-world effectiveness are commonly found (i.e., patients with co-morbidities or groups poorly represented in clinical trials).

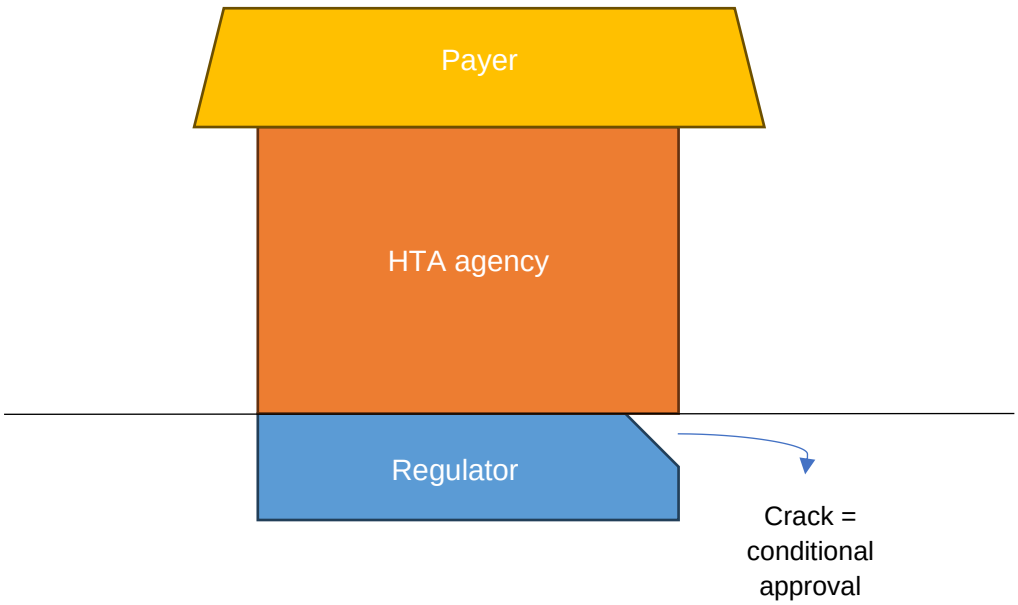
For each drug type, syndicates were asked to identify aspects of uncertainty, list tools for assessment of uncertainty, identify approaches to help reduce uncertainty in the development, review and reimbursement process and propose approaches to manage or mitigate uncertainty. Summaries of these discussions including recommendations for future work, are presented in session 5.

Session 5: Syndicate sessions feedback

Syndicate Discussion – Topic A: How can particular aspects of uncertainty around drugs that go through an accelerated/priority or provisional/conditional approval be managed or mitigated?

Chair	**Prof John Lim**, Executive Director, Centre of Regulatory Excellence (CoRE), Duke-NUS Medical School, Singapore
Rapporteur	**Nina Barchha,** Senior Director, Group Lead Regulatory Affairs – Oncology, Astellas, USA

The syndicate group illustrated their thinking around uncertainty in the context of conditional approvals through an analogy of building a house (see below). The regulator sets the foundation of the house (blue), then the HTA agency builds the walls/windows etc (orange) and finally the payer adds the roof (yellow). If the foundation of the house has a crack in it due to conditional approval, this gives uncertainty over the stability of the house, which may crumble over time unless the crack is filled. This analogy shows that each stakeholder builds upon one another, and so the regulator foundation must be strong for the house to stay standing.



Discussions around key questions were summarised as follows:

Question 1- What are the particular aspects of uncertainty around these drugs from each stakeholder's perspective?

Aspect of uncertainty	Which stakeholder does this apply to?				
	Company	Regulator	HTA	Payer	Other
Maturity of data	✓	✓	✓		
Strength of endpoint – Validity/relevance – Meaningfulness – Magnitude of effect	✓	✓	✓	✓	Patient
Long term safety and efficacy	✓	✓	✓		Patient
Benefit over existing therapy – Degree of benefit-risk – Strength of initial data		✓	✓		
Cost effectiveness	✓		✓	✓	
Additional data collection – How will sponsors be held accountable for collecting additional data? – Which factors will influence this data collection? E.g., standard of care changes	✓	✓	✓	✓	
Representativeness of population		✓	✓		
Relevance of the comparator May be different in different regions and within a region	✓	✓	✓	✓	
Differing perspectives between: – HTA vs regulator i.e. subgroup assessment – Regional regulatory decisions/assessments (or even within regions)	✓	✓	✓	✓	

Question 2 - Are there additional tools that can be used to assess uncertainty for these drugs?

List of additional tools	Which stakeholder does this apply to?				
	Company	Regulator	HTA	Payer	Other
Detailed reports and transparency (in all forms of assessment)	✓	✓	✓		
Decision making/analysis/uncertainty tools - some of which may be used in other industries	✓	✓	✓	✓	
Value of information analysis/tools - could fill information gaps or assess the degree of gap in information and the value of filling that gap	✓	✓	✓	✓	
Incorporating **multistakeholder feedback** i.e., health authority meetings, patient input	✓	✓	✓		Patient
Real-world evidence (RWE)	✓	✓	✓		

Question 3 - Identify approaches that can help reduce uncertainty in the development, review and reimbursement of these drugs?

Approaches that help reduce uncertainty	Which area does this relate to?		
	Development	Review	Reimbursement
Post-marketing requirements, registries, risk evaluation and mitigation strategies	✓	✓	✓
RWE and other evidence generation outside clinical trials i.e., research on cost of care of existing standards • e.g., managing the cost of cytokine release syndrome resulting from CAR-T cell therapy	✓	✓	✓
Reliance approach to bridge/share uncertainty		✓	?
Multi-timepoint analysis in clinical trials (i.e., interim analysis, stopping rules, etc.)	✓	✓	
More dialogue, transparency and framing of uncertainty between stakeholders	✓	✓	✓

Question 4 - Are there new regulatory or HTA approaches that could manage or mitigate uncertainty (pre or post approval) for these drugs?

New approaches that could be considered pre or post approval to manage or mitigate uncertainty	**Which stakeholder does this apply to?**				
	Company	**Regulator**	**HTA**	**Payer**	**Other**
Obtaining **patient and caregiver feedback** during and after clinical investigation i.e., ongoing qualitative interviews, exit interviews – expanding upon this to understand impact on quality of life	✓	✓	✓		Patients, healthcare professionals
Early HTA signals (vs full assessment) combined with special commercial arrangements	✓		✓	✓	
Sharing of data across countries (real world/health plans) and combining these to understand/manage uncertainty	✓	✓	✓	✓	
Innovation sandbox – learning across multiple stakeholders	✓	✓	✓	✓	
Payment models i.e., risk sharing	✓		✓	✓	

Recommendations including future work (noting the need to remember that there are avoidable and unavoidable uncertainties):

All stakeholders (both short and long term)	• Recognition that all stakeholders have a shared purpose in reducing uncertainty. • Proactive establishing of multistakeholder platforms and strengthening existing platforms to improve dialogue and progress actions to reduce uncertainty.
All stakeholders (both short and long term)	• Acknowledgment of evidence gap depending on timepoint of development (pre-approval or post-approval). • Alignment on the best approach to fill the gap i.e., utilisation of sandbox. For example, pre-approval this could be an additional study or amendment of studies.
CIRS with support from all stakeholders (short term)	• CIRS to investigate successes with commercial arrangements (risk sharing/time limits around reimbursement conditions) for drugs that have received accelerated/priority or provisional/conditional approval. • Learnings need to be translated across disease states and regions.
CIRS with support of all stakeholders (short term)	• CIRS to conduct a deeper dive into which uncertainties are avoidable/unavoidable, and discuss planning tools around avoidable ones.

Syndicate Discussion – Topic B: How can uncertainty for drugs trialled in small populations (e.g., orphan drugs, rare diseases), "single shot" cell, gene and tissue therapies or potentially curative or preventative therapies be managed or mitigated?

Chair	**Prof Steffen Thirstrup,** Chief Medical Officer, EMA
Rapporteur	**Sana Hussain,** Director, US Regulatory Policy, GlaxoSmithKline, USA

Discussions around key questions were summarised as follows:

Question 1- What are the particular aspects of uncertainty around these drugs from each stakeholder's perspective?

Aspect of uncertainty	Which stakeholder does this apply to?				
	Company	Regulator	HTA	Payer	Other
Durability of response - ensuring the durability of the treatment effect, including understanding how long the therapy's benefits are sustained and whether the response remains effective long term	✓	✓	✓		
Clinical efficacy - long-term impact on disease progression and patient outcomes is often uncertain; patient-reported outcome evaluations are challenging	✓	✓	✓		
Patient relevance - understanding the relationship between endpoints and clinical meaningfulness to patients/caregivers	✓	✓	✓		
Patient population • Heterogenicity - limited diversity in patient characteristics • Paediatric • Comorbidities	✓	✓	✓		
Reimbursement and access - coverage policies, pricing, patient access and equity	✓	✓	✓		
Safety profile - rare or long-term adverse effects may be unclear	✓	✓			
Concept of value of products - is a product able to change the course of disease and to what extent; return on investment	✓	✓	✓		

Question 2 - Are there additional tools that can be used to assess uncertainty for these drugs?

List of additional tools	Which stakeholder does this apply to?				
	Company	Regulator	HTA	Payer	Other
Value of information analysis - quantitative approach to assess the potential value of collecting additional information or conducting further research to reduce uncertainties in decision making: • Identify and prioritise key uncertainties that have significant impact • Assess the value of reducing uncertainties	✓	✓	✓		
Forecasting tools - e.g., budget impact models (forecast the financial impact of adopting a new therapy), multicriteria decision analysis (MCDA)	✓		✓		
Horizon scanning - identify and monitor emerging trends, innovations and factors that impact the landscape	✓	✓	✓		
Techniques to assess stakeholder tolerance - e.g., surveys, preference techniques	✓	✓	✓		

Question 3 - Identify approaches that can help reduce uncertainty in the development, review and reimbursement of these drugs?

Approaches that help reduce uncertainty	Which area does this relate to?		
	Development	Review	Reimbursement
Long-term follow-up programmes and post-market surveillance - to track long term safety and effectiveness of these therapies • e.g., Disease registries and monitoring programmes	✓	✓	✓
Knowledge sharing and collaboration - facilitates pooling of resources, expertise and data and drives collective efforts to address uncertainties	✓	✓	✓
Patient experience data – must ensure data is regulatory and HTA grade	✓	✓	✓
Early transparent/confidential dialogues and parallel consultations - with regulatory and HTA agencies by seeking early feedback and alignment to address potential uncertainties more effectively	✓	✓	✓

Use of precedents, including learnings from success and failures to inform development programmes	✓	✓	✓

Question 4 - Are there new regulatory or HTA approaches that could manage or mitigate uncertainty (pre or post approval) for these drugs?

New approaches that could be considered pre or post approval to manage or mitigate uncertainty	**Which stakeholder does this apply to?**				
	Company	**Regulator**	**HTA**	**Payer**	**Other**
Co-construction - agreement among stakeholders regarding risk and uncertainty assessment, including multiple meeting points/checkpoints to maintain alignment	✓	✓	✓		Patients
Real world data/evidence - better monitoring of patients and establish a better understanding of relevant outcomes; agreement on uncertainties and data sets to address uncertainty	✓	✓	✓	✓	Patients
Innovative reimbursement models - e.g., outcome based or value-based agreements, pay for performance	✓		✓	✓	
Shared risk among stakeholders - e.g., international funding/resource mechanism for certain rare diseases	TBD				

Recommendations including future work:

All stakeholders	*Knowledge sharing and collaboration to identify uncertainties*: • Leverage existing infrastructure (e.g., Centers of Excellence for rare diseases, patient advocacy groups, RWE) • Enhance education and awareness of efforts among stakeholders • Develop further infrastructures to be able to identify rare disease areas and therapies where uncertainties can be shared among stakeholders • Early stakeholder engagement • Develop opportunities for cross-learnings • Next steps - CIRS workshop to drill this down further
Regulator, company, HTA	*Co-construction approach to uncertainty assessment* - post-approval as the first step (ultimately including pre-approval).
All stakeholders	*Knowledge sharing in a global forum* – discussions on how to develop therapies for rare diseases and how they arrive to the patients.
All stakeholders	*Evaluation of existing tools* used by multiple stakeholders - ensure they are being used in a meaningful way.

Syndicate Discussion – Topic C: Differences between drug efficacy observed in clinical trials and real-world effectiveness gap have commonly been found, especially for patients with co-morbidities or groups poorly represented in the clinical trials. How should uncertainty in the real world be managed or mitigated?

Chair	**Dr Murray Lumpkin,** Deputy Director – Integrated Development / Lead for Global Regulatory Systems Initiatives, Bill and Melinda Gates Foundation, USA
Rapporteur	**Aideen McGee,** Associate Director, HTA Strategy, AbbVie, USA

Discussions around key questions were summarised as follows:

Question 1- What are the particular aspects of uncertainty around these drugs from each stakeholder's perspective?

Aspect of uncertainty	Which stakeholder does this apply to?
Acceptability not to include underserved populations in trials, as the trial is approved to answer the scientific question proposed	Regulator
Speed, cost and predictable requirements (regulatory/HTA) are critical for drug development and commercialisation	Company
Difficulty in reimbursing patients not included in clinical trials - label may be broader than the study population	Payer
Hesitancy and lack of dialogue regarding underserved populations	Multi-stakeholder
Less advocacy/voice for underserved populations	Patients

Question 2 - Are there additional tools that can be used to assess uncertainty for these drugs?

List of additional tools	Which stakeholder does this apply to?
Synthetic data for smaller populations	All
Extrapolate data from trials where populations were included and provide access to this data	Regulator, HTA
Consensus that some groups may not be included e.g., pregnant women	All

Question 3 - Identify approaches that can help reduce uncertainty in the development, review and reimbursement of these drugs?

Approaches that help reduce uncertainty	Which area does this relate to?
Strengthen the ecosystem to include underserved populations e.g., Decentralised trials to allow for inclusion of unreached populations	Development
Incentivise including sub-populations - provide faster approval (Examples from paediatrics, orphan drugs)	Regulator - mitigate risk for companies (timing, cost). The FDA may be the potential innovator in this area
Understand the reason behind the uncertainty –scientific, political, geographical, commercial etc.	Development, reimbursement
Strategic approach to ethically include underserved populations and support their inclusion pre- and post-market approval	All stakeholders
Extend clinical trial diversity programmes	Company

Question 4 - Are there new regulatory or HTA approaches that could manage or mitigate uncertainty (pre or post approval) for these drugs?

New approaches that could be considered pre or post approval to manage or mitigate uncertainty	Which stakeholder does this apply to?
Alignment on how to use data (synthetic controls, RWE, intermediate endpoints, surrogate endpoints)	All
Different approach on using the labelling tool effectively	Regulators
Iterative approach to authorisation, assessment and reimbursement; a continuous build of data	Regulators, HTA

Recommendations including future work:

Regulator/company	• Economic incentives and commitments to include under-served patient populations in trials or in post marketing studies.
Regulator/HTA/company	• Early scientific advice includes questions on patient population, patient reported outcomes and how best to approach uncertainty.
Regulator	• Ethics committee to review the diversity of the population included in trials.

An overarching comment was made to jointly own uncertainty and innovation, so that stakeholders are aligned. The group noted that general educational and advocacy are required for those populations not currently served by clinical trials. They also noted that inclusion of populations should not delay a trial (and ultimately delay access to the majority of the population).

The group felt that this was an ideal time to put forward recommendations on this topic, as companies are focusing more on emerging markets because of the impact of the Inflation Reduction Act (IRA) in the US.

Panel discussion

Three representatives from regulatory, industry and payers were asked to provide their reflections on what should be future considerations for managing uncertainty and next steps.

Regulatory: Dr Supriya Sharma, Chief Medical Advisor, Health Canada

In looking back to the last CIRS workshop on uncertainty many themes were similar, but much progress has been made, including increased use of real-world evidence, more crosstalk between regulators and HTA assessors, advancements in priority pathways and innovations in clinical trial design.

Industry and regulators have continued to work together on developing guidance documents, in addition to those from the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). There is cause for cautious optimism. As regulators, there is a sense of being part of an ecosystem and more often a holistic approach is being adopted.

Having open, frank discussions, as we have just done in the workshop syndicate sessions, is key to understanding different stakeholder perspectives around uncertainty. This gives opportunity to dig down into fundamental questions such as, what do regulators, HTA and payers want to see addressed? What are the levers for mitigating uncertainty? It is important that we admit to each other when things are not going well or slower than expected; it is OK for change to be incremental rather than monumental.

The general environment can be risk averse but there seems to be a willingness to turn our minds to uncertainty and communicate about it. We have better general knowledge of the issues that are facing us but there is work to do in terms of where we can effect change for patients. We need to ensure equality, diversity and inclusion within the work we do. There can be a tendency to make patriarchal/matriarchal decisions on behalf of patients so we need to find ways in which we can be more inclusive in those types of discussions. We are making progress and will be better for it.

Projects or initiatives like Project Orbis have given insights into how Tier 1 regulators like the FDA work. International collaborations have also provided an avenue to ensure that the views of midsize regulators are reflected. In turn, as a collective, they can have an influence on those decisions that will ultimately guide global development and product assessment.

Company: Dr Felipe Dolz, Global Regulatory Affairs Innovation Lead, Sanofi, USA

Learnings from the workshop sessions have provided a good understanding between different stakeholders of what the sources of uncertainty are and potential ways to address and mitigate them, especially within the known uncertainties that are inherent to the existing system.

It was noted by a couple of speakers that uncertainty has increased over the last few years, and this will likely be true in the future too. Uncertainty will continue to grow because our science is more complex. The processes and pathways are also very complex and diverse. There are new technologies that are starting to play a more critical role. Also, the expectations for society from all of us have a huge impact. This gives an incentive for all of us to align and streamline the processes that move the system forward today. More specifically, there are opportunities to initiate conversations with all stakeholders early on regarding endpoint selection, enrolment criteria and patient needs and diversity.

International work-sharing opportunities such as Project Orbis provide a path forward to different thinking and collective knowledge. Also, how can we use patient-friendly technology to help us in any number of ways? For example, with apps, wearables, and decentralised clinical trials. How can we incentivise patients to participate in trials? It is also important to ensure that we collect information from patients in a friendly manner that allows us to understand, not only what we may need for a particular trial, but disease conditions, history, needs of the patient population, where the patients are and what may help them to eventually receive medications at the right time for the right condition.

We should all be very proud of how the system works as it is. COVID-19 was a magnificent demonstration that the system did work. However, there is an opportunity to rethink some of the infrastructure needs and the financials and incentives that would allow the system to continue to be fit for the future so we can continue to provide the medicines that patients need.

Payer: Dr Detlev Parow, Former Head, Department of Medicines, Medical Remedies and Selective Contracts, DAK – Gesundheit, Germany

Firstly, a note about what uncertainty means for payers. 88% of all EMA approved drugs are available in Germany. They are reimbursed from the first day and are available within a median of 47 days. This is uncertainty in quantity and in speed. Germany is often the first in Europe to find an answer to uncertainty i.e., whether the drug is superior to what we already have and what price we think is appropriate. There is a lot of pressure on German payers to find these answers. Drugs and the related uncertainty to drugs is becoming more and more important financially, not only in Germany, but elsewhere as well. We are seeing more and more conditional approvals or early access, so the quantity of uncertainty is increasing.

Multi-stakeholder meetings are very valuable for discussing uncertainty but sometimes payers are underrepresented and can feel like they have little opportunity to interact. They are often presented with what was created by others and so may have to “take it or to leave it”. Payers have the possibility to decide whether to reimburse or not to reimburse, or to find an appropriate price or not to find the appropriate price, but they have very little influence on what is going to happen during the complete chain, from the first idea of the product to the approval, and then the regulatory and HTA aspects.

It is important to note that learning from previous assessments does not make you certain in regard to future assessments. What you know does not give you an answer for what you do not know so far.

Panel members were also asked to suggest potential actions for CIRS in its work programme around uncertainty that would add value based on the discussions at the meeting:

- How do we address the benefit-risk issues of uncertainty for the future? What are the potential timelines and/or milestones that need to happen?
- With new technology and new ways of working, what would be the best way to think about how to optimise/maximise the flow of RWD to different parties?
- Following on from the current meeting, hold another session that is more focused on levers, clinical trial design, and making a fundamental difference in development pathways.
- Best practices around patient engagement and patient involvement (accepting that there will be unique considerations in different jurisdictions).

Session 6: Communication of uncertainty – can this improve trust and confidence in regulatory and HTA decisions?

Building confidence in agency decision making – Do public reports (regulatory and HTA) provide clarity on source and agencies perspective of uncertainty surrounding the decision and how identified uncertainties both real and potential will be resolved?

Regulatory agency viewpoint

Karen Reynolds, Director General, Pharmaceutical Drugs Directorate, Health Canada

Background

The pharmaceutical landscape is evolving globally. Health products are becoming increasingly personalised and precise, and patients are demanding faster access to products based on less or more preliminary data. These trends are especially present for rare diseases, pediatric conditions, and oncology. In response, Health Canada is adapting its regulatory framework for drugs by utilising an increasingly lifecycle-based approach. Various premarket regulatory pathways are available depending on the level of evidence and uncertainty present in the drug submission, and requirements in the post-market space help to support in decision making around uncertainty. Identifying, documenting and communicating the uncertainty around a product throughout its life cycle is increasingly key to the successful management of these products in the health system. However, any such public reports are only as good as the foundational elements on which they rely.

Rigorous documentation and transparency are the bedrock of Health Canada's regulatory framework

Acknowledging, documenting and communicating about uncertainty is a key part of the benefit-risk balance. Over the past number of years, Health Canada has been implementing a quality management system and good review practices. In turn, these are supported by its Regulatory Decision Guide, which articulates the code of conduct for good regulatory decision making. All of this work serves to ensure well-made, well-documented and well-described decisions that can then be communicated to Canadians. Implementation of these elements has been supported through training to ensure that scientific review staff have a common foundational understanding of how decisions are to be made and documented.

Transparency in decision making, starting in the premarket, is a key part of communicating the uncertainty related to approved products and is useful to health system partners, HTA agencies, payers, healthcare professionals and patients. Health Canada has been evolving towards increased transparency for more than 20 years. Most substantially, in 2015, Health Canada released the Drug and Health Product Register, which has subsequently evolved into the Drug and Health Product Portal (DHPP).The portal includes enhanced search capabilities and serves as a central repository for consumers, healthcare professionals and researchers to view the information on drug products available in Canada.

Some of Health Canada's key transparency initiatives include the Summary Basis of Decision (SBD), which describes the scientific and benefit-risk analysis that factored into the decision to approve a novel product, and the Regulatory Decision Summary, which summarises the purpose of the submission and why the decision was issued. These documents are publicly available in the DHPP and provide a means

for Health Canada to communicate on the uncertainties related to the regulatory decisions, including, for example, uncertainty in long-term safety and efficacy, and use in special populations.

In 2019 Health Canada launched an initiative called the Public Release of Clinical Information, which provides public access to the clinical information submitted for regulatory reviews, whether that be a positive or negative decision. This can foster new research questions and support further health system decision-making.

Notice of compliance with conditions pathway

Health Canada's Notice of Compliance with Conditions (NOC/c pathway) is a key pathway for Canada's pre-market regulatory review of products with greater levels of uncertainty. It supports earlier access to promising new drugs for patients suffering from serious life-threatening or severely debilitating diseases or conditions where there is an unmet medical need, or where a product has substantial improvement in its benefit-risk profile over products already on the market. Evidence to support safety must be robust while evidence to support efficacy must be promising but not necessarily substantive.

As part of the conditions attached to the NOC/c, the sponsor must undertake confirmatory trials to verify the benefit and must conduct enhanced post-market surveillance activities. Transparency on this conditional approval is key to health technology assessors, payers, patients, and clinicians. This includes issuing a 'Qualifying Notice' that is published on the Health Canada website upon authorisation, which outlines the additional evidence to be provided in the confirmatory trial or trials, as well as the post-market surveillance responsibilities for the sponsor, including associated advertising, labelling, and distribution requirements. The NOC/c is also reflected in product labelling, such as the product monograph and patient information, which includes a text box that indicates that the market authorisation is conditional and pending results of confirmatory trials and that those conditions should be communicated to the patient.

Evolution in the post-market space helps address uncertainties in the pre-market space

Uncertainty in the pre-market space necessitates more collaboration and fluidity of engagement between pre- and post-market spaces. As a result, Health Canada has created a more robust post-market safety monitoring framework to address questions of known and potential risk and dissemination of information to the public. A significant part of this work includes Post-Authorization Activity Tables, which are published along with SBDs in the DHPP and include post-market submissions filed to help meet conditions under the NOC/c guidance. Additional changes include publication of ongoing safety reviews and summaries of review findings, introduction of Risk Management Plans and increased international collaboration facilitating earlier signal detection and more robust data gathering.

Looking ahead

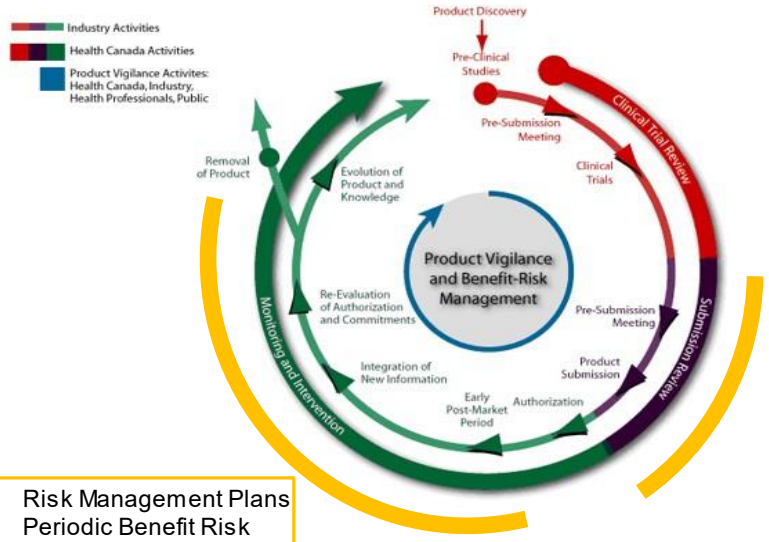
Much progress has been made over the past couple of decades in terms of how uncertainty is managed and communicated. Health Canada is looking forward with an ambitious regulatory innovation agenda. One of the key elements of this agenda is the 'agile licensing for drugs initiative'. This project includes further development of risk management plans, establishing terms and conditions for product approvals, accepting rolling reviews for some drug submissions and revisiting accelerated reviews. All of these projects have links to uncertainty, decision making and transparency.

Summary

The approach taken to the management of uncertainty in Canada continues to be dynamic, with learnings and adaption based on experience. Transparency will continue to be an essential tool to manage not only

the regulatory process but to enable Canadians, most importantly, to make informed decisions about their health. Challenges remain but initiatives are evolving in the right direction.

Health Canada's lifecycle approach to the regulation of drugs considers uncertainty



- Risk Management Plans
- Periodic Benefit Risk Evaluation Reports
- Periodic Safety Update Evaluation Reports

- Special Access Program
- Urgent Public Health Need
- Notice of Compliance with Conditions
- Priority Review
- Traditional review

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Building confidence in agency decision making – Do public reports (regulatory and HTA) provide clarity on source and agencies perspective of uncertainty surrounding the decision and how identified uncertainties both real and potential will be resolved?

HTA agency viewpoint

Pauline McGuire, Principal Pharmacist, Scottish Medicines Consortium

Background

The Scottish Medicines Consortium (SMC) provides advice to NHS Scotland about the value of newly licensed medicines. Scotland has 14 health boards that make their own decisions about what goes to the formularies, but the SMC is the national organisation that issues advice. This advice is advisory but is generally followed. The SMC communicates their decisions (and uncertainties) to the health boards through public output that also goes on their website.

Current challenges for HTA include the complexity of new technologies, medicines licensed with limited evidence, financial context, complexity of the HTA process, a desire for different funding models and increased assessment activity.

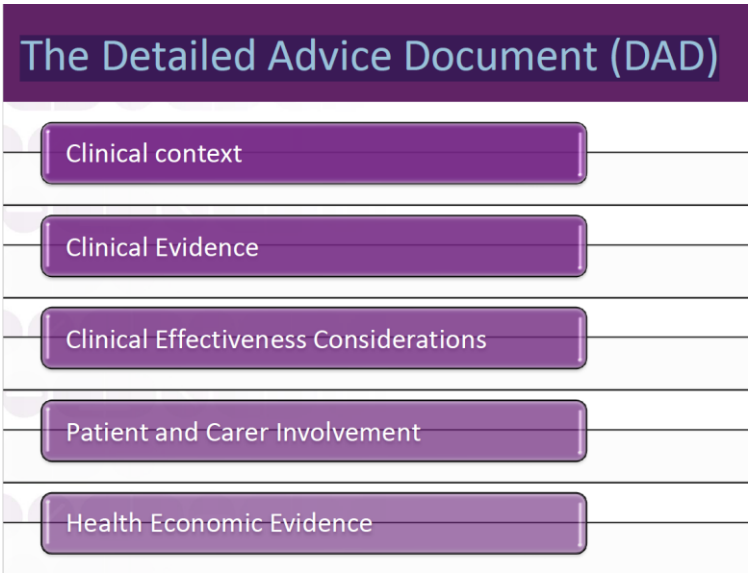
While the SMC does not take affordability into account, it does consider the opportunity cost of the decisions it makes. When sitting with uncertainty this becomes even more important. As the medicines are getting more complex, the previous ‘one size fits all’ process is no longer as nimble. The SMC’s process is getting more complex too. Therefore, less resource is put into the more straightforward medicines, freeing up time to concentrate on the medicines where there is more uncertainty.

The SMC has a long tradition of including clinical experts and patient groups to add context to uncertain decisions. For all medicines the SMC contacts clinical experts for their testimony. It also has patient group submissions for most medicines. Following government review, the SMC introduced the Patient and Clinician Engagement (PACE) process which has given a stronger voice for medicines used at the end of life (usually cancer medicines) and for rare conditions.

The SMC has patient groups round the table when the committee is making their decisions, which allows the patient voice to be heard by the committee members to help understanding of uncertainty, but equally, it helps patient groups to understand what the areas of uncertainty were and what was important to committee.

The Detailed Advice Document (DAD)

Following feedback from its clinical stakeholders, the SMC improved the Detailed Advice Document (DAD), which is a summary document broken down into five manageable sections (see below). The DAD starts with the clinical information (clinical expert views of how the medicines have been used, the pathway information, clinical evidence, critical appraisal etc) as this were identified as the most important section to busy clinicians. This is followed by clinical evidence, then clinical effectiveness including key strengths and uncertainties. The DAD then covers patient and carer involvement and finally economic evidence. To further improve the DAD, the SMC is planning to add an executive summary and develop a more interactive format.



Interim acceptance

In 2018, the SMC introduced 'acceptance on an interim basis, subject to ongoing evaluation and reassessment', as it was felt that the binary 'accepted for use'/ 'not recommended for use' outcomes were not enough. Interim acceptance is for medicines where there is much uncertainty but there is an unmet need.

The SMC first used the interim acceptance system in its assessment of medicines that have a conditional marketing authorisation. It has since expanded out to medicines that are part of the Medicines and Healthcare products Regulatory Agency's (MHRA's) Early Access to Medicine Scheme (EAMS) and the Innovative Licensing and Access Pathway (ILAP). 12 medicines have been given interim acceptance over the last few years (all single-arm, uncontrolled studies with highly promising overall response rates). It is important to make it clear in the output that a medicine is accepted on an interim basis because it is promising in an area of unmet need.

Ultra-orphan pathway

Another pathway of uncertainty is the ultra-orphan pathway introduced in 2018. This pathway is specifically for medicines that treat extremely rare conditions requiring specialist management. Within the SMC, these medicines are validated, and the boards informed that they are suitable. The SMC conducts an initial assessment of the evidence and points out what the key strengths and uncertainties are. The company commits to a data collection plan to ideally address these uncertainties. The medicine can be used for three years, after which the SMC will re-review. The SMC expects to get rich qualitative data from the actual experience of using the medicines and what has been the impact, and then to make a final decision at that point.

Summary

The SMC's public reports are vital and clearly describe uncertainty in decision making. As policy direction to increase access to new medicines is adding uncertainty, thoughts on how to address this are required. Real-world evidence provides exciting opportunities to add context to these uncertain decisions.

Communicating uncertainty - What are good practices in communicating uncertainty and risk to key stakeholders at the time of product approval/recommendation?

Patient perspective

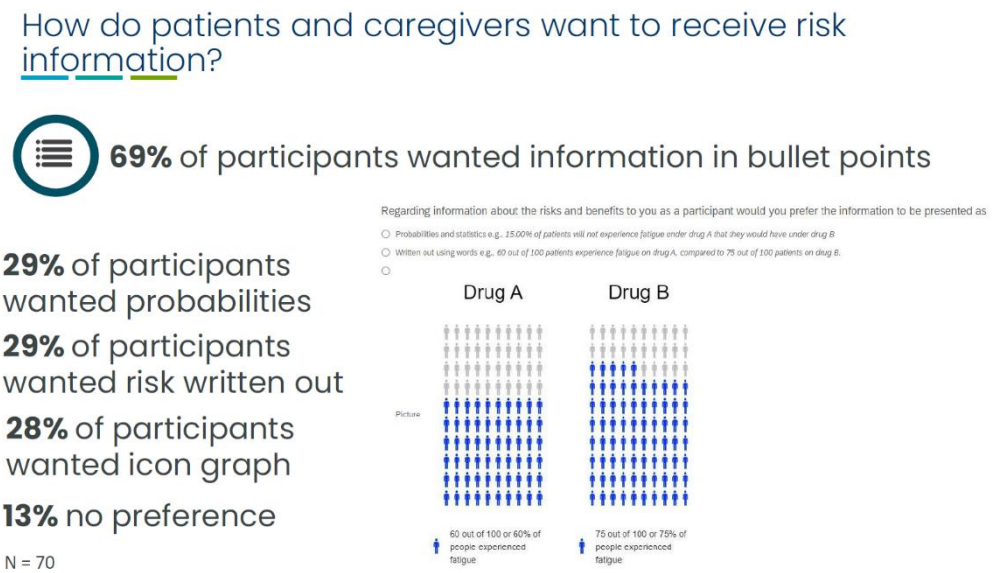
Dr Bellinda King-Kallimanis, Director of Patient-Focused Research, LUNGevity Foundation, USA

Background

LUNGevity Foundation is a lung cancer non-profit in the US. Its mandate is to connect the patient voice with stakeholders to help in decision making. Two major inflection points for patients regarding uncertainty are: clinical trial participation and standard treatment planning at diagnosis, progression or recurrence.

Informed consent - are we communicating uncertainty accurately?

In theory, the purpose of the informed consent form is to outline risks and benefits. However, in reality the forms are long and filled with jargon and information that is irrelevant to the patient. LUNGevity is running a multi-phase project that involves both patients and their caregivers, trialists, regulators and clinical trial sponsors, as well as institutional review board chairs, ethicists and legal representatives, because this is an ecosystem problem. The project is currently in phase four, in which there is a short survey looking at themes that are important to patients and caregivers. Interviews are also being conducted with a variety of stakeholders because there has been much work in this space for several decades, yet no change has really happened. At the time of this workshop, 70 people had completed the survey and responded to the question of how they would like to receive risk information as follows:



This survey indicates that when information is communicated, there is not a one-size-fits-all approach to presentation. Technology solutions for improving informed consent could be innovative and allow tailoring to patient preferences.

Standard treatment planning

Regarding uncertainty when planning treatments, the focus has been about uncertainty upstream. Regulators are assessing safety and efficacy of a new medicine while payers are assessing that value, and both are making population-level decisions. However, downstream, patients and their doctors are sitting down to create a treatment plan and they are weighing the benefits and costs of different treatment options, or sometimes no treatment if that fits the context of the person's life and prognosis.

A clinical trial will include strict eligibility and inclusion criteria but downstream, the person is less worried about that information. They are worried about whether their condition can be treated and whether they will experience or avoid unacceptable risk based on their life circumstances and treatment goals. Risk assessment can mean many things; and the information is often ambiguous and means different things at different stages and to different stakeholders.

In clinical decision making, downstream, licensed medicines are considered safe and effective because the evidence around each of the medicines has been judged as supportive of this. However, some medicines are riskier than others and some are more efficacious than others and this is not easily conveyed to patients. Given the excess of information around some diseases and therapies, simple information that is relevant and presented in plain language is also very important for clinicians.

Uncertainty at the point of care

When people are diagnosed with a life-threatening illness their ability to think through uncertainty around treatments may be clouded. People are considering how their health will be after treatment, i.e., side effects of the treatment that they might experience both short-term and long-term. This is not something that regulators and payers are necessarily thinking about. Also, what are the direct and indirect monetary expenses? In the US this is particularly critical to peoples' decisions. Also, how much potential loss of income might they incur? All this is to say, we must pay attention to what we are communicating and who we are communicating to. This may require more targeting than just patient and healthcare provider.

Summary

Individual factors influence how people hear uncertainty. These may include expertise, attitudes/optimism, numeracy skills/education and personal goals and preferences. We need to use these models of uncertainty and realise that patient centricity is much more than engaging with certain patients/patient groups at certain points in drug development. This may require multiple tools to communicate the benefits and risks of new treatments to patients when they are making their treatment choices.

Communicating uncertainty - What are good practices in communicating uncertainty and risk to key stakeholders at the time of product approval/recommendation?

Communicating regulatory outcomes

Dr Finnuala Lonsdale, Director Human Product Authorisation and Registration, Health Products Regulatory Authority, Ireland

This presentation covered four main themes, which are summarised below.

1) Identify the desired outcome(s)

Better health outcomes are a key goal for regulators and requires prescribers, patients and payers to feel empowered. For patients this is meaningless unless it can be bridged to the individual prescriber-patient decision (whilst also remembering that patients have the right to make decisions that we would not necessarily make for them).

Communicating risk and uncertainty are not the same thing but some of the science around communication of risk applies to the science about communicating uncertainty. The key question is 'how do we make better decisions?' Both the patient's outcome and the patient's ability to make the right decision for themselves is what this should be judged on.

2) Learn from the experts

Public health requires decision making, and information and communication of that information is an important component. The right people need to have the right information in the right way to make the decision they need to make (and everybody makes decisions slightly differently). Insights about how people make decisions can be gleaned from the fields of behavioral psychology and behavioral economics. Communication needs to be objective. If there are different ways to present information that will bias peoples' decision making, they need to be given all the facts. This applies especially to statistical communication or communication of numbers.

People do not make decisions that are always in their best interests or that are rational. We need to understand the biases and impacts that affect people in their decision making. Behavioral psychology has clearly shown that people want certainty and will avoid ambiguity. Therefore, if we make uncertainty very transparent, the tendency of individuals will be to delay making a decision until the information is available. While there needs to be an awareness that that is how people work psychologically, transparency is still important. People are also more sensitive to loss, so if a drug is taken off the market, that will have a different psychological effect to never having had the drug in the first place. Individual perspective in decision making is key. There can be cultural differences (from countries to microenvironments) about what risk and uncertainty is acceptable and what risk-taking is.

3) Communication is a team effort

Communication is a marathon not a sprint. It requires a team effort between health system partners, who need to have clear roles and responsibilities. Regulators and HTA agencies should be encouraged to go into education settings to talk about drug development, regulation and statistics/risk/uncertainty, so that over time there is a gradual enhancement of overall numeracy and understanding.

4) Changing regulatory competencies

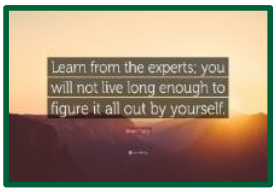
We need to set an expectation that for regulators now, stakeholder engagement, partnerships and communication skills are a fundamental part of the job. Agility is key. This means thinking about recruitment and retainment to develop regulators with these competencies.

Key themes

HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

1. Identify the desired **outcomes**

2. Learn from the **experts**



3. Communication is a **team** effort

4. Changing regulatory **competencies**

3

Communicating uncertainty - What are good practices in communicating uncertainty and risk to key stakeholders at the time of product approval/recommendation?

Communicating HTA outcomes

Dr Gowri Raman, Associate Director, Patient-Centered Outcomes Research Institute, USA

Background

Patient-Centered Outcomes Research Institute (PCORI) is a nonprofit independent research funding organisation established in 2010 by the US Congress. PCORI is governed by a 23-member board of governors that represents the entire healthcare community (including payers). PCORI was established primarily to conduct comparative clinical effectiveness research by engaging stakeholders, with a primary focus on patients and their caregivers, throughout the entire spectrum of the research. Through its funding, PCORI aims to answer real-world questions from patients and to help patients and other stakeholders make informed healthcare decisions.

One of PCORI's five national priorities is to increase evidence for existing interventions and emerging interventions in health. PCORI funds horizon scanning reports, emerging technology reports, evidence maps and rapid reviews, systematic reviews, focused observation research, phased trials and pragmatic and research studies. All work related to development of reports is contracted except for the development of key questions that is developed internally through engagement with a broad range of stakeholders.

Dissemination and engagement activities

PCORI has dissemination/implementation and engagement activities throughout its process. Patients and other stakeholders are engaged from the initiation of projects in terms of developing key questions. Products are mapped throughout the life cycle of healthcare technology. PCORI does not fund cost-effectiveness studies. In terms of emerging interventions, PCORI undertakes healthcare horizon scanning in six disease topics and monitors trends across many clinical conditions. It also produces Emerging Technology and Therapeutics Reports accompanied by issue brief that is a lay 2–3-page summary of the large reports. Topics to-date have been nominated by payers or by the board of governors or by PCORI's senior leadership team.

PCORI's horizon scanning has three products that continuously monitor and provide updates on emerging interventions. The first product in the Health Care Horizon Scanning System is an electronic, freely available, publicly available database that is updated daily. A second product is an Emerging Healthcare Innovation Brief, which is published twice a month. A third product is the High Potential Disruption Report. This is published twice a year and reports on a subset of interventions from the horizon scanning database, which are selected by stakeholders (see below).

Stakeholder Input and Engagement in Horizon Scanning

Multi-stakeholder engagement

Between June 28 and July 18, 2022, **seven stakeholders**, reflecting clinical, health systems, health systems administration, patient or patient representative and research perspectives provided comments and ratings on tisagenlecleucel to treat relapsed or refractory follicular lymphoma (FL).

- ***A clinically effective option as a one-time*** treatment for relapsed or refractory FL.
- ***Frequent adverse events***, including cytokine release syndrome, are associated with chimeric antigen receptor T-cell therapy.
- Multiple stakeholders noted ***these adverse events are generally considered manageable*** and ***are acceptable risks*** if tisagenlecleucel proves to be a curative therapy.
- Tisagenlecleucel's anticipated ***high cost might lead to health disparities*** for underinsured patients or for patients with insurance who cannot afford their copayments.

How do we communicate on uncertainties in HTA outcomes?

The above are not necessarily HTA products but are supporting products for HTA and can help to identify gaps that may create funding opportunities to conduct primary research. There are additional opportunities to communicate uncertainty of outcomes through visualisations. Infographics (that may be interactive) could also be utilised within issue briefs, rather than just describing uncertainties.

Traditional HTA and communication of their outcomes rely on an evidence base at a fixed point in time. Potential solutions to this could be to:

- Acknowledge changing value priorities over time among healthcare stakeholders and the wider public.
- Continue ongoing engagement with multiple stakeholders to create a living HTA, updated in regular intervals as evidence evolves, or sunset report(s) when a technology is no longer relevant.

Summary

PCORI utilises a multi-stakeholder engagement process to elicit uncertainty in health outcomes for emerging interventions, in addition to available data. PCORI descriptively communicates uncertainty in outcomes as elicited by stakeholders. Future opportunities could focus on communicating uncertainty in outcomes using visualisation tools.

Appendix: Workshop attendees

Affiliations are stated as they were at the time of the meeting.

Dr Sara Abdollahi	ORISE Fellow, Center for Drug Evaluation and Research	**Food and Drug Administration, USA**
Dr Indranil Bagchi	VP, Global Pricing and Market Access Head	**GlaxoSmithKline, USA**
Nina Barchha	Senior Director, Group Lead Regulatory Affairs - Oncology	**Astellas, USA**
Amy Bertha	Executive Director, Regulatory Policy	**Bayer, USA**
Fabio Bisordi	Global Head International Regulatory Policy	**F.Hoffmann-La Roche, Switzerland**
Dr Claus Bolte	Deputy Chief Executive and Head of Marketing Authorisation	**Swissmedic**
Dr Magda Bujar	Senior Manager, Regulatory Programme and Strategic Development	**Centre for Innovation in Regulatory Science**
Dr Jon Campbell	Senior Vice President for Health Economics	**Institute for Clinical and Economic Review, USA**
Mélanie Caron	Assistant Director of Evaluation of Medication and Technology,	**Institut national d'excellence en santé et en services sociaux (INESSS), Canada**
Chris Celeste	Director, Regulatory Policy and Intelligence	**LEO Pharma, USA**
Dr Agnes Chan	Director, Therapeutic Products Branch	**Health Sciences Authority, Singapore**
Dr Nimi Chhina	Executive Director, Head of Global R&D and Regulatory Policy	**BioMarin, USA**
Dr Blair Coleman	Social Scientist, Decision Support and Analysis Staff, Center for Drug Evaluation and Research	**Food and Drug Administration, USA**
Dr Nick Crabb	Programme Director, Scientific Affairs	**National Institute for Health and Care Excellence (NICE), UK**
Dr Felipe Dolz	Global Regulatory Affairs Innovation Lead	**Sanofi, USA**
Dr Sara Eggers	Director, Decision Support and Analysis Staff	**Food and Drug Administration, USA**
Jeff Francer	Head of Regulatory Policy	**Eli Lilly and Company, USA**
Danielle Friend	Director, Regulatory Policy and Intelligence	**Janssen, USA**
Isabella do Carmo Gomes	Manager of Safety and Efficacy Assessment	**ANVISA, Brazil**
Melinda Hanisch	Director, Data Strategy and Partnerships	**Merck, USA**
Gill Hepton	Administrator	**Centre for Innovation in Regulatory Science**
Keiko Higuchi	Global/US Health Economics Value Assessment Therapeutic Lead, Neurology and Immunology	**Sanofi, USA**
Sana Hussain	Director, US Regulatory Policy	**GlaxoSmithKline, USA**
Dr David Jefferys	Senior Vice President, Global Regulatory, Government Relations, Public Affairs and European Product Safety	**Eisai, UK**
Dr Bellinda King-Kallimanis	Director of Patient-Focused Research	**LUNGevity Foundation, USA**
Sudha Kutty	Executive Vice President – Evidence, Products and Services	**CADTH – Canadian Agency for Drugs and Technologies in Health, Canada**

Dr Leila Lackey	Program Lead, Decision Support Service, Center for Drug Evaluation and Research	**Food and Drug Administration, USA**
Dr Lawrence Liberti	Senior Advisor	**Centre for Innovation in Regulatory Science**
Dr Bengt Liljas	Group Director, Health Economics & Payer Evidence	**AstraZeneca, USA**
Prof John Lim	Executive Director	**Centre of Regulatory Excellence (CoRE), Duke-NUS Medical School and Senior Advisor, Ministry of Health, Singapore**
Heather Logan	Vice President, Strategic Initiatives and Relationships	**CADTH – Canadian Agency for Drugs and Technologies in Health, Canada**
Dr Finnuala Lonsdale	Director Human Product Authorisation and Registration	**Health Products Regulatory Authority, Ireland**
Dr Murray Lumpkin	Deputy Director – Integrated Development / Lead for Global Regulatory Systems Initiatives	**Bill and Melinda Gates Foundation, USA**
Judith Macdonald	Head of International Regulatory Policy	**Pfizer, UK**
Dr Peter Marks	Director, Center for Biologics Evaluation and Research (CBER)	**Food and Drug Administration, USA**
Jewell Martin	Associate Director of US R&D and Regulatory Policy	**BioMarin, USA**
Dr Jacques Mascaro	Senior Vice President, Oncology Regulatory Science, Strategy and Excellence	**AstraZeneca, USA**
Dr Neil McAuslane	Director	**Centre for Innovation in Regulatory Science**
Aideen McGee	Associate Director, HTA Strategy	**AbbVie, USA**
Pauline McGuire	Principal Pharmacist, Healthcare Improvement Scotland	**Scottish Medicines Consortium**
Alexis Reisin Miller	Executive Director, US Lead, Global Regulatory Policy (US Lead)	**Merck, USA**
Anderson Vezali Montai	Manager of Biological Products Office	**ANVISA, Brazil**
Prof Mamoru Narukawa	Professor, Pharmaceutical Medicine	**Kitasato University Graduate School of Pharmaceutical Sciences, Japan**
Adriane Alves de Oliveira	Deputy Coordinator of Clinical Trials Office	**ANVISA, Brazil**
Dr Detlev Parow	Former Head, Department of Medicines, Medical Remedies and Selective Contracts	**DAK – Gesundheit, Germany**
Dr Charlie Preston	Senior Program Officer	**Bill and Melinda Gates Foundation, USA**
Dr Gowri Raman	Associate Director, New Technology, Engagement	**Patient-Centered Outcomes Research Institute, USA**
Karen Reynolds	Director General, Pharmaceutical Drugs Directorate	**Health Canada**
Sarah Riordan	Operations Research Analyst, CDER	**Food and Drug Administration, USA**
Dr Andrew Robertson	Vice President, Head of Global Regulatory Policy and Innovation	**Takeda, USA**
Danielle Rollmann	Vice President, Market Access Policy	**Janssen, USA**
Dr Michael Rozycki	Senior Vice President, Regulatory Affairs	**Pacira Biosciences, USA**
Christophe Sauboin	HEOR Excellence Lead	**Boehringer Ingelheim, Germany**
Dr Supriya Sharma	Chief Medical Advisor	**Health Canada**

Adj Prof John Skerritt	Adjunct Professor, and Chair, Scientific Advisory Council, CIRS	**University of Sydney, Australia**
Dr Belen Sola	Research Analyst	**Centre for Innovation in Regulatory Science**
Dr Álmath Spooner	Director, Regulatory Policy and Intelligence	**AbbVie, Ireland**
Jerry Stewart	Vice President, Head of Global Regulatory Policy and Intelligence	**GlaxoSmithKline, USA**
Prof Steffen Thirstrup	Chief Medical Officer	**European Medicines Agency**
Irwin Tran	Global Access Evidence Enabler	**Roche, USA**
Prof Stuart Walker	Founder	**Centre for Innovation in Regulatory Science**
Martine Zimmerman	Senior Vice President, Head of Regulatory and Quality R&D	**Ipsen, France**