What new research can enable a joint approach by regulatory and HTA agencies to manage uncertainties for products using early access pathways?

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REPORT

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The Utrecht WHO Collaborating Centre for Pharmaceutical Policy and Regulation is located at the Division of Pharmacoepidemiology and Clinical Pharmacology of Utrecht University. Our mission is to conduct academic research at the interface of pharmacoepidemiology and policy analysis. We are also a platform for dialogue and learning and offer a professional PhD programme and advanced training opportunities to a global network of healthcare professionals, policy makers and regulatory experts.

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BACKGROUND

This one-day Forum brought together regulatory, health technology assessment, industry and academic perspectives with the aim of identifying novel research that is needed to inform new initiatives being proposed or piloted by key stakeholders to ensure that medicines approved through facilitated regulatory pathways will be aligned with the appropriate flexible access schemes. The premise of this session is that aligned interactions will lead to aligned criteria or an understanding of what the uncertainties are for each stakeholder.

Healthcare professionals and patients may be confused by divergent regulatory and access decisions; therefore, identifying the most efficient ways for regulators and health technology assessors to engage and address their expectations should encourage the creation of efficient development programmes that meet as many aligned needs as possible without burdening the systems or delaying review or access to important new medicines.

It was envisioned that the outcome of this meeting would be to identify novel areas of research that will improve how the uncertainties around the safety, efficacy (effectiveness) and value of therapies that use early access development programmes can be mitigated. The goal is to identify the types of new research that can provide quantitative and qualitative actionable information to help inform efficient processes that can ensure medicines for high priority health care needs can benefit from aligned regulatory and HTA interactions and evidence generation to address stakeholder expectations.

AGENDA

Keynote: How research will enable the management of uncertainty	**Prof Hubert Leufkens,** *Professor of Pharmaceutical Policy and Regulatory Science Utrecht University*
Why it is smart to share your uncertainties	**Prof Thomas Kühler**, *Head, Global Regulatory Science and Policy, Sanofi, Denmark*
HTA: Making recommendations in the face of uncertainty: The challenges of early-access medicines	**Dr Wim Goettsch**, *Special Advisor, Zorginstituut Nederland, Associate Professor, Utrecht University*
A holistic approach: Should regulatory criteria be designed to address HTA needs?	**Dr Giovanni Tafuri**, *Senior Scientific Officer EUnetHTA*
Research presentations: "Quick-shot" presentations with topics selected to stimulate the Roundtable discussions	
Blending randomised clinical trial and real-world evidence – A case study of the Innovation in Medicine Initiative (IMI - GetReal). **What new research can enable a joint approach by regulatory and HTA agencies to manage uncertainties for products using early access pathways?** **Dealing with uncertainties: Next steps** **How do we determine what makes joint HTA/regulator scientific advice efficient and effective?**	**Dr Michael Happich**, *HTA Director, Eli Lilly, Germany* **Dr Peter Stolk,** *Programme Manager Lygature* **Prof Dr Aukje Mantel-Teeuwisse,** *Director, School of Pharmacy, Utrecht University, the Netherlands* **Jeanette Kusel**, *Director for Scientific Advice, NICE*
Roundtable discussions	
Roundtable reports	
Close	

PRESENTATIONS

Keynote: How research will enable the management of uncertainty – If it were easy, we wouldn't be here

Prof Hubert Leufkens, *Professor of Pharmaceutical Policy and Regulatory Science Utrecht University*

Recent years have seen tremendous increases in innovation and expedited access to complex medicines, contrasted with ongoing challenges in safety, pricing and equitable global availability. But while research into the development of and payment for new innovative targeted medicines consumes much of the public healthcare discourse, access to simple or generic medicines remains a challenge to much of the world. Similarly, new methods for facilitating and expediting medicines' regulation are the subjects of many workshops and research articles, but a significant portion of the world still struggles to develop the resources and expertise to regulate the safety of needed medicines for its population, and regulatory strengthening remains an important global goal.

There are several topics, however, that highlight the interactions and collaboration aimed at managing uncertainty experienced by the research community, the regulators and those concerned with developing regulatory and health technology assessment policy.

The fate of medicines through their lifecycle

A 2012 report detailed the factors associated with 24 of 42 medicines in a 2009-2010 cohort that were approved by the European Medicines Agency (EMA) despite clinical uncertainties in their confirmatory phase as well as those of 5 of 26 products in this same cohort that were not approved despite a convincingly positive confirmatory phase.[1] Nearly ten years after their regulatory review, Bloem and colleagues are now investigating to determine if any of the 24 approved medicines represented a Type 1 (approved in error) mistake or if any of the 5 medicines that were not approved represented a Type 2 (rejected in error) mistake. Although this research is still in progress, an overall positive outlook for the decision making surrounding these medications has been observed despite, or perhaps because of the fact that their review collectively represented a disproportionately high number of discussions and careful examination by the Committee for Medicinal Products for Human Use (CHMP) and Pharmacovigilance Risk Assessment Committee (PRAC).

New sources for evidence building

Escalating costs for traditional clinical trials have raised concerns as to their sustainability. A recent study of the costs of clinical trials for products approved by the US FDA in 2015-2016 showed that it cost almost three times as much to conduct trials for hard clinical endpoints compared with those conducted for

surrogate endpoints. Furthermore, increasing the number of patients studied also greatly added to the cost: trials of 1 to 100 patients cost a mean of approximately $6 million USD, whilst trials of more than 1000 patients cost a mean of approximately $77 million USD.[2]

New methods such as the use of real-world evidence have shown utility in the accrual of safety data for new medicines compared with the substantial financial cost of traditional randomised clinical trials but more work is required in their use in establishing efficacy/relative effectiveness. Although a recent report showed that real-world data has been used in both relative and comparative effectiveness assessments by some health technology assessment agencies in Europe,[3] other authors have pointed to the challenges represented by real-world evidence such as their heterogeneity, lack of accepted analysis methodology and issues in patient confidentiality.[4] In addition, information from active comparator trials was available for less than half of 122 new medicines approved from 1999 to 2005, creating an evidence gap with serious consequences for comparative healthcare decision making around those new medicines.[5]

Regulatory/HTA interface encounters

Although different perspectives, needs, stakeholders and jurisdictions continue to drive regulators and health technology assessors, the most important common driver is the increased demand for faster patient access to new medicines. Research has shown that both this demand and information sharing to reduce duplication of work were the most important factors for regulatory and HTA collaboration to 86% and 71% of surveyed regulators respectively. Meanwhile, public demand for faster access to new medicines and the support of relevant evidence generation during drug development were the two most important factors for collaboration for the majority of health technology assessor surveyed (both by 63%).[6]

Systems therapeutics

Finally, many believe the paradigm for the research, development and use of medicines is changing to accommodate new therapies that are directed at affecting disease processes rather than single transduction pathways. This change will positively impact the healthcare environment through the development of new early disease interception strategies and will dictate the regulatory and health technology assessment policy discussions of the future.[7] The strong will toward stakeholder collaboration evidenced by participation in meetings such as these will move us all forward in this important direction.

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Why it is smart to share your uncertainties

Prof Thomas Kühler

Head Global Regulatory Science and Policy, Sanofi, Denmark

Challenges in managing uncertainty

Numerous conditions in the global pharmaceutical environment contribute to the current climate of uncertainty. Regulatory and health technology assessment alignment is weak, requirements differ among HTA bodies, payers do not follow the HTA recommendations of their own jurisdictions, reimbursement is not consistent among countries and prevailing clinical practice rules over evidence-based medicines. Given these hurdles, the return on investment for research and development has become increasingly more unpredictable while the research and development process itself is rendered less effective. Ultimately and most importantly, patient access to new medicines is often delayed or denied as a result of these uncertainties.

Scientific advice and managing uncertainty

Even when pharmaceutical companies endeavour to mitigate uncertainties around a new medicine by seeking scientific advice from either a single agency or from regulatory and health technology assessment agencies in parallel, complications are inherent in this advice, including the fact that the timings around feedback loops for the advice are extremely long. In addition, scientific advice is not always followed and even when it is, there is no guaranteed correlation between the advice given and the final outcome.

Nonetheless, scientific advice and parallel consultations, which can be a significant factor in the internal go/no go decision-making process, represent an opportunity to align internal strategies on an evidence generation plan, test the proposed evidence generation plans against expectations of health authorities, share knowledge on disease and product specificities and conduct a transparent and constructive discussion with stakeholders on the target value proposition.

Sanofi Integrated Evidence Generation Plan

Sanofi is currently moving from product plans with indistinct engagement procedures to its new Integrated Evidence Generation Plan (IEGP), a structured process for value-based evidence generation, broadly taking stakeholders' insights into consideration. IEGP represents a transversal effort in which functional input and stakeholder insights are shared in team workshops. The plan includes an IT solution to support teams in gathering existing documents in a single place to facilitate access to the right and most current

knowledge. The IEGP includes all stages of product planning from development through to patient access (Figure 1).

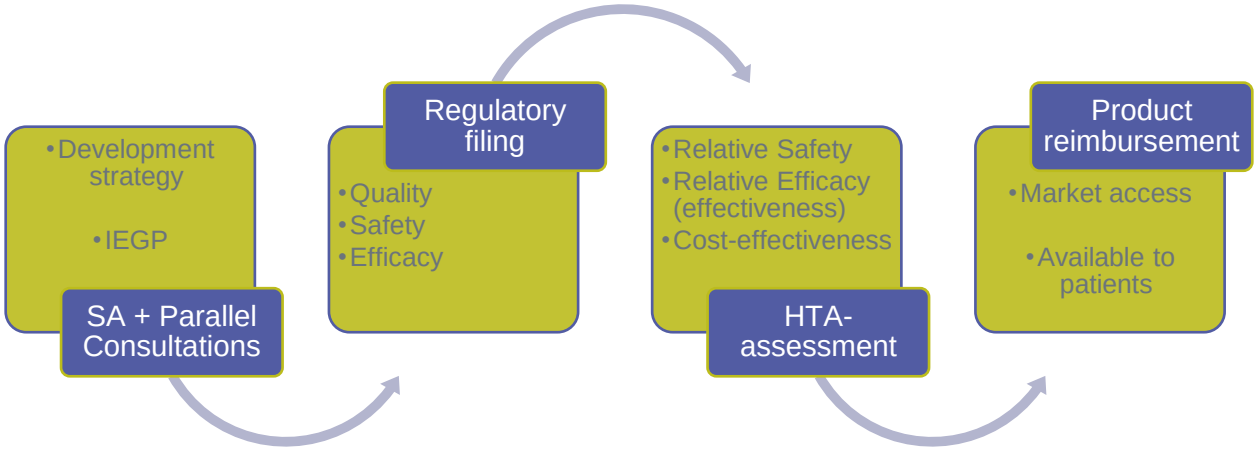

Figure 1. The Sanofi Integrated Evidence Generation Plan includes structured planning for all stages of product development, including reimbursement and patient access.

Conclusions

To manage uncertainty surrounding new products, it is critical to understand the evidence needs of all stakeholders, including patients, healthcare professionals, regulators, health technology assessment bodies and payers. It is equally important to understand the existing evidence gaps and to develop robust strategies to address these gaps. Medicines' developers must be transparent regarding the strengths and limitations of their product, should strive to enhance internal alignment, build processes that support communication and decision making within their company, striving to work across company functions early on in the development process.

HTA: Making recommendations in the face of uncertainty: the challenges of early access medicines

Dr Wim Goettsch, *Special Advisor, Zorginstituut Nederland, Associate Professor, Utrecht University*, *the Netherlands*

The context for reimbursement in the Netherlands

Recently, Zorginstituut (ZIN) in the Netherlands has not recommended reimbursement for several new conditionally approved therapies because of uncertainties as to their effectiveness, including Fampyra (fampridine) for multiple sclerosis, Translarna (ataluren) for Duchenne's Muscular Dystrophy and an enzyme therapy for morquio A syndrome. To fully appreciate the rationale for these decisions, it is necessary to examine the context in which they were made.

In the past several years, there has been an annual cost increase of 5% to 10% for medicines in the Netherlands, compared with an annual increase of 1.6% in the government budget to pay for those medicines, resulting in yearly funding shortfall of 50 to 100 million Euros. At the same time, the cost-effectiveness of some new medicines has declined; for example, to obtain 3.48 quality-adjusted life years (QALYs) with ivacaftor, which is used in cystic fibrosis, costs 1.5 million Euros, an amount that would generate 36.59 QALYs with the use of a common cardiology therapy.

Comparative trial data and reimbursement

In Europe, after a marketing authorisation decision by the European Commission, the national pricing and reimbursement processes of EU member states include a relative effectiveness assessment (REA) and there may be additional types of evaluations in other jurisdictions, such as the cost-effectiveness assessment practiced in England and Scotland. REA can be defined as the extent to which an intervention does more good than harm compared with one or more intervention alternatives for achieving the desired results when provided under the usual circumstances of healthcare practice. This may also be referred to as *benefit assessment* or *therapeutic value assessment* or *clinical assessment.* However, having the comparative trial data to perform REA at the time of marketing authorisation does not necessarily result in an unrestricted recommendation from health technology assessment bodies. Vreeman and colleagues studied 27 medicines that received conditional marketing authorisation which were reviewed by 5 health technology assessment bodies and found that irrespective of whether there were any controlled data available, those medicines rarely received unrestricted positive recommendations. The authors suggested that efficient early collaboration and additional data collection after marketing authorisation might be helpful to increase the rate of HTA recommendations.[1] This

suggests the wider use of an approach that includes more of a focus on the life cycle of medicines (Figure 2).

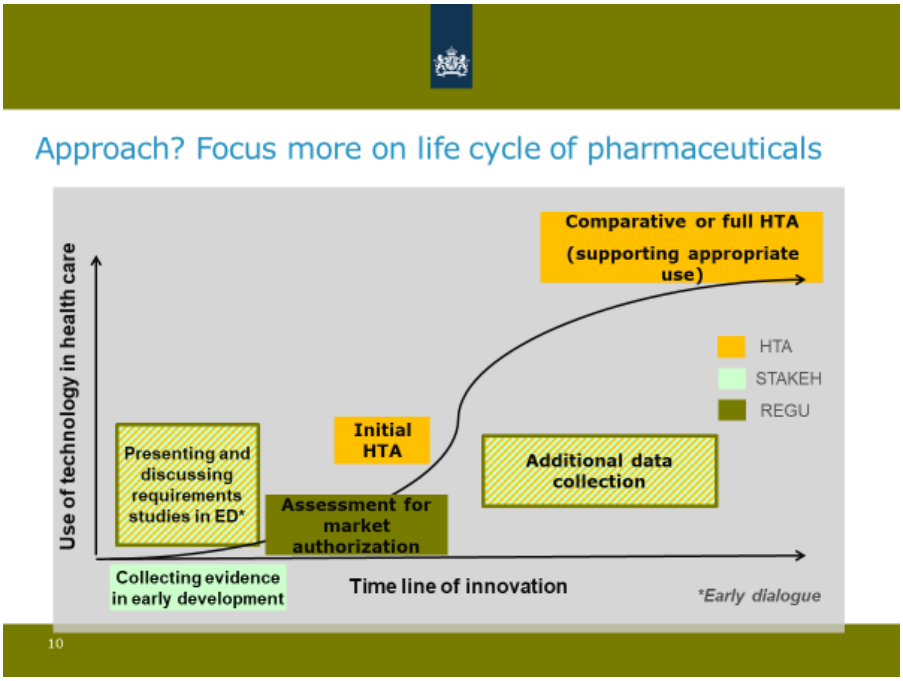

Figure 2. A life cycle focus may increase the level of HTA recommendations for new medicines.

In this approach, early access would be combined with additional data collection processes to obtain real-world evidence. Practical implications of this include the need for early dialogues among manufacturers, regulators and HTA bodies. Better alignment and communication between the market authorisation process and relative effectiveness assessment would also be required, both at the European (EUnetHTA-EMA) and national level. In addition, processes for conditional marketing authorisation, coverage with evidence development and data collection must be more aligned and clarity for exit strategies and differential pricing plans for levels of uncertainty must be developed.

Conditional reimbursement: the Dutch experience

From 2006 to 2012, the Netherlands evaluated a programme of conditional reimbursement in which 12 products were reimbursed under the condition of additional evidence generation over a 4-year period. Only 1 of the 12 products conformed to the designated 4-year evidence collection period and the average duration of evidence collection for the other 11 products was 5.9 years. For those 11 products, ZIN advice to the Netherlands Ministry of Health was to continue reimbursement for 3 products, continue reimbursement conditionally for 6 products and to discontinue reimbursement for 2 products. Ultimately, however, the Ministry determined that it would be too problematic to withdraw reimbursement for those 2 products.

Of 30 surveyed healthcare stakeholders in the Netherlands, 14% indicated that they thought that the conditional reimbursement programme achieved its goals, while 50% indicated that it did not. Other survey participants felt that the programme partially achieved its goal of early access to medicines (28%) and additional evidence generation (14%). In deciding the future of conditional reimbursement in the Netherlands, 37% of those surveyed felt that conditional reimbursement should be replaced with adaptive pathways reimbursement, 30% indicated that it should be replaced with another, unnamed programme, 27% indicated that the conditional reimbursement programme should be improved and re-introduced and 6% that the conditional reimbursement programme should be discontinued altogether.

Moving forward

Elements of the Dutch experience with conditional reimbursement should be taken into account in development of broader reimbursement policy. There is a need for patient registries to obtain real-world evidence for expensive medicines but more coordination, a minimal dataset and agreed methodological toolbox to improve their use in HTA decision making are required and it should be determined if participation in patient registries should be mandatory. If receiving a very expensive treatment is to be considered a patient right, should the provision of health data to improve therapeutic options become a public duty? The future governance/funding models for registries, whether public, private or a public-private combination along with other ethical and technical issues must also be determined. These issues include identification of data ownership, the methodology for guaranteed linkage of databases, assurance of European collaboration on patient registries of rare diseases, international collaboration in those registries and the investigation of new methods for real-world evidence collection.

There are numerous international initiatives that are engaging in research into the collection of real-world evidence.

- The European Union Network for Health Technology Assessment (EUnetHTA) Work Package 5B includes the development of core datasets for HTA registries.
- The European Medicines Agency (EMA) Adaptive Pathways is a programme for iterative evidence development and assessment.
- The Innovative Medicines Initiative (IMI)-GetReal I and II projects include the study of the use of real-world evidence in the clinical effectiveness of drugs.
- IMI-BigData projects, IMI-European Health Data and Evidence Network (EHDEN) use registries and big data as real-world evidence and collect health data using a common data structure.
- The Reproducible Evidence: Practices to Enhance and Achieve Transparency (REPEAT) initiative seeks to confirm the reliability and reproducibility of results from real-world evidence studies.
- New Drug Development Paradigms (NEWDIGS) studies the use of drug development paradigms including adaptive pathways.

- International Society for Pharmacoeconomics and Health Outcomes Research/International Society for Pharmacoepidemiology (ISPOR/ISPE) Special Task Force is conducting research into good procedural and reporting practices for real-world studies.
- Horizon 2020 Health Technology Assessment (H2020 HTx) project is developing methods that can integrate real-world evidence and randomised clinical trials in order to predict effectiveness and cost-effectiveness in small populations.

Whenever it is feasible, the results of these international efforts should be connected to the accrual of real-world evidence. In addition, payers should take the initiative in pricing conditionally approved products, moving negotiated prices upward as supportive evidence increases (Figure 3).

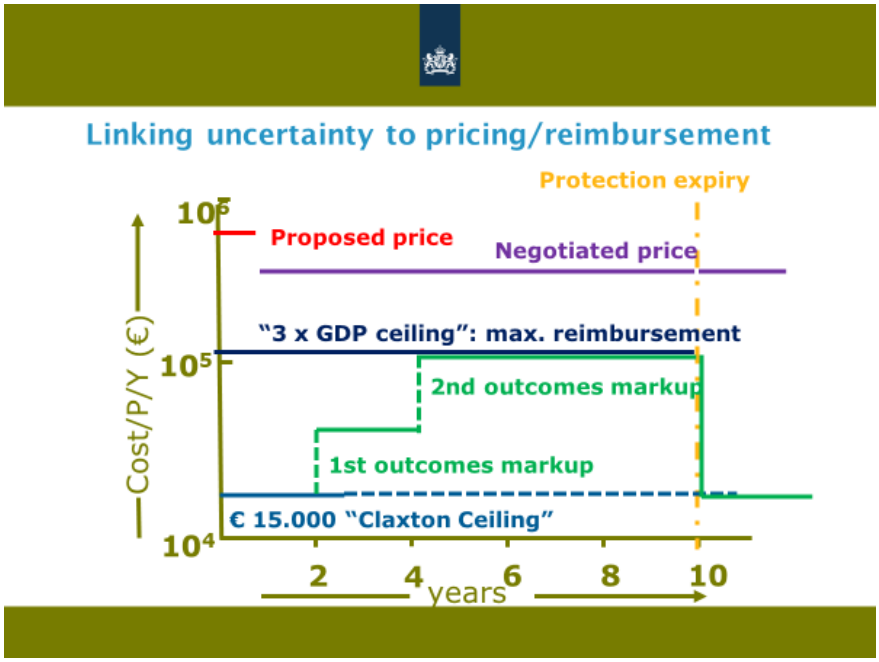

Figure 3. Payers should take the initiative in with "bottom-up" pricing negotiations for products associated with uncertainty.

Conclusions

Conditional processes for reimbursement may facilitate uptake of expensive pharmaceuticals; well-designed patient registries should be required and include the methodology to translate the data from these registries to trustworthy real-world evidence. Additionally, jurisdictions should pay prices for these drugs that reflect their uncertainty and there should be tailored evaluation processes for individual products with the registry and real-world evidence collection linked as much as possible to European regulatory and HTA initiatives.

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A holistic approach: Should regulatory criteria be designed to address HTA needs?

Dr Giovanni Tafuri, *Senior Scientific Officer, EUnetHTA*

Regulatory/HTA alignment: research and progress to date

Currently, there is a single regulatory authorisation system in Europe, with single legislation, and well-defined assessment criteria. This is compared with the environment for 28 different European health technology assessment bodies, which operate under different legislations, methodologies, criteria and reimbursement systems. In considering how these two very different systems might be aligned, Eichler and colleagues published a paper in 2010, outlining the current and potential future paradigms for interaction between regulators and health technology assessors.[1] Since that time, many other authors have examined the differences and consequences of those differences between the two groups of stakeholders. For example, these publications have discussed the lack of information about overall survival and quality of life for oncology drugs provided for market authorisation, which HTA bodies need for their evaluations;[2] additional evidence required by HTA bodies compared to regulatory authorities ;[4] the high cost of some medicines receiving accelerated approvals but whose benefit/risk profile remains uncertain at the time of marketing authorisation ;[5] the issue of post approval studies not always filling the evidence gaps identified at the time of marketing authorisation ;[6] and the variability in time to reimbursement among EU countries.[7]

In 2016 a reflection paper of the HTA Network - discussed the potential for synergies betweeen regulatory and HTA agencies..[8] Indeed, when analysing the interaction between regulatory and HTA issues, three phases need to be distinguished: a) the pre-marketing phase, b) the phase of actual market entry and c) the post-marketing launch phase.Accordingly, the joint European Medicines Agency (EMA)/EUnetHTA work plan (https://www.ema.europa.eu/en/documents/other/ema-eunethta-three-year-work-plan-2017-2020_en.pdf) has developed activities to implent such synergies during each stage of a medicinal product life cycle. During the pre-marketing stage, through the activity of parallel scientific advice, manufacturers can receive simultaneous feedback from regulators and HTA bodies on their clinical development.

A retrospective analysis based on a cohort of procedures of parallel scientific advice between 2010 and 2015 found that there was commonality in evidence requirements between reagulators and HTA bodiess. Whilst there was somewhat less commonality for the advice on comparators, the investigators noted an overall high degree of alignment between the EMA and HTA bodies.[9] Another analysis explored the actual impact of parallel scientific advice on clinical developments, assessing the uptake of regulatory and health technology assessment recommendations. . One of the key findings was that manufacturers tend

to implement changes to the development programme based on both regulatory and HTA advice with regards to the choice of primary endpoint and comparator, however the analysis also confirmed the challenging choice of the study comparator, for which manufacturers seem to be more inclined to satisfy the regulatory advice..[10]

Other activities of the EMA/EUnetHTA Work Plan aim to facilitate mutual understanding through collaboration at the time of market entry of new medicinal products. . Bentgen and colleagues reported EMA/EUnetHTA efforts to improve the presentation of data and information in European Public Assessment Reports (EPARs) to enhance their useabliity by HTA bodies. While this project represented an opportunity to engage in dialogue around collaboration, the different remits of regulatory evaluations and health technology assessments were acknowledged.[11] These different remits were reflected in a comparison of the EMA EPAR and HTA body REA for regorafenib for hepatocellular carcinoma, which showed overlapping opinions regarding the uncertainties that surrounded the drug at the time of regulatory approval but differing responses to those uncertainties (Figure 4).

Another important area of collaboration at the time of regulatory approval is the one on the wording of therapeutic indications . The regulatory perspective regarding therapeutic indications is that they should reflect positive benefit-risk evaluations for use of a drug in a particular disease state and population. The wording of indications may have important implications for HTA and reimbursement therefore a thorough understanding of the rationale underlying specific indication wordings is fostered through this collaboration.

Patient-reported outcomes

Patient-reported outcomes (PROs) represent another important area for regulatory/HTA cooperation and several publications have reported on efforts to standardise the analysis of health-related quality of life (HRQOL) and other PRO data in cancer randomised trials;[12] PRO data are recognised as a potential key component of the payer decision-making process and as a key requirement in the EUnetHTA assessment reports.[14]

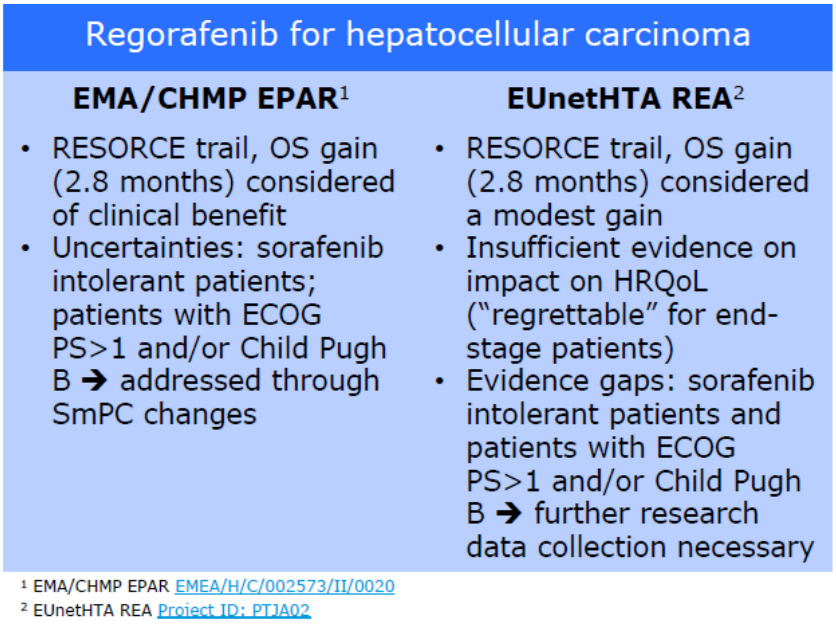

Figure 4. Comparison of EMA European Public Assessment Report and EUnetHTA relative effectiveness assement for regorafenib shows differing requirements for resolving uncertainties.

Innovation

The identification of criteria to characterise *innovation* is another potentially vital point of regulatory/HTA convergence. HTA bodies have differing definitions of innovation; for example, the Italian Medicines Agency (AIFA) defines innovation based on three criteria: unmet medical need, added therapeutic value and the quality of clinical evidence. In the regulatory arena, whilst there are numerous programmes to expedite the review of promising medicines , there are no commonly accepted criteria that identify innovation. Identifying common criteria for innovation is critical to both regulators and HTA bodies, as recognising innovation enables the prioritisation of resources and the sustainability of healthcare systems.

Conclusions

Despite different remits and objectives, opportunities for collaboration and mutual learnings between EMA and HTA bodies such as those now taking place through the EMA/EUnetHTA Workplan have increased. There is now stronger awareness of HTA evidence needs and continued regulatory/HTA collaboration during each step of product life cycle, ranging fom horizon scanning and joint scientific advice, to the and the development of EPARs and REAs and post-marketing evidence generation.

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Blending randomised clinical trial and real-world evidence – A case study of the Innovation in Medicine Initiative (IMI - GetReal).

Dr Michael Happich, *HTA Director, Eli Lilly and Company, Germany*

IMI GetReal

Initiated in 2007, the Innovative Medicines Initiative (IMI) is a collaboration among the European Commission the European Federation of Pharmaceutical Industries and Associations (EFPIA), academia, HTA bodies, regulatory agencies, patients and small and medium enterprises. The goals of IMI are to improve the efficiency and effectiveness of the drug development process, ultimately resulting in the production of safer and more effective, innovative medicines. IMI supports a number of projects, including the GetReal initiative, which seeks to demonstrate the feasibility of the earlier adoption of new methods for the collection and analysis of real-world evidence (RWE). Among the methods to achieve this goal, Get Real assesses existing processes, methodologies, and key research issues; proposes innovative trial designs and assesses the value of information; and proposes and tests innovative analytical and predictive modelling approaches.

Case study methods

Accordingly, the case study, “Blending randomised clinical trial and real-world evidence” was presented at the 2016 European ISPOR meeting.[1] In this case study, investigators analysed the generalisability of the overall survival results from a randomised clinical trial (RCT) for pemetrexed versus gemcitabine in the treatment of non-squamous non-small cell lung cancer,[2] reweighting these results through the use of real-world data from the prospective observational FRAME study.[3] In this reweighting approach, RWE and RCT data are pooled and the propensity score model predicts participation in either RWE or RCT, given a set of covariates (Figure 4). Resulting propensity scores were used to quantify the difference between the two cohorts, and match, subclassify or weight the RCT outcomes to the RWE population. Classic propensity scoring is often used to mimic RCTs in a RWE setting. Here, propensity scoring was used to mimic RWE in an RCT setting. Prior to launch, only baseline RWE information is needed to assess RCT outcomes under RWE conditions.

Results

After reweighting, differences in overall survival for pemetrexed compared with gemcitabine were slightly higher; however, the hazard ratio (HR) for the clinical trial was closer to 1, with greater uncertainty HR,0.92 (95% CI: 0.60 to 1.33) compared with HR, 0.81 (95% CI: 0.70 to 0.94) in a similar population in the clinical trial. Sensitivity analyses produced similar results (Figure 5) Analysis, therefore, showed that

reweighting did not invalidate RCT results and those RCT results for the treatment of non-squamous NSCLC could be projected to a real-world population.

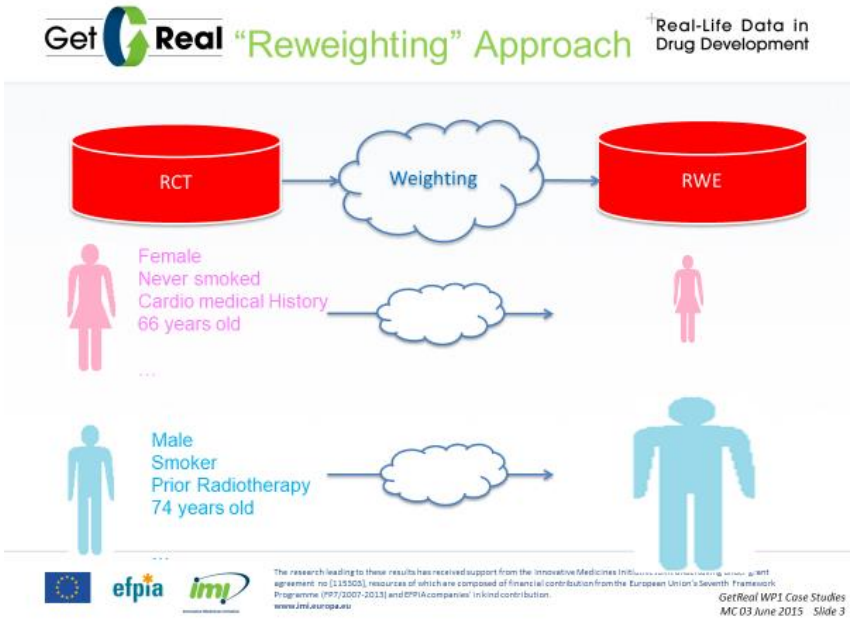

Figure 4. Randomised clinical trial data was reweighted through the use of real-world data.

Category	Treatment	N	Median time to Death (months)	Hazard ratio	95% LCL	95% UCL
No weighting	Gemcitabine	608	10.15	0.851	0.746	0.972
	Pemetrexed	614	11.14			
					Bootstrap 2.5th perc	**Bootstrap 97.5th perc**
Weighted*	Gemcitabine	593	10.15	0.915	0.599	1.333
	Pemetrexed	616	15.57			

Figure 5. Results of reweighting RCT data.

Study limitations and conclusions

Limitations to this type of analysis include the fact that the definitions of variables and baseline characteristics and outcome measures can be different between RCTs and RWE studies and specific categories of variables present in RWE trials may not be available in RCTs. Other issues may include unmeasured confounders and non-overlapping propensity scores. Although the level of blended RCT results and RWE in the evidence hierarchy has yet to be determined, this model has the potential to make

a positive impact in healthcare decision making.

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What new research can enable a joint approach by regulatory and HTA agencies to manage uncertainties for products using early access pathways?

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Joint approach

In order to consider this topic, the operational aspects of a joint approach should be determined; that is, the different types of joint approaches should be identified, as should the consensus of stakeholders as to which type of approach is considered to be most effective. Additional considerations include the required resources for each method as well as the appropriate rules of disengagement. The nature of evidence used in joint approaches must also be ascertained, as well as its acceptability to both regulatory and HTA discussions and the points of divergence in acceptability by the two groups. Finally, the impact of these new joint regulatory HTA interactions on regulatory processes and discussions and on society in general should also be determined.

Managing uncertainty

What exactly do we mean by *managing uncertainty* in the context of regulatory decision making and adaptive pathways? Renn defines uncertainty as “A state of knowledge in which, although the factors influencing the issues are identified, the likelihood of any adverse effect or the effects themselves cannot be precisely described.”[1] Three types of uncertainty are all at work in decision making for adaptive pathways, and each require different approaches.

- *stochastic uncertainty*, or uncertainty resulting from unpredictable conditions;
- *epistemic uncertainty*, or uncertainty that can be mitigated by additional information; and
- *decision uncertainty,* or uncertainty that is inherent in decisions made with the best available knowledge weighed in the light of specific external parameters such as budgets or specific patient needs

Decision makers must determine how they can accept more uncertainty at the time of product approval without lowering the established standards for product safety and efficacy and how they can be transparent and communicate about these uncertainties to healthcare stakeholders and society at large.

Pre- and post-launch RWE tools such as pragmatic trials, basket trials, umbrella trials, trials within cohorts and network meta-analyses may help achieve the overall goals of early access pathways; however, whilst these methods may decrease *clinical* uncertainty, they may come with increased *methodological* and *statistical* uncertainty. Through its various activities the IMI GetReal initiative seeks to determine to what extent different RWE sources are able to reduce (clinical) uncertainty in a convincing way, what impact RWE has had on decision making, what drives regulatory/HTA acceptability of RWE and what influences companies to decide to include RWE, especially pre-launch. In addition, the management of the uncertainties surrounding new products has been further complicated by the emergence of the "system therapeutics" concept in which these new products focus on the treatment of disease *processes* rather than individual transduction pathways.[2]

Early access pathways

The ambition of early access pathways is well captured in the ADAPTSMART (The Accelerated Development of Appropriate Patient Therapies a Sustainable, Multi-stakeholder Approach from Research to Treatment-outcomes) definition of Medicines Adaptive Pathways for Patients (MAPPs)

> "To foster access to beneficial treatments for the right patient groups with high unmet medical needs at the earliest appropriate time in the product life span in a sustainable fashion."

ADAPTSMART has also listed and described the elements of early access pathways as well as the relevant questions being researched through ADAPTSMART activities (Figure 6).

Using early access pathways

Elements	Description	Research questions
Beneficial treatments	Clinical data must show that the benefits will very likely outweigh the risks in the defined patient group.	How is the collection of evidence for quality, safety and efficacy evaluations governed within an early access approach governed, and how can RWE generate evidence both pre- and post-launch with acceptable levels of uncertainty
Right patient groups	A product is initially "fast-tracked" exclusively for patients who will benefit the most. It is therefore important that in the beginning only those patients will get the new medicine.	How can we ensure that medicinal products approved under MAPPs are appropriately used? What is the evidence for different tools?
High unmet medical needs	Focus on products that offer a credible promise to address a patients' unmet medical need in a meaningful way.	How do we define and operationalise 'medical need'?
Earliest appropriate time	bring the treatment to market at the earliest appropriate time in the product life-span.	How can early access to novel treatments through a MAPPs approach be achieved within the current regulatory framework?
Sustainable fashion	Find solutions for this emerging financial constraint by ensuring the sustainability of innovation and healthcare systems.	How can flexible pricing and reimbursement schemes contribute to a MAPPs approach in a sustainable healthcare system?

Figure 6. The elements of early access being researched by ADAPTSMART activities.

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Dealing with uncertainties: Next steps

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Whether to satisfy paediatric regulations, orphan drug incentives or risk management plans, regulators and health technology assessors frequently require more data from pharmaceutical manufacturers in an effort to resolve uncertainties surrounding new medicines. However, it remains to be determined which of these requirements are fulfilled, how they are fulfilled and most important, which uncertainties they ultimately resolve.

In a 2009 evaluation of post-authorisation safety studies planned at the time of regulatory approval in the first cohort of EU risk management plans, none of the risk management plans proposed by manufacturers were accompanied by a full study protocol. Most plans included a limited study protocol, study synopsis or very short study descriptor and a few plans included a commitment to perform a study with no further information.[1]

In 2017, Woloshin and colleagues reviewed 614 post-approval and commitments made to the US FDA in 2009-2010, determining that 20% of post-approval studies had not been initiated, 25% were delayed or ongoing and 54% had been completed. It was not determined; however, if the relevant uncertainties associated with the new medicines had been resolved by the 54% of post-approval commitments that had been met.[2]

Of 26 medicines conditionally authorised by the EMA between 2006 and 2016, Bloem and associates identified subsequent changes to 39% of manufacturer-agreed obligations and delays in fulfilment of 55% of obligations. These researchers concluded that although the delays might subject patients to unknown risks, especially in conditions of substantial uncertainty, the changes were “potentially indicative of a continuous search by regulators to reduce uncertainties”.[3]

The 2016 publication, “EMA conditional marketing authorisation: Report on ten years of experience at the European Medicines Agency”, included a discussion of those same changes to conditional marketing obligation plans in which the changes were also regarded as being reflective of the need for continuous regulatory learning to reduce the uncertainties of conditionally approved medicines.[4] However, authors of a 2017 editorial about the EMA report challenged that position, calling it “unlikely” that the additional forthcoming data would contribute to the needed clinical knowledge base about these medicines.[5]

Moving forward, to close knowledge gaps and improve the learning potential not just for regulators but for all healthcare stakeholders about conditionally approved medicines requires a shift in focus from process to content. It must be determined which additional data are needed, are feasible to acquire and will actually resolve uncertainties.

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How do we determine what makes joint HTA/regulatory scientific advice efficient and effective?

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Paths for advice

The first pilots for the provision of parallel European Medicines Agency (EMA)/HTA advice on evidence-generation plans for new medicines began in 2010 and in July 2017, the EMA and the European Union Network for Health Technology Assessment (EUnetHTA) began to offer a single gateway for parallel consultations with EMA, EUnetHTA, and HTA bodies.

Currently, sponsors of new medicines who appear before the Early Dialogue Secretary of EUnetHTA chose to apply for multi-HTA advice, which does not involve the EMA and which is funded by the

European Commission or parallel consultation with the EMA and HTA bodies (HTABs). Applications for parallel consultation are then selected based on prioritisation factors for either advice from the EMA plus consolidated advice from HTABs which is coordinated by the Early Dialogue Working Party and currently funded by the European Commission or advice from the EMA plus individual advice from multiple HTABs which is funded by the applicant (Figure 7).

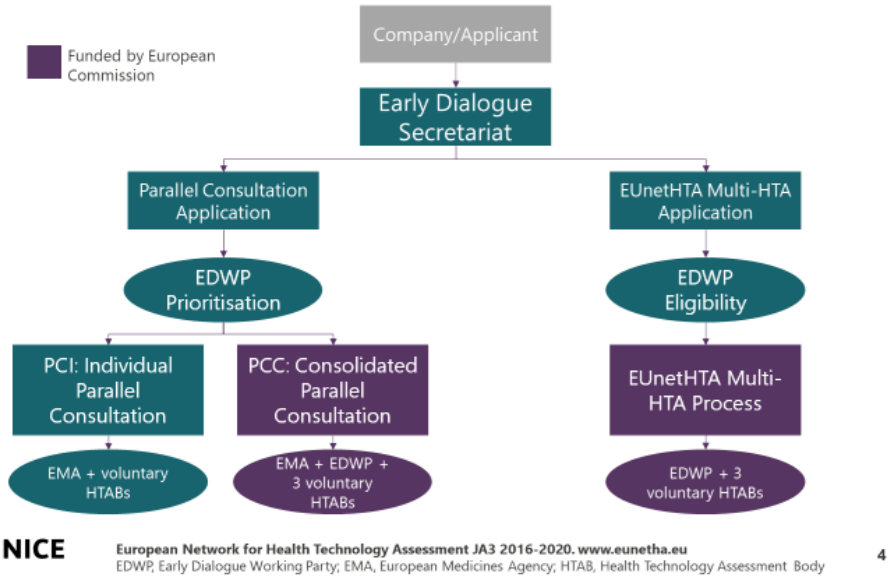

Figure 7. Paths for parallel EMA/EUnetHTA scientific advice.

Efficiency considerations

In evaluating the efficiency of parallel consultations, elements for consideration include financial and political constraints, expertise and resourcing and the logistic challenges presented by the interaction of multiple stakeholders. Before the introduction of EUnetHTA/HTA parallel advice procedure, timelines for parallel regulatory/HTA consultation were adapted from the EMA process and some HTABs were unclear as to procedural timelines and requirements, leading to difficulties in coordination. Since the initiation of the EUnetHTA/EMA consolidated advice process, however, efficiency is achieved through HTAB participants who are designated as scientific coordinators and rapporteurs on a rota basis. As part of this process, HTABs share their positions among the group prior to the meeting and one report from all HTABs is collated, including a summary of common advice.

Effectiveness considerations

In evaluating the effectiveness of parallel consultations, surrogate outcomes for consideration include *demand from companies, company feedback, participation by HTABs, changes to clinical trials and HTA approaches and impact on regulatory and HTA decisions*.

Demand: Company demand for advice from the National Institute for Health and Care Excellence (NICE) continues to grow and since 2017 has included both individual and consolidated HTA advice in parallel with EMA. (Figure 8).

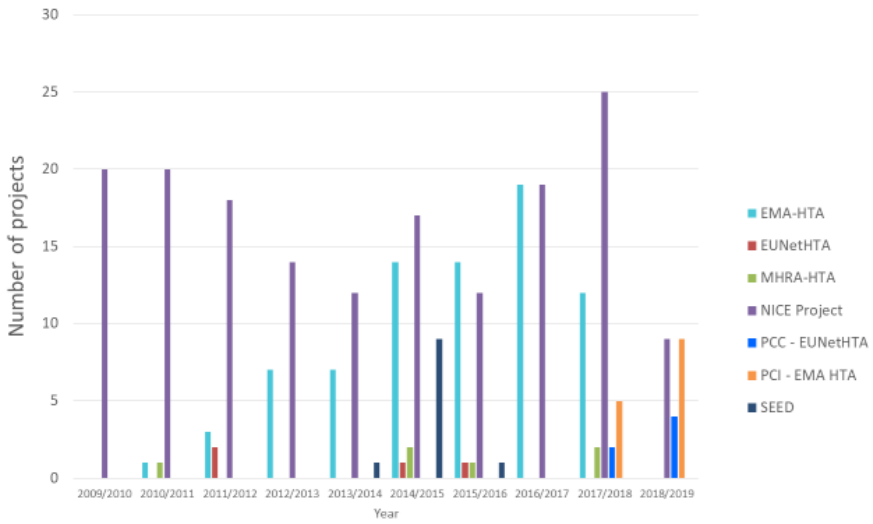

Figure 8. Demand for NICE services from companies has increased over time.

Feedback: EUnetHTA send out a client feedback request after each joint procedure, but to date, response has been very low and the reason for this nonresponse remains to be determined. NICE request for feedback on historical projects before involvement of EUnetHTA resulted in a score of 4.1/5 in overall satisfaction with one respondent remarking “This experience provides for good collaborative discussion and simultaneous feedback so is a very good use of time and resource compared with other individual procedures.”

HTAB participation: Tafuri and colleagues noted the participation of eight HTABs in 31 EUnetHTA parallel procedures, the three most frequent participants were England’s HTAB, NICE, 90% of procedures; Germany’s Gemeinsamer Bundesausschuss (GBA), 65% of procedures and Italy’s Agenzia Italiana del Farmaco (AIFA), 45% of procedures.[1]

Linking advice to outcomes: Obtaining advice for evidence-generation programmes is a resource-intensive activity, with a long lag time from advice to decisions; for example, of 166 NICE scientific advice projects in 2016, as of November 2018, only 9 had completed technology appraisals (100% recommended).[2] In addition, because of the bias toward positive recommendations that is inherent in using a sample of products for which scientific advice was sought, other markers might be used to indicate the effectiveness of parallel scientific advice, such as the percentage of changes to clinical development plans, the percentage of clinical trials that include key HTA elements such as health-related

quality of life, or the percentage of negative recommendations due to evidence gaps.

Although divergent regulatory and HTA advice would seem to be problematic, in reality, part of the value of receiving advice in parallel is to highlight and capture elements of difference. Tafuri and colleagues analysed EMA/HTA concordance in 31 parallel advice procedures and determined complete or partial agreement regarding population in 91% of procedures, regarding comparator in 69% of procedures, endpoints in 88% of procedures, other study design characteristics in 79% of procedures and overall efficacy and data packages in 77% of procedures. Furthermore, in evaluating the uptake of regulatory advice in these procedures, the researchers noted that 100% of the recommendations for primary endpoint were followed by sponsoring companies. As might be expected, recommendations for comparators were followed somewhat less frequently (57%) and 38% of the combined recommendations from the EMA and more than one HTAB were followed. [1]

Conclusions

Collaboration, coordination and communication has improved with the introduction of the EUnetHTA/EMA parallel advice process under EUnetHTA Joint Action 3. What is more, as additional experience is accrued in these procedures, there is scope for even more savings in efficiency. Indications are that this type of advice is effective, but measurement of effectiveness is challenging and the optimal method for measurement has yet to be elucidated. Furthermore, as international political systems evolve and medicines themselves grown in complexity stakeholders should be prepared for additional challenges.

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ROUNDTABLE DISCUSSIONS

Discussion question: What research can enable a joint approach by regulatory and HTA agencies to manage uncertainty for products using early access?

Four groups were asked to agree on one to two areas of potential future research in this area, which is practical, feasible and able to generate impact.

Group 1

This group agreed that appropriate research topics would include the need to focus on understanding the impact of joint regulatory-HTA joint assessments, including the potential impact on drug development. Evaluations should include the immediate intended impact for those directly connected to the joint assessments as well as the "trickle down," possibly unintended impact that may affect therapeutic areas and other groups such as patients and even healthcare systems and infrastructure over time. Importantly, even if regulatory and HTA stakeholders are fully aligned, the impact of joint assessments on payers must be evaluated and the type of evidence that would be required for payer alignment and the methods for collection of that evidence must be determined.

It would be valuable to research how to eliminate avoidable uncertainties, not just in regulatory and HTA contexts but also for payers and clinicians. These are not just uncertainties in terms of safety but also in efficacy, effectiveness and clinical use. That is, we should determine if a tool to assess effectiveness would be useful and what data the tool would have to generate to be of value. A potential method for generating these data would be to use retrospective modelling for a particular drug or therapeutic area and then to review how that model might be used going forward. Despite potential issues in generalisability, such a model may generate some new insights.

It may be valuable to consider the value of a "reset button" for guidance. That is, to determine what the choices would be if the drug development paradigm were to be completely redesigned, using all of the elements now required by the EMA, FDA and various HTA bodies. What progress could we then anticipate in the evidence-planning process and what value would be generated in innovation relative to the cost of such a programme? In very novel technologies, industry, regulatory and HTA stakeholders have been forced into an environment where there are no entrenched systems and it may be worthwhile to consider the expansion of this model.

Other potential research topics identified by the group:

- Given the nature of global development, it may be useful to investigate how companies integrate received advice, not just across regulatory and HTA concerns in Europe, but across the world, particularly in larger markets such as the United States and markets of growing importance such as China.
- Consider to what extent regulatory and HTA advice might be used to address issues around prevention, which has direct impact on healthcare demands.
- Investigate which evidence for conditionally approved products is of interest to HTA stakeholders. There may a potential link to the EMA-EUnetHTA workstream in post-licensing evidence generation that could help support this understanding.
- Evaluate how innovative therapies could address the different healthcare contexts caused by substantive clinical differentiation across Europe.

Question for the group: Are there any learnings from programmes such as 21st Century Cures in the United States, to "reset the button" and reinvent the way that drug development occurs and how novel forms of data can be used to inform processes?

Answer: Although we were thinking about an entire new start, it would interesting to determine to what extent 21st Century Cures achieves some of that reset effect and if it has been of value.

Question for the group: Drug development should be a question-based exercise and you should make sure that you use proper methodologies in order to achieve your targets. In your discussion about avoidable and unavoidable uncertainties, did you formulate a specific method to investigate those elements?

Answer: Ours was more of a preliminary discussion, but we agreed that first you would need to agree on and potentially map what different stakeholders think is avoidable versus unavoidable. Once these different perspectives are understood, we could go onto determine the best methodology for the resolution of those uncertainties.

Group 2

Rather than eliminate current regulatory and HTA guidance to start over, this group would first recommend research to determine the value of scientific advice, that is, they would evaluate what regulatory and HTA advice provides in terms of outcomes and assess its role in increasing the predictability of drug development. Theoretically, scientific advice should facilitate the most efficient use of resources and the development of targeted value propositions for new medicines. For scientific advice to optimally achieve these results, however, it may be beneficial for it to become a more public and continuous process used through the life cycle of medicines and this would require both more transparency and resources. Currently, scientific advice is kept confidential, but if advice was made public, at least retrospectively or for a select number of advice procedures, it would facilitate the determination of the predictability of advice and of its effect on outcomes. A continuous assessment process would require a framework for the exploration of new information as it becomes available. Potential automation of some functions might mitigate resource implications of this process.

In order to foster effective and efficient joint assessments, the interaction of all stakeholders and their mutual knowledge and understanding of both regulatory and HTA perspectives and requirements must continue to improve. In addition, in order for all participants to embrace the use of methodological tools such as the indirect comparisons used in many HTA evaluations, more validation and assessment of the predictability of the tools is required, ideally in comparison to benchmarks. A cohort comparison could be used to assess real-world evidence versus clinical trials.

Question for the group: With the work of IMI and other groups, don't we yet have a body of knowledge including best practice for single and parallel scientific advice?

Participant: There are a number of examples but also a number of errors and too many individual cases. We still may be lacking critical mass.

Participant: You are saying we should distil the knowledge we gain from scientific advice into generalisable ideas, but that is essentially what we have done for the last 20 years. Guidance documents from agencies all represent the distilled knowledge from the experience of providing scientific advice.

Participant: Guidelines on how to develop a new drug for a particular therapeutic area are based on the first 3-5 cases of scientific advice for the area. That process is there and is well developed. What are still required are methodologies. Regulators are reluctant to accept and companies are therefore reluctant to present innovative methodologies such as the weighting methodology presented by Dr Happich (page 18) More methodologies are required. It is not about the endpoints – they come naturally – it is the methodologies that need to be better described.

Group 3

It was the consensus of Group 3 that an important piece of research would involve mapping the main drivers of uncertainty for each group of stakeholders. From an understanding of the groupings and differences among stakeholders that would emerge, it may be possible to determine the evidence that would satisfy the particular uncertainties of those groups. Moving forward, different uncertainties among countries could also be examined and then uncertainties relative to therapeutic areas or types of intervention.

In addition to a financial cost, resolving uncertainties for new medicines also has a time component, which could also be explored, including the impact of uncertainties relative to launch timing in different jurisdictions. For example, companies may be asked to resolve fewer uncertainties in the United States and be ready to launch in that country in advance of Europe, where HTA data may still need to be accrued. What are the consequences of those delays?

It may also be relevant to determine if there is a shelf life for uncertainties and what that shelf life could be. Unmet post-approval commitments could be assessed to understand what could have occurred over time to change what seemed to be critical questions into issues that are either irrelevant or unfeasible or unethical to resolve. These changes may vary among therapeutic areas, particularly for disease states with rapidly evolving standards of care.

It would also be valuable to evaluate changes in uncertainty over time, examining samples from each HTA and regulatory body during individual years to observe trends. If samples sizes are large enough, the influence of uncertainty in decision making among HTA bodies and the acceptability of different uncertainties between HTA bodies and regulators could also be examined.

Finally, although it may not lead to actionable outcomes that would improve the process, the interaction of stakeholders in parallel advice procedures would be an interesting research question.

Group 4

This group also focused on early dialogue and scientific advice. Although there has been research showing that most advice given to companies is subsequently incorporated into development plans, especially advice on clinical outcomes, this group was interested in the possibility of researching scientific advice that was not adopted by the companies. Specifically, the group would like to investigate the reasons advice was not followed and what could be done by all stakeholder to improve the advice process.

To improve predictability further along the development pathway, research could be conducted into HTA sensitivity toward and acceptance of therapies approved via facilitated pathways such as conditional marketing authorisation. Existing research has shown that while regulators may consider factors such as a product's potential to treat an unmet medical need when evaluating benefit-risk, HTA bodies tend to review these products in the same way as products utilising standard development and review pathways. Therefore, it would be important to understand what criteria would allow HTA authorities to accept prioritised assessments.

Question for the group: Understanding how different stakeholders codify unmet medical need may help us understand the rationale for regulator versus health technology assessor acceptance of facilitated pathways. Did the group discuss how to help stakeholders characterise the concept of unmet medical need?

Answer: Stakeholder perspectives on unmet need are central to discourse and alignment on facilitated pathways. Research into stakeholder characterisation of unmet need is ongoing, but there could always be more investigations that include additional perspectives.

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