



Visualising benefit-risk of assessment of medicines:

The key to developing a framework
that informs stakeholder perspective
and clarity of decision making

WORKSHOP SYNOPSIS

16 – 17 June 2011

Washington, DC

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The following is a high-level summary of key points from a Workshop conducted by the Centre for Innovation in Regulatory Science (CIRS) on 16 – 17 June 2011, in Washington, DC. A complete Workshop Report including full presentation summaries and syndicate recommendations will be forthcoming.

Background to the Workshop

In June 2010 CIRS held its annual meeting on the benefit-risk assessment of medicines in Washington, DC to discuss the use of weightings and values within benefit-risk (BR) frameworks. It was agreed at that meeting that one way of ensuring the development of the most effective BR framework is by working through real-life scenarios with different stakeholders and products. This practical approach can facilitate the identification of ways in which agencies and companies will use the framework and establish practical methodologies to be used by regulators in the review of new medicines.

That Workshop also identified a number of barriers to the acceptance of a BR framework and possible solutions, which included continuing the dialogue between agencies and companies and working through case study examples as a way of both evolving the thinking and gaining acceptance of the value of a process for articulating benefit-risk in a transparent manner.

In 2011, as the development of BR frameworks moves forward through US Food and Drug Administration, the European Medicines Agency, the Benefit-Risk Action Team of the Pharmaceutical Research and Manufacturers of America and the consortium of four agencies comprising Health Canada, Swissmedic, Australia's Therapeutic Goods Administration and Singapore's Health Science Authority being facilitated by CIRS, this Workshop again brought these groups together with industry, academic and regulatory colleagues, many of whom are developing their own methodology with common objectives of improving the clarity of communication and decision making by using a formal BR assessment methodology.

Workshop Objectives

- **Discussing the progress** made since 2010 by the different groups working towards defining and implementing a benefit-risk framework within their organisations.
- **Furthering the thinking** regarding how to undertake weightings and valuing within a framework using worked examples/ scenarios and evaluating the difference between stakeholders using practical examples
- **Identifying how and what** visualisation techniques can aid both the inputs and outputs of the process of describing benefits and risks and how this enables stakeholders to a better articulation, understanding and clarity of the benefit-risk decision

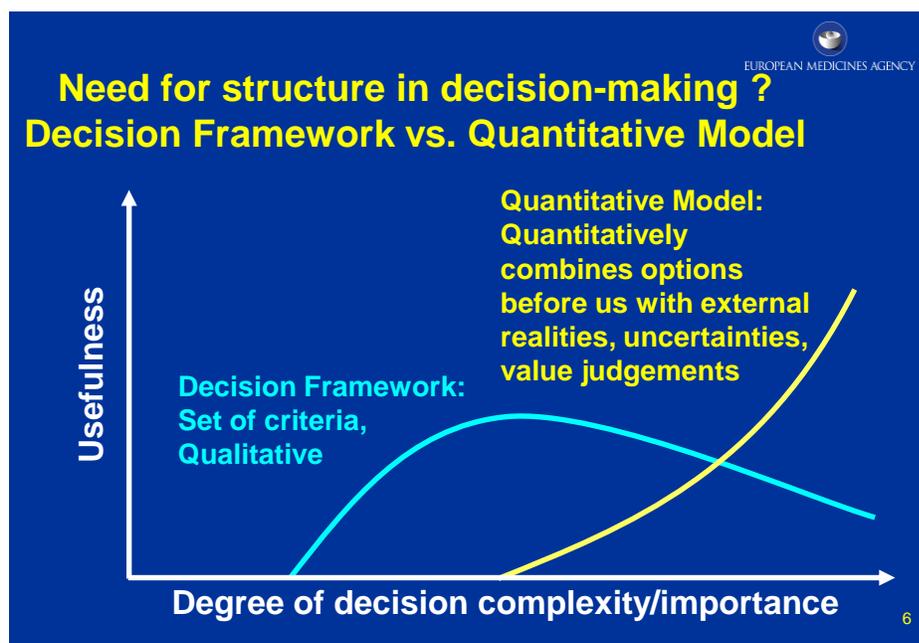
Key points from presentations

SESSION: DEVELOPMENT OF A FRAMEWORK FOR BENEFIT-RISK: CHALLENGES AND ARE WE THERE YET?

Is there a need for an internationally accepted approach for the systematic routine and standardised documentation of decision making in the benefit-risk assessment of medicines?

Day 1 Chairman, Professor Bruno Flamion, *Chairman, Belgian Committee for Reimbursement of Medicines, Belgian National Institute for Health and Disability Insurance*, opened the Workshop with a challenge to participants to demonstrate that the development of a standardised benefit-risk (BR) framework will improve the three most important aspects of regulatory decision making: transparency, consistency and communication.

Those three aspects of decision making are indeed being enhanced by the movement toward an internationally accepted, systematic, routine and standardised documentation of BR decisions, according to **Professor Hans-Georg Eichler**, *Senior Medical Officer, European Medicines Agency*. As methodology and presentation evolve from providing implicit to explicit value judgements and from being a reflection of regulators' values to those of patients, the development of a toolkit for BR assessment will further enhance the predictability and auditability of regulatory decisions. Dr Eichler illustrated that as the decisions regarding the BR profile of a medicine require more complex assessments, integrating a quantitative component in to a BR model will increase its power and usefulness.



Those sentiments were echoed by **Dr Theresa Mullin**, *Director, Office of Planning and Informatics, CDER, US Food and Drug Administration (FDA)* who, in her presentation of the BR framework under development at the FDA, said that this framework had the potential to improve the predictability and consistency of decision-making through a standardised structure. The power of the framework to clearly outline both the available evidence and the uncertainties and articulate the thinking and judgement behind regulatory decisions can improve transparency of the decision-making process.

Although **Dr Ellen Strahlman**, *Chief Medical Officer GlaxoSmithKline, USA*, also agreed that a standardised framework for BR assessment is necessary, she outlined some of the challenges to its development, including international and regional differences in available tools, rigor with which these tools are used, the limitations imposed by jurisdictional regulatory processes, and the complexity of addressing diverse clinical guidelines and labelling requirements. Dr Strahlman emphasised the need to extend BR assessment as early and as late as possible in the development continuum and to examine benefits as closely as harms, tracking their impact over time.

Dr Neil McAuslane, *Director, Centre for Innovation in Regulatory Science (CIRS)* reported on the preliminary results of a survey conducted by CIRS to determine, among other things, pharmaceutical companies' and regulatory agencies' current approaches and attitudes toward BR assessment. The key perceived advantages identified for implementing a BR framework were as a tool for communication, to facilitate structured discussion and to enhance transparency and accountability. Although there is generally a good agreement between agencies and companies on the need and function of an appropriate BR framework, development of visualisation tools for communicating benefit risk balance within companies and agencies seems currently limited to a few organisations.

Communication

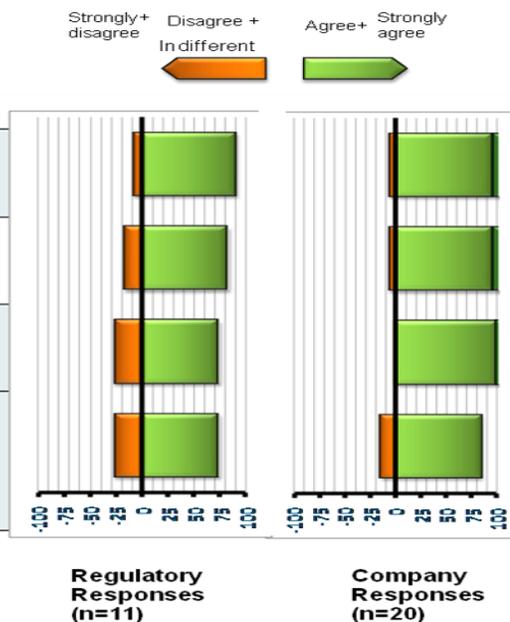
Statement

The purpose of establishing an appropriate BR framework is to improve: **The transparency of decision making** (Q9.6b)

The purpose of establishing an appropriate BR framework is to improve: **Communication of the decision** (Q9.6c)

The purpose of establishing an appropriate BR framework is to improve: **The consistency of decision making** (Q9.6a)

There is a **need for a coordinating group** including representatives from all relevant stakeholders to ensure the appropriate direction and application of a benefit-risk systematic standardized framework (Q 9.13)



Un-audited data

Benefit-Risk framework development and visualisation: Current status and forward plans

The status of the development of the European Medicines Agency (EMA) BR framework was provided by **Dr Lawrence D. Phillips**, *Professor, London School of Economics and Political Science, UK*. The first two work packages of the EMA BR Project: *Current practice of benefit-risk assessment for centralised procedures in the EU regulatory network* and *Applicability of currently available tools and processes for regulatory benefit-risk assessment* have been completed; the third, *Adaptation and field testing of recognized tools and processes (from WP 2)* is underway and the last two *Development of a benefit-risk tool/method that can add value in the regulatory process* and *Development of a training package on the new tool/method for regulatory assessors* are currently under development.

To facilitate the opportunity for shared or joint review, the Four-Agency Consortium comprising Health Canada, Swissmedic, Australia's Therapeutic Goods Administration and Singapore's Health Science Authority has been collaborating with CIRS to develop and test a draft pro forma for a qualitative BR framework. **Dr Supriya Sharma**, *Director General, Therapeutic Products Directorate, Health Canada* reported that although certain topics such as the weighting of risks and benefits and visualisation methods are still under discussion, a prospective pilot study using this CIRS framework is planned for the latter half of 2011.

Dr Diana Hughes, *Vice President, Worldwide Safety Strategy, Primary Care Business Unit Lead, Pfizer Inc, USA* explained that the Soft Pilot Program (SPP) of the Pharmaceutical Research and Manufacturers of America Benefit-Risk Action Team (PhRMA BRAT) was developed and implemented to gain experience with the BRAT BR framework in a real-world environment. To date, ten companies are participating in the SPP, and findings and accomplishments of the programme will be disseminated after its completion in 2011.

The goal of Work Package 5 of the PROTECT (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium) project is to develop methods for continuous benefit-risk monitoring of medicines, by integrating data on benefits and risks from clinical trials, observational studies and spontaneous post-approval reports, including both the underpinning, modelling and the presentation of the results, with a particular emphasis on graphical methods. **Dr Alain Micaleff**, *Senior Medical Safety Advisor, MerckSerono SA, Switzerland*, reported that ongoing activities of the programme, which is a project of the Innovative Medicines Initiative (IMI), including the planned publication of their review of benefit-risk methodologies and visualisation methods and the selection of a second wave of products for further case study evaluation.

SESSION: CHALLENGES AND DIFFICULTIES OF PRESENTING BENEFIT-RISK INFORMATION TO STAKEHOLDERS – IS VISUALISATION THE KEY TO INFORMED DECISION MAKING AND INFORMATION SYMMETRY?

Day 2 Chairman, Professor Sir Alasdair Breckenridge, *Chairman, Medicines and Healthcare products Regulatory Agency, UK* summarised the first day's proceedings and introduced this session's presentations, saying that he would add a fourth item to the three most important aspects of regulatory decision making proposed by Professor Flamion on Day 1: defining and clarifying treatment populations.

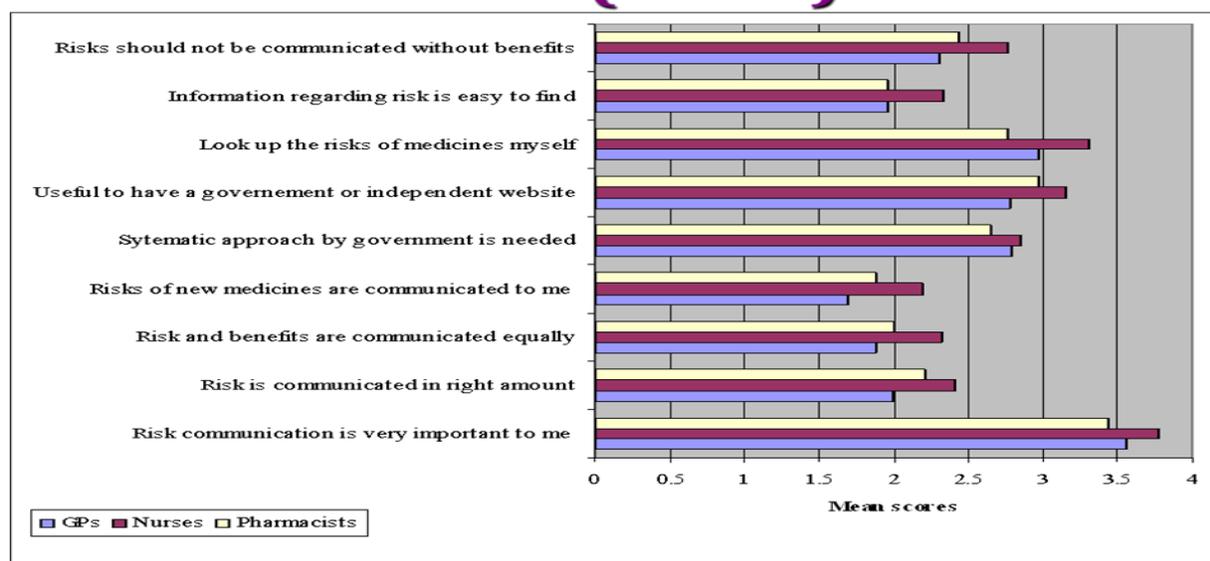
The size of a medicine's beneficial and harmful effects are revealed by data and described and scored for decision makers, whose interpretation is subject to individual perspective and willingness to trade off risks and benefits. The power of visualisation tools to integrate data and to communicate the implications of these tradeoffs was discussed by **Dr James Felli**, *Research Fellow, Eli Lilly & Co, USA*.

Using the integrated computing system Mathematica® **Dr Mark Walderhaug**, *Associate Office Director for Risk Assessment CBER, Food and Drug Administration, USA* and colleagues have developed a theoretical model that represents the benefit-risk-uncertainty profile of a medical product, integrating and unifying data on multiple properties and allowing the visual comparison of the benefits and risks of two products.

The Medical Products Agency (MPA) of Sweden produces national product monographs containing unbiased information regarding new medicines that are used by health technology assessors and the health authorities to inform therapeutic and reimbursement decisions. **Dr Jane Ahlqvist-Rastad**, *Senior Expert, MPA*, presented case studies of two MPA product monographs that demonstrated negative benefit-risk balances and the consequences of those evaluations.

To learn about the ways in which benefit-risk is communicated to patients and healthcare professionals (HCPs), **Professor Sam Salek**, *Professor of Pharmacoepidemiology, Cardiff University*, posted the *Benefit-Risk Communication Index* to a random sampling of physicians, nurses and pharmacists. More than half of the 1167 responding HCPs felt that a more systematic approach to risk communication by the government and companies is needed. Professor Salek's recommendations include additional research and training in the communication of benefit-risk to HCPs and by HCPs to their patients and the adoption of a systematic approach to risk communication by the government and industry.

BRIC (Part I)



Professor Ruth Day, *Director, Medical Cognition Laboratory, Duke University, USA*, explained that barriers to effective BR communication such as heavy loads of complex, technical information lead to “cognitive inaccessibility”. These can be easily overcome with small changes to written communication using techniques such as the *chunking*, *clustering* and *coding*, resulting in major positive consequences for comprehension, memory and decision making.

Describing her experience of enhancing pharmacovigilance in clinical practice with community pharmacists collecting data from their patients' perspective in real clinical practice, **Professor Sylvie Perreault**, *Faculty of Pharmacy, University of Montreal, Canada*, explained that this type of active surveillance programme, which builds upon multiple existing resources, can potentially monitor clinical signs and symptoms, determine whether anticipated health outcomes are attained and capture information regarding positive or negative unanticipated health-related events.

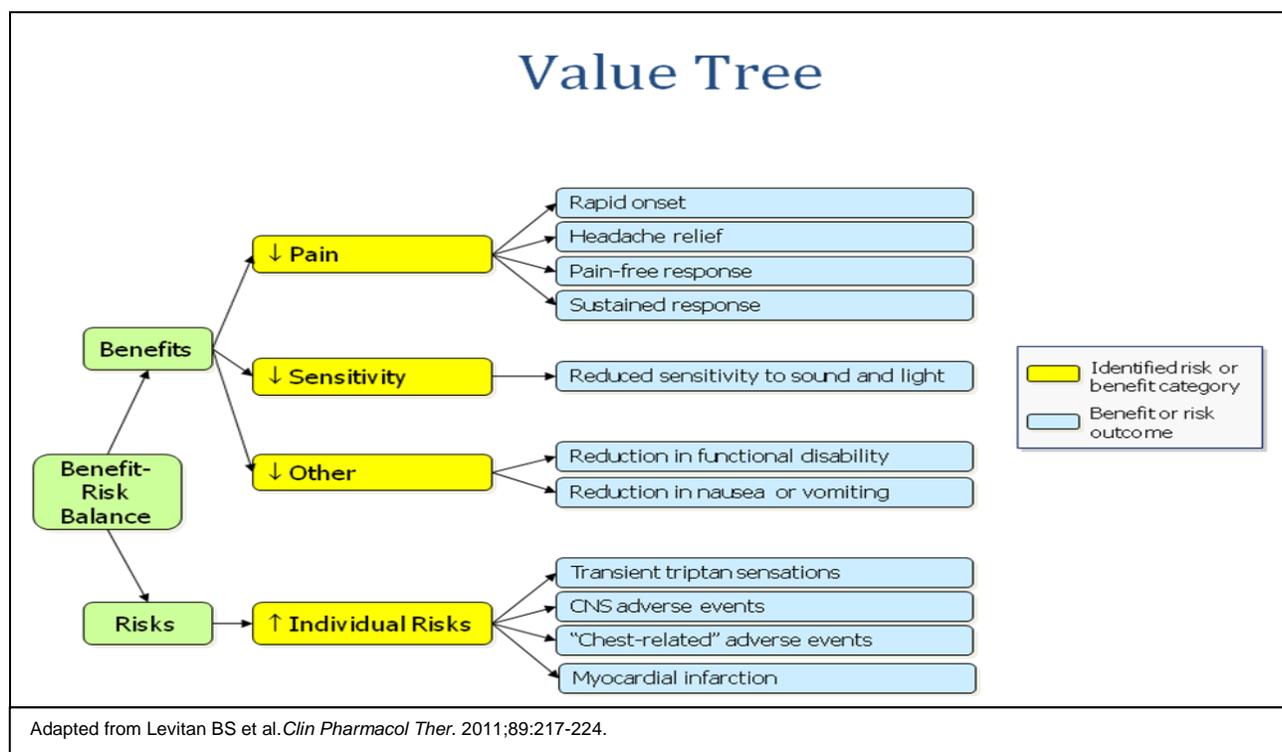
Professor Stuart Walker, *Founder, Centre for Innovation in Regulatory Science* concluded the presentations, informing Workshop participants that next year's annual benefit-risk Workshop would likely be somewhat extended to accommodate the vast influx of new material emerging on this important topic. He additionally reported that seven companies and seven agencies have expressed interest in joining the CIRS-sponsored Benefit-Risk Taskforce. The goal of this group will be the facilitation of productivity and the avoidance of duplicative efforts through ongoing knowledge sharing and the dissemination of reports and other learnings in the critical field of the benefit- risk assessment of medicines.

Session: Syndicate Discussions

At prior CIRS Workshops, participants agreed that an efficient way to test the relevance of proposed BR frameworks would be by working through real-life scenarios with different stakeholders and products. This practical approach was shown in our 2010 Workshop to facilitate the identification of the best practices among each of these methodologies. Syndicate groups at this year's Workshop conducted a structured benefit-risk discussion as to whether a hypothetical triptan submitted for approval for the acute treatment of migraine in patients with one or two cardiovascular risk factors should be approved at a high or low dosage or not at all. The scenarios were designed by **Dr Bennett Levitan**, *Director, Epidemiology, Johnson & Johnson PRD, USA*, who as a member of the PhRMA BRAT, derived the scenarios from the considerable body of original work and research he and the BRAT group conducted to refine a BR framework model.

Before the discussions, Dr Levitan provided background information regarding triptans and migraine as well as an orientation to data on the mock triptan. Key aspects of the hypothetical product's BR profile were provided by in the form of a value tree. Each syndicate used a structured format relating to the same scenario: two syndicates used a qualitative approach and one syndicate was tasked with using a quantitative approach, which was constructed and run by **Dr Lawrence D. Phillips**, *Professor, London School of Economics and Political Science, UK*, who had collaborated with Dr Levitan prior to the Workshop.

The results of these Syndicates indicated that by using either qualitative or quantitative methodologies, a decision process that was informed by the patient's perspective, could reach a consistent conclusion whose rationale could be communicated clearly and transparently to other stakeholders.



Key Points from the Syndicate Discussion 1: A Qualitative Approach from Regulators' Perspective

- To this group, defining and focusing on the decision context was key. That is, it was essential to clearly articulate and agree on the research question and meticulously delineate the target population with appropriate granularity.
- Patient input was also determined to be vital. Participants repeatedly turned to “patients” in the group (those who had been treated for migraine) to inform their thinking process. Most importantly, this information altered decision framing and was particularly important in providing the patient’s perspective on the benefits and harms. Patients were typically interested in benefits not usually considered to be the primary outcomes by the regulators or sponsors and were always more willing to take risks that exceeded those assumed by the developers or regulators.
- Visualisation tools, such as value trees, tables of key benefits and Forest plots helped to structure discussions, by providing a focus on critical issues and identifying gaps. It was determined that these tools, which have been used to inform regulatory Advisory Committee decisions, can also help to expose overlapping benefits and harms, provide a succinct summary of key information needed to make the BR decisions and facilitate sensitivity analyses. The value tree, in particular, facilitated comprehension and communication, working within the constraints for the average 5-7 item cognitive limit of most reviewers. In addition the tree-focused questions allowed issues to surface, supported the selection of the primary benefit to be evaluated and exposed the need for a clear label lexicon. Visualisation tools, however, do require training for optimal use and interpretation and will benefit from ongoing refinement.
- Syndicate 1 decided that implicit and explicit weighting is an inescapable aspect of benefit-risk decision making. Although a simple and accessible approach may suffice, more developmental work is required to construct a widely acceptable BR framework. Subjective interpretations of harms and benefits remain an issue.
- Conclusion: It was the consensus of this Syndicate that the triptan should be approved, with at least one participant feeling that the use of both proposed doses was appropriate.

Key Points from the Syndicate Discussion 2: A Qualitative Approach from an Industry Perspective

- Certain benefits and risks provided in the case study were removed or retained in the value tree by this Syndicate. For example, “Pain-Free Response” was removed because participants who were also migraine sufferers in this group noted that the background state of pain in migraine is such that pain-free status might not be expected. “Sustained Response” was maintained because of its importance to predict pending disability (patient perspective) and additional emergency room visits (physician perspective).
- The Syndicate indicated that having highly informed, health literate “patients” in an atmosphere of free discussion, with excellent facilitation greatly optimised the exercise. The weighting exercise went quickly and the group was reasonably comfortable with the methodology. Real-time tabular and graphic feedback was extremely valuable for the assessment.

- According to this group, the assessment exercise could be improved with the benefit of having had more context and discussion regarding the disease state and treatment options. Moreover, the group felt that it would have been optimal to have had a representative from clinical development present and Medical Affairs input would be required to assist with the eventual communication of the assessment to regulators, patients and healthcare professionals.
- Conclusion: In the opinion of this Syndicate, the low-dose version of the triptan would be recommended for approval for patients who do not respond to NSAIDs, as this population has high unmet medical need. Data for migraine relief and functional improvement were both compelling enough to outweigh the risks. Although myocardial infarction (MI) is a serious outcome, its incidence in the triptan group compared with those receiving NSAIDs was considered to be very low, and considered a potentially manageable risk if subgroup data identifying patients with highest risk and benefit were available. A robust risk management plan and dose titration labelling would be recommended.
- The high-dose version of the triptan would also be recommended for approval. The tradeoffs in this evaluation were very similar to those for the low-dose version. Although additional therapeutic benefit would be expected in patients receiving the higher dose, the risk of MI would also be expected to increase.

Key Points from the Syndicate Discussion 3: A Quantitative Approach

- This syndicate agreed that use of the value tree was the most important part of the decision-making process. There were more favourable than unfavourable effects listed, however; although many of the favourable effects were interrelated. Three out of four unfavourable effects were “tolerability issues” while only one was considered to be a serious adverse event (MI).
- In the weighting process the group first identified the range of treatment effects. For each effect, a swing-weight was assigned based on the added preference value. These values were based on which attributes were viewed as clinically important, meaningful or valuable, especially from a patient’s perspective, with several syndicate participants who had experienced migraines provided input as “patients.”
- The main benefit-risk trade-off was between reduction of functional disability and MI. For unfavourable effects, the three tolerability effects were assigned a very low swing weight, whilst MI was assigned a swing weight of 100. This evaluation assumed a linear value function between effect size and weighting for all favourable and unfavourable effects.
- In communicating its rationale for the assessment to stakeholders, the Syndicate explained its methodology, including inclusion of weighting based on patients’ feedback. Prescribing physicians would require some education on interpreting methodology. Results could be simplified for patients by providing a quantification of the trade-off showing the number of migraines improved with the triptan compared with NSAIDs and number of MIs that would occur with triptan compared with NSAIDs, based on 100 patients treated for 1 year.
- Conclusion: Based on weighting scores, both doses of the triptan were deemed approvable by this Syndicate group.

Conclusions

- Visualisation tools help to focus benefit-risk discussions on critical issues, identifying gaps and exposing overlapping benefits and harms and providing a succinct summary of the information needed to make benefit risk decisions.
- In addition to transparency, consistency and communication, articulating and reaching consensus on research questions and meticulously delineating target populations are essential to benefit-risk evaluation.
- For conditions involving subjective benefits and harms, patient input is invaluable in informing the thinking of decision makers such as regulators and researchers.
- Communicating decision rationales reached through multi-criteria decision analysis to prescribing physicians may require some education on methodology. Results could be simplified for patients by providing a graphically displayed quantification of trade-offs.
- Work in the development of an internationally accepted approach for the systematic, routine and standardised documentation of decision making in the benefit-risk assessment of medicines is ongoing on many fronts; the CIRS-sponsored Benefit-Risk Taskforce is being formed to facilitate productivity and the avoid duplicative efforts though ongoing knowledge sharing.

SPECIAL THANKS TO

The Workshop Chairs

Prof Bruno Flamion, Chairman, Belgian Committee for Reimbursement of Medicines, Belgian National Institute for Health and Disability Insurance

Prof Sir Alasdair Breckenridge, Chairman, Medicines and Healthcare products Regulatory Agency, UK

Presenters

Prof Hans-Georg Eichler, Senior Medical Officer, European Medicines Agency

Prof Ruth Day, Director, Medical Cognition Laboratory, Duke University, USA

Dr Theresa Mullin, Director, Office of Planning and Informatics, CDER, Food and Drug Administration

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Prof Stuart Walker, Founder, Centre for Innovation in Regulatory Science

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Syndicate 2: Dr Filip Mussen, Senior Director, Global Regulatory Affairs Neurosciences, Janssen R&D, Belgium

Dr Diana Hughes, Vice President, Worldwide Safety Strategy, Primary Care Business Unit Lead, Pfizer Inc, USA

Syndicate 3: Prof Hans-Georg Eichler, Senior Medical Officer, European Medicines Agency

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Dr James Felli, Research Fellow, Eli Lilly & Co, USA

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