Building the Benefit-Risk Toolbox:

Are there enough common elements across the different methodologies to enable a consensus on a scientifically acceptable framework for making benefit-risk decisions?

WORKSHOP SYNOPSIS
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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 20 – 21 June 2021, in Washington, DC. A complete Workshop Report including full presentation summaries and syndicate recommendations will be forthcoming.
Background to the Workshop

A survey undertaken by CIRS in 2011 identified the biggest barrier to implementing a formal benefit-risk framework within companies and agencies as the lack of a scientifically accepted model. This barrier exists despite the fact that there is generally good agreement as to the need and function of an appropriate framework as well as to the perceived advantages for implementing a framework as a tool for communication, structured discussion and enhancing transparency and accountability. A consensus is also starting to emerge that rather than a single benefit-risk methodology, a toolbox of methodologies derived from a common framework may be required that are flexible and adaptable for different situations (Figure 1). However, for this concept to be taken forward, agreement must be reached amongst the major stakeholders on a general scientifically acceptable benefit-risk framework.

Figure 1. A common framework facilitates the development of flexible methodologies.

Over the last five years, a number of initiatives have emerged from regulatory agencies such as the EMA, FDA and members of the Consortium on Benefit-Risk Assessment (COBRA) and from individual companies and industry consortia such as the Benefit-Risk Action Team. These initiatives have developed qualitative and semi-quantitative methodologies, all of which have a number of common elements and which are being undertaken as pilot projects to test their application in real-world cases. In 2012, as the development of benefit-risk methodologies moves forward through these initiatives, this Workshop was designed to bring together the various stakeholders to discuss case studies in the context of the common elements of the various methodologies. The question is can the stakeholders agree on a scientifically acceptable overarching framework for the benefit-risk assessment of medicines?

Workshop Objectives

- **Discuss the progress** made since 2011 by different groups on defining and implementing a benefit-risk framework and specific methodologies within their organisations

- **Further the thinking as to what can be learnt** from case studies and from each other about the different methodologies that can be used to make explicit benefit-risk decisions?

- **Identify the common elements** across methodologies and **discuss how to achieve a consensus** on a scientifically acceptable overarching framework for making benefit-risk decisions
Introduction

Lawrence Liberti, Executive Director, CIRS, London, opened the Workshop with an update on the evolution of benefit-risk assessment activities at CIRS. CIRS undertakes its various benefit-risk assessment activities under its UMBRA – Unified Methodologies for Benefit-Risk Assessment - initiative. UMBRA provides the platform for the development, assessment, implementation and ongoing refinement of an internationally acceptable, structured, systematic, standardised approach for the benefit-risk assessment of medicines (Figure 2). CIRS established the UMBRA initiative to serve as the information-sharing and -coordinating entity for global benefit-risk activities, to work cooperatively with all stakeholders to develop the science and art of benefit-risk decision making and communication and to help centralise the development and dissemination of a globally acceptable framework. To this end, CIRS will look for best practices from which companies, agencies and other stakeholders can develop and evolve a tool box of specialised methodologies to make and communicate benefit-risk assessments.

Figure 2. The UMBRA initiative: a neutral platform for benefit-risk activities.

Key points from presentations

SESSION: DEVELOPMENT OF A FRAMEWORK FOR BENEFIT-RISK: WHAT HAS BEEN LEARNT THROUGH CASE STUDIES?

Day 1 Chairman, Dr Murray Lumpkin, Commissioner’s Senior Advisor and Representative for Global Issues, US Food and Drug Administration (FDA) welcomed participants to the annual CIRS Benefit-Risk Workshop in Washington DC, remarking that as this Workshop took place, legislators in Washington were making final refinements to the fifth Prescription Drug User Fee Act (PDUFA V) submitted for consideration by the FDA. He invited one of the Act’s primary developers, Dr Theresa Mullin, Director, Office of Planning and Informatics, Center for Drug Evaluation and Research (CDER), FDA, USA, to further discuss this legislation.

Dr Mullin explained that PDUFA provides more than 60% of support for the review of drugs in the United States. It has been recognised within the FDA that a framework that accurately and concisely describes benefit and risk considerations would help reviewers apply a structured approach in regulatory decision making and product assessment and a more systematic and open discussion with all stakeholders. In particular, informed patients could provide valuable insights.
regarding a given disease and the potential gaps or limitations in available therapies. Accordingly, PDUFA V includes recommendations to develop and implement a plan to integrate a benefit-risk framework in the drug review process and to conduct public meetings with relevant patient advocacy communities within specific disease states.

In addition to the benefit-risk framework being developed at the US FDA, Dr Tim Garnett, Chief Medical Officer and Senior Vice President, Eli Lilly and Company, USA, cited three other frameworks that represent a significant step forward in developing a consistent, transparent and structured approach to benefit-risk assessment: those developed by the European Medicines Agency (EMA), the Consortium on Benefit-Risk Assessment (COBRA) and the Benefit-Risk Action Team (BRAT). Each of these four frameworks recognises that a structured and systematic process plays an essential and fundamental role in assisting and improving decision making. Dr Garnett called for next steps that included the accumulation of additional stakeholder input, collaboration toward a common framework and the ongoing use of a forum such as the CIRS-coordinated Benefit-Risk Taskforce to share implementation experiences and best practices.

Calling the framework being developed by the EMA a simple qualitative tool, Prof Hans-Georg Eichler, Senior Medical Officer, European Medicines Agency considers implementation of such tools among the next steps in the development of a benefit-risk “tool box.” After this implementation, he recommended that stakeholders explore and familiarise assessors and decision makers with more complex quantitative tools and address how the values of the various stakeholders are being considered in benefit-risk assessments by developing methods that combine the technical expertise of regulatory scientists and patients to address the diverse spectrum of value judgements.

Australia’s Therapeutic Goods Administration (TGA), Singapore’s Health Sciences Authority (HSA), Health Canada and Swissmedic are the four agencies making up the Consortium on Benefit-Risk Assessment (COBRA). Dr Jason Ferla, Director, Prescription Medicines Clinical Unit 3, Office of Medicines Authorisation, Therapeutic Goods Administration, Australia provided an update on the work of COBRA. This aims to develop a systematic qualitative approach for the benefit-risk assessment of medicines in order to facilitate the opportunity for joint or shared reviews by the four agencies. Having developed a framework “proforma”, the consortium is currently reviewing the results of a retrospective study employing its use (Figure 3) with plans for making the template more reflective of actual practice, integrating the ability to graphically visualise the data and initiating a prospective study.

Figure 3. The COBRA benefit-risk framework has been tested in a retrospective study.

Dr Francesco Pignatti, Head of Section Oncology Safety and Efficacy of Medicines, European Medicines Agency reported on an EMA field test of PrOACT-URL, a qualitative framework for structured decision making. In this test, the
identified **Problem** was medullary thyroid cancer; the **Objectives** were to determine the effect of treatment on overall and progression-free survival and toxicity. The **Alternatives** (available therapies) were vandetanib and placebo and the **Consequences** of the treatments were presented in an effects table (a tabular summary of the favourable and unfavourable events associated with treatment) with **Tradeoffs** determined through swing weighting of those events. Data were subjected to a sensitivity analysis to determine the level of **Uncertainty**. **Risk tolerance** for vandetanib was reflected in the restricted approval granted to the product for use in a limited controlled set of patients. **Links** to other decisions will be determined by the long-term use of the effects table in regulatory assessments. The EMA hopes to implement the effects table through a pilot programme to determine if its use is more generally fit for purpose.

Field tests of the US FDA benefit-risk framework are ongoing for six products being assessed in the Center for Drug Evaluation and Research (CDER). **Patrick Frey**, **Director, Office of Planning and Analysis, CDER, FDA, USA** said that it is hoped that these tests will help evaluate and further refine the framework and support its implementation into the CDER review process. Additional FDA benefit-risk initiatives planned as part of PDUFA V include the publication of a five-year plan for the implementation of the framework and an evaluation of its impact as well as public workshops on benefit-risk from the perspective of regulators and other stakeholders.

A case study of the use of the benefit-risk framework developed by the Benefit-Risk Action Team (BRAT) in the evaluation of rivaroxaban, a factor Xa inhibitor, revealed that such methodology can add rigor and transparency to the decision-making process, seems appropriate for most benefit-risk decisions and can be easily used, especially in regulatory settings such as FDA Advisory Committee meetings (Figure 4). Although progress has been made through the development of this methodology and others, **Dr Filip Mussen**, **Head, Global Labeling Center of Excellence, Janssen Research and Development, Belgium**, believes that there is currently no common set of terms, definitions or agreed methodology for capturing "values" that can be applied in these methodologies and additional discussion, application and piloting is required for the further development of globally acceptable methodologies.

![Risk Differences for Composite Endpoints and Components Safety/On-Treatment](image)

**Figure 4.** A case study of the BRAT framework in evaluation of a factor Xa inhibitor.

The objective of the EMA Work Package V is to develop methods for use in benefit-risk assessment, including both the underpinning modelling and the presentation of the results, with a particular emphasis on graphical methods. In fulfilment of that objective **Dr Diana Hughes**, **Vice President, Worldwide Safety Strategy, Primary Care Business Unit Lead, Pfizer Inc, USA** reported that the members of the Innovative Medicine Initiative Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium (IMI PROTECT) reviewed benefit-risk frameworks and tested a
first wave of thirteen methodologies using a case study approach. The group deliberately selected more complex cases for evaluation to stretch the use of the methodologies and explore the use of visual representation. A summary report being developed will critically appraise the methodologies and a second wave of case studies has begun.

**Jean Mossman, Policy Lead, European Federation of Neurological Associations** reminded Workshop participants that in addition to the risk of adverse effects from medication, illness can represent may types of risk to patients, all of which may influence their decision making. These include the risk of not getting the correct diagnosis or of not getting a diagnosis in a timely manner; the risk of not getting treatment, of not getting treatment from an expert or even of getting the wrong treatment. Patients also run the risk of not taking the treatment as scheduled. In fact, for a variety of reasons, patients often do not take medicines as prescribed and industry, regulators and clinicians should work harder to help patients understand the potential benefits and risk of taking – or not taking medicines (Figure 5). They should also work harder at understanding that the benefits of treatment, important to patients, may not be captured as clinical trial endpoints and ensuring that the people who must live every day with the potential of associated benefits and harms of medicines are involved in decisions about those medicines throughout the product lifecycle. Perhaps the most obvious consideration is that patients should be informed of the results of their input and of the ongoing status of a therapy’s development, as they often feel left out of the information loop despite their key contribution of time and effort to research programmes.

![Do patients understand risk as it is currently presented?](image)

*Figure 5. Many patients need assistance in the interpretation of the benefits and risks of new medicines.*

Patients and FDA regulators are engaged early and often when the Amyotrophic Lateral Sclerosis (ALS) Association is developing new clinical or preclinical trials. **Dr Lucie Bruijn, Chief Scientist, ALS Association, USA** explained that the work of the ALS association is divided into research, public policy and care services, with patients at the centre. The Association’s Clinical Research Learning Program, for example, is geared toward patients to help ameliorate concerns that benefits of certain treatments and study results may be over-interpreted. ALS affects 30,000 Americans at any given time; worldwide, there are two cases per 100,000. Most patients die within two to five years of diagnosis. However, recent years have seen an improved understanding of disease and care, and one therapy has already been approved and many others are in the development pipeline. The patient’s role in helping to develop novel ALS therapies can serve as a model for other disease areas.

In her second Workshop presentation, **Dr Diana Hughes** provided an industry perspective on involving patients in benefit-risk assessments, emphasising that patients want to be heard and to have their perspectives incorporated into the
decision-making process. Work toward that end within the pharmaceutical industry is ongoing, with organised patient input to help identify key facets of disease targets, to inform on the collection of patient-centric views for development programmes and to provide insights into the assessment of the disease and the symptoms that are of most value to patients. For their part, patients and patient advocacy groups recognise the need to better organise, establish credibility and productively contribute to the discussion based on scientific merits and to develop an understanding of the growing role of health technology assessment in the availability of novel medicines. Next steps should include continued outreach to and collaboration with advocacy groups; the formation of an industry consortium to understand unmet medical need and patient experience; the development of patient educational programmes to help elicit information on the most relevant aspects of the disease and methodological work to advance a common approach to valuing and weighting (relative importance).

Patient input regarding the real-world effectiveness and tolerability of currently available therapy can help to establish if an unmet medical need exists. Furthermore, the largely untapped ability of patients to provide insights and help identify important dimensions of benefit not adequately captured in current studies points to the need for validated tools for patient-reported outcomes (PROs; Figure 6). Dr Theresa Mullin reiterated the FDA’s ongoing commitment to enable more patient-focused drug development, illustrated by such initiatives as its Patient Representative Program in which selected patients receive training for participation in disease state advisory committees and involvement in the drug review process. Among several patient-centred activities planned for 2012, the FDA expects to develop a basic roadmap that could be used by patient groups interested in pursuing the development of PRO measures in a specific disease area.

![Patient-focused development diagram](image)

**Figure 6.** Patients can help establish unmet medical need and identify patient-relevant trial endpoints.

Although there is an increasing use of decision-support frameworks including benefit-risk frameworks as well as simulation and modelling to aid decision-making in drug development, this process can be subjective and as such is influenced by an individual’s knowledge, ability and motivation. As part of a doctoral research programme, under the sponsorship of the Welsh School of Pharmacy at Cardiff University and CIRS, Ronan Donelan, Head of Regulatory Affairs EMEA and ANZ, Quintiles, Ireland is investigating how individuals and organisations manage decision making within the drug development arena. The Quality of Decision-Making Orientation Scheme (QoDoS) is an instrument being developed in the doctoral programme through qualitative research and validation with key opinion leaders, regulatory agencies, pharmaceutical companies and contract research organisations, which aims to improve the linkage of the science and art components of decision making (Figure 7).
**QoDoS: Study methodology overview**

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
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<tbody>
<tr>
<td>Recognition of paucity of understanding on quality decision-making</td>
<td>Supervise/peer discussion and research strategy definition</td>
</tr>
<tr>
<td>1st round construct development and item generation</td>
<td>Transcription, coding, analysis, themes (manual and Nvivo)</td>
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<tr>
<td>1st version of Quality Instrument (QoDoS)</td>
<td>Saturation level (n = 30)</td>
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<tr>
<td>QoDoS Tool</td>
<td>Conduct of semi-structured interviews with KOLs</td>
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<td>Refinement of interview checklist</td>
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<td>Content validity and panel review</td>
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<td>Washington Cohort</td>
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<td>QoDoS Instrument (76 items)</td>
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<td><strong>Cohort 3Q2012</strong></td>
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**Figure 7. Schema for developing the QDos tool.**

At GlaxoSmithKline (GSK) as at other major pharmaceutical companies, complex decisions are made at multiple levels on a continual basis. **Dr Paul Huckle, Chief Regulatory Officer, GlaxoSmithKline, USA** described the key factors that assist industry in meeting this challenge and ensuring good decision making, including clarity of accountability, timeliness, and the establishment of mechanisms to ensure objectivity such as peer review by specialised advisory groups. Most importantly, consistency of decision making at GSK is accomplished through adherence to its corporate values of patient focus, transparency, respect and integrity.

Sponsors and regulators have committed to safeguard public health through the formal assessment of the benefit-risk balance of medicines. **Prof Sir Alasdair Breckenridge, Chairman, Medicines and Healthcare products Regulatory Agency, UK** reported that there has been a convergence of thought by global regulators regarding the necessity to make this assessment an ongoing process throughout a medicine’s lifecycle. For example, the European Pharmacovigilance regulation in force as of July 2012 emphasise the importance of ongoing risk management plans for all newly approved products, improve the legal basis for post-authorisation studies of safety and effectiveness and seek to enhance transparency of and access to long-term safety data. Similarly, the US FDA benefit-risk assessment management plans are now part of regulatory submissions initiated by sponsors of new drugs and must be approved by FDA and updated over the life cycle of the medicine.

According to **Day 2 Chairman, Dr Frank Rockhold, Senior Vice President, Global Clinical Safety and Pharmacovigilance, GlaxoSmithKline, USA**, the content of the first day’s presentations and discussions were a good preparation for the Syndicate discussions that would occur on day 2. That is, irrespective of whether a qualitative or semi-quantitative methodology is used, stakeholders in the development of medicines have agreed that a structured, disciplined thought process is needed to apply the right information and perspectives to benefit-risk decisions.

Considerations in methodologies to assess benefit-risk in Canada were presented by **Barbara Sabourin, Director General, Therapeutic Products Directorate, Health Canada** who provided the regulatory viewpoint and **Dr Chander Sehgal, Director of the Common Drug Review (CDR) program, Canadian Agency for Drugs and Technologies in Health**.
(CADTH), who discussed the health technology assessment perspective. Ms Sabourin explained that evaluation processes at Health Canada are continuing to evolve as they seek to meet the challenges presented by the need for more rigorous, analytical standards and to desire for consistency of decision processes by developing a qualitative or semi-quantitative framework for benefit-risk analysis. The agency has also embarked on a programme of increasing collaboration with CADTH, including shared information and understanding of requirements.

Dr Sehgal said that whilst regulators evaluate safety, efficacy and quality, with comparisons frequently solely made to placebos, health technology assessors must evaluate that medicine’s comparative effectiveness, cost and cost-effectiveness and relevance to patient input compared with the best publicly funded alternative. Indeed, patient input plays an important role in CADTH evaluations and this input is reflected in CADTH recommendations to Canadian payer agencies (Figure 8). Future CADTH plans include making CDR review reports publicly available and the exploration of parallel review mechanisms with Health Canada.

![How Patient Input Evidence is Used](image)

**Figure 8.** Patient input is central to CADTH recommendations.

Prof Sir Alasdair Breckenridge, informed the group of the activities of the CIRS Benefit-Risk Task Force. Chaired by Sir Alasdair, the Taskforce comprises representatives from all the major benefit-risk initiatives, including eight regulatory agencies and six pharmaceutical companies. Its purpose is to facilitate knowledge exchange in the area of the benefit-risk and to make recommendations for workshops, surveys and research that should be undertaken to develop the appropriate toolbox for benefit-risk assessment.

A final reflection was provided by **CIRS founder Professor Stuart Walker** who reviewed the recent progress made in the area of benefit-risk and discussed CIRS activities planned for the near future including proposed pilots using the COBRA framework in select agencies in South East Asia and Europe. In addition, CIRS Senior Research Fellow Art Gertel will perform research in valuing and weighting benefit-risk parameters and a focussed technical Workshop has been planned for 13 December 2012 to discuss the research results and to develop relevant recommendations. Finally, CIRS will also seek to conduct two surveys, one of regulatory agencies and industry examining the role of patients in clinical development and regulatory assessment, and the second to elucidate the current use of benefit-risk assessment frameworks by health technology assessment agencies.
Session: Syndicate Discussions

Key Points from the Syndicate Discussion A

Can there be agreement or alignment on the various components that should be included in an ideal benefit-risk model or framework?

- **Differences and commonalities among stakeholders in benefit-risk decision making must be recognised and respected.** As in many past Syndicate discussions of harmonisation, this Syndicate agreed on the need for a common lexicon as a prerequisite to the alignment of the components of various benefit-risk frameworks. That is, a common understanding must be developed of the meanings of terms such as *framework*, *methodology*, *model* and *weighting*. However, because the acceptance of explicit weighting of benefit-risk parameters varies widely among agencies, differences in regional regulatory and cultural viewpoints must also be considered.

- **Methodology alignment should not be rushed.** Rather, upon agreement of a common framework, time should be allowed for pragmatic methodological approaches to be developed including adequate timing for feedback on best practices to emerge. It must be recognised that alignment will also require resources from many stakeholders and the establishment of processes for the management and archiving of information to support iterative improvements in techniques for benefit-risk assessments.

- **Uncertainty must be formally incorporated into the framework.** This parameter should not be limited solely to statistical uncertainty or to a single step of benefit-risk assessment, but should encompass the entire process.

A key milestone was accomplished at this Workshop: The syndicate proposed and the Workshop attendees agreed on the common elements of an overarching, internationally acceptable, standardised benefit-risk framework (Figure 9). Furthermore, this framework was endorsed following the Workshop by the Benefit-risk Taskforce and will serve as the ongoing basis for discussions around the development of novel, dynamic methodological tools to address the diverse needs of benefit-risk assessment throughout a product’s lifecycle by diverse stakeholders.

**Common Elements of the Core B-R Framework**

![Diagram of Common Elements of the Core B-R Framework](image)

**Figure 9. The 2012 UMBRA benefit-risk framework**
Key Points from the Syndicate Discussion B

What are the challenges to companies and agencies in making quality decisions in benefit-risk assessments?

- Internal organisational challenges to making quality decisions that are specific to benefit-risk decisions include difficulties inherent in valuing and weighting specific elements in the decisions, in communicating problem statements and in defining or explaining uncertainties around specific benefits and harms.

- It should be remembered that stakeholders may have incentives that differ according to their responsibilities and be influenced by contexts that may be institutional, regional or global. However, Syndicate members agreed that regardless of individual perspectives or contexts, these decision makers must apply validated decision tools that are appropriate to individual circumstances and to the stage of the medicine’s life cycle.

What are the principles, practices, and elements that companies and agencies can build into a quality decision-making process?

- It was the consensus of this group that benefit-risk evaluators need to learn from prior decisions and experiences. Processes must be transparent, documented and communicated. Training supported by standard operating procedure documents and guidelines is also key. Organisational roles and responsibilities need to be clearly defined, with a person designated as accountable for senior decision making coupled with a defined escalation process.

- Although a common framework encourages standard decision making, independent objective points of view within an organisation should be encouraged and a “devil’s advocate” can be assigned to challenge assumptions or proposals. Teams need to offer a primary solution but an accepting environment should be created for alternative strategies and out-of-the-box ideas. It has been the experience of members of the group that analysis of such alternative options often leads to better decisions. The long-term impact of decisions should be considered in addition to short-term effects.

How might organisations measure the quality of their decision making?

- Quality can be measured based on a comparison of the desired versus the actual impact of a decision, and by evaluating adherence to process. A repetition of the analysis over time verifies or qualifies initial decisions and demonstrates the value of the process.

- Asking the right questions up-front allows the development of a question database that informs good-quality decisions. Decisions should also include a demonstration of the rationale.

Key Points from the Syndicate Discussion C

When and how should patients be involved and what would facilitate their involvement with regard to the benefit-risk assessment of new medicines?

- Along with other Workshop Syndicates, this Syndicate agreed that patient engagement should occur throughout the development of medicines. However, patient advocacy groups report that engagement has been intermittent at best. More effective forums are needed for industry, regulators, academics, and payers to hear the voice of the patient.
• The content, format and timing of questions for patients need to be clarified. Examples of questions that may be appropriate include:
  o What matters to you?
  o How can we measure that reliably?
  o What benefits and risks are you willing to trade?
  o What do you want to tell us?

• Industry’s engagement with patients through its commercial divisions has created a negative perception of the potential influence of the Marketing Department. Sponsors need to ensure that when sponsorship of patient groups is involved, patient advocacy is separated from product advocacy.

• Clinical development often relies on well-established endpoints, but the group questioned whether these adequately or correctly address patients’ needs. New endpoints and methodologies for their development and validation must be considered to address the patient voice in the development process. The regulatory and HTA implications of using such PROs need to be assessed during the earliest phases of a medicine’s development.

Panel Discussion of Syndicate Results: Key points

• Harmonisation
  o Existing benefit-risk approaches have enough commonalities that their alignment and the development of a common framework was accepted by the Workshop participants.
  o The common framework such as the UMBRA Framework developed at this Workshop and by the benefit-risk Taskforce provides a solid basis for the ongoing evolution of novel assessment methodological tools.
  o While most tools now rely on descriptive or qualitative assessments, it was noted that the use of varying supplementary quantitative models and elements, especially quantitative visualisation tools, can be considered for more complex evaluations. However, others feel that complex issues do not necessarily require complex decision-making methodologies. Rather, the use of simple tools such as an effects table can serve as the basis for an organised and structured benefit-risk discussion.

• Benefit-risk frameworks and industry
  o Industry has accepted the need for benefit-risk methodologies based on a common framework, and these methodologies should continue to be developed through consortia to avoid duplication of effort and to encourage shared learnings.

• Patient input
  o Rules of engagement with patients must be established to avoid misperceptions around conflict of interest and to ensure a methodology for consistent, scheduled and balanced input.
  o Patients should be informed of the results of their input as they often feel left out of the loop when they contribute time and effort to research programmes.
  o Patients will benefit from education regarding the inherent nature of uncertainty in benefit-risk decisions.
  o Successful patient input into the development, regulation and coverage of new medicines will be directly connected to the use of the most clinically relevant patient-reported outcomes as part of clinical trial design.
  o The value of patient input appears implicit, but needs to be demonstrated to a wider audience through further research and communication.
SPECIAL THANKS TO

The Workshop Chairs
Dr Murray Lumpkin, Commissioner’s Senior Advisor and Representative for Global Issues, US Food and Drug Administration

Dr Frank Rockhold, Senior Vice President, Global Clinical Safety and Pharmacovigilance, GlaxoSmithKline, USA

Dr Chander Sehgal, Director of the CADTH Common Drug Review program, Canadian Agency for Drugs and Technologies in Health

Presenters
Dr Theresa Mullin, Director, Office of Planning and Informatics, Center for Drug Evaluation and Research, Food and Drug Administration, USA

Dr Tim Garnett, Chief Medical Officer and Senior Vice President, Eli Lilly and Company, USA

Dr Frank Rockhold, Senior Vice President, Global Clinical Safety and Pharmacovigilance, GlaxoSmithKline, USA

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

Dr Chander Sehgal, Director of the CADTH Common Drug Review program, Canadian Agency for Drugs and Technologies in Health

Dr Jason Ferla, Director, Prescription Medicines Clinical Unit 3, Office of Medicines Authorisation, Therapeutic Goods Administration, Australia

Dr Francesco Pignatti, Head of Section Oncology Safety and Efficacy of Medicines, European Medicines Agency

The Syndicate Chairs
Syndicate 1: Prof Sir Alasdair Breckenridge, Chairman, Medicines and Healthcare products Regulatory Agency, UK

Syndicate 2: Professor Sam Salek, Director, Centre for Socioeconomic Research, Cardiff University, UK

Syndicate 3: Dr Paul Huckle, Chief Regulatory Officer, GlaxoSmithKline, USA

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Syndicate 2: Dr Mark Goldberger, Divisional Vice President, Regulatory Policy and Intelligence, Abbott, USA

Syndicate 3: Dr Nadine Cohen, Senior Vice President, Regulatory Affairs, Biogen Idec, USA

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Dr Susan Welsh, Vice President, Global Pharmacovigilance and Epidemiology, Medical Safety Assessment Therapeutic Area Head - Head, Oncology & Immunology, Bristol-Myers Squibb, USA

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

Dr Theresa Mullin, Director, Office of Planning and Informatics, Center for Drug Evaluation and Research, Food and Drug Administration, USA

Jean Mossman, Policy Lead, European Federation of Neurological Associations

Dr Lucie Bruijn, Chief Scientist, ALS Association, USA

Ronan Donelan, Head of Regulatory Affairs EMEA and ANZ, Quintiles, Ireland

Dr Paul Huckle, Chief Regulatory Officer, GlaxoSmithKline, USA

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

Barbara Sabourin, Director General, Therapeutic Products Directorate, Health Canada

Jean Mossman, Policy Lead, European Federation of Neurological Associations
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Dr Jason Ferla, Director, Prescription Medicines Clinical Unit 3, TGA, Australia
Dr Huei-Xin Lou, Director, Pharmaceuticals and Biologics Branch, Pre-marketing Division, HSA, Singapore
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Dr Bennett Levitan, Director, Epidemiology, Johnson & Johnson, USA
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Dr Susan Welsh, VP, Global Pharmacovigilance and Epidemiology, Bristol-Myers Squibb

Professor Stuart Walker, Founder, CIRS
Lawrence Liberti, Executive Director, CIRS
Dr Neil McAuslane, Scientific Director, CIRS, Secretary to the Task Force
Art Gertel, Senior Research Fellow, CIRS

CIRS 2013 BENEFIT-RISK WORKSHOPS (TO BE CONFIRMED)

- **13-14 March**: Patient voice in clinical development: Can patients contribute to the benefit-risk assessment of new medicines? UK

- **20-21 June**: Implementing an internationally acceptable framework for the benefit-risk assessment of medicines: How close are we to this objective? Washington, DC, USA

- **2-3 October**: Utilisation of an agreed overarching benefit-risk decision framework by both HTA and regulatory agencies: Would this facilitate understanding of different outcomes? Germany