THE PATIENT VOICE IN CLINICAL DEVELOPMENT:

Can patients contribute to the benefit-risk assessment of new medicines?

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WORKSHOP REPORT

CIRS Centre for Innovation in Regulatory Science

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Section 1: Executive Summary

Background to the Workshop

As companies and agencies work on the development of methodologies for making benefit-risk decisions for new medicines as well as for communicating those decisions to stakeholders, there is a growing awareness that inclusion of perhaps the most important stakeholder voice, the patient, is a critical component to this work. This is true in the development phase when companies should ensure that they are developing medicines of value to patients as well as in the regulatory review timeframe, when there may be differences between what patients and regulatory agencies consider to be maximum acceptable risks and minimum acceptable efficacy.

The consensus developed at the April 2012 CIRS Workshop, *The Patient's Role in the Benefit-Risk Assessment for the Submission and Review of New Medicines* was that patients should be involved in providing information for benefit-risk decisions throughout the lifecycle of a medicine, including the early and late stages of development and the regulatory review. However, questions remain as to the appropriate methodologies for obtaining this information, whether the information should be at the disease or product level, the identity of the company personnel responsible for acquiring the information and regulators' and decision-makers' views regarding the integrity of data generated by companies for patients. In addition, other issues for discussion include methods for ensuring the separation of patient and product advocacy, the potential for industry and agency collaboration in patient issues and whether patient advocates represent all patients with a specific disease. This Workshop explored these issues by providing a perspective from various stakeholders in the development and review of new medicines with a particular emphasis on potential methodologies and opportunities and barriers to including patients' perspectives on benefits and risks at both the disease and product level.

Workshop Objectives

- **Identify key methodologies that are being used** to capture patient's needs in relation to benefits and risks by companies and regulators at both the disease and product level
- **Discuss the potential opportunities for utilisation of current and new approaches** as well as the hurdles in both acquiring patient's views and subsequently how these are being incorporated into the benefit-risk assessment of new medicines
- **Develop proposals for appropriate patient "voice" pathways in clinical development,** identifying which methodologies can be used to achieve scientifically acceptable approaches for including patients' perspectives in the construction of the benefit-risk decision

Introduction

CIRS Executive Director, **Lawrence Liberti**, welcomed Workshop participants to the second in a series of CIRS patient-focused Workshops, explaining that several of the recommendations made by participants of the first CIRS Patient Workshop in April 2012 would be incorporated into the agenda for this meeting, including discussions regarding the potential to develop an industry consortium in the precompetitive space to uncover patient priorities and look at patient-reported outcomes, the use of the Unified Methodologies for Benefit-Risk Assessment (UMBRA) standardised framework for assessing benefit-risk and a survey concerning ideas about patient involvement in medicines development.

Day 1 Chair, Dr Mary Baker, *President, European Brain Council*, reminded participants that people living with disease are a rich source of valuable information concerning illnesses and their treatments and she urged all healthcare stakeholders to make the best use of the insights that can be obtained through patient input into medicine development.

Key points from presentations

SESSION: THE INCLUSION OF PATIENTS' PERSPECTIVES IN UNDERSTANDING THEIR NEEDS IN TERMS OF BENEFITS AND RISKS AT THE DISEASE AND PRODUCT LEVEL

The Innovative Medicines Initiative (IMI) is the largest public-private partnership in life science today. In his Keynote Presentation, *Executive Director*, **Dr Michel Goldman** discussed some of the forty IMI projects that have been launched to date by consortia that include regulators, patient organisations, academia and pharmaceutical companies collaborating in the precompetitive space. The long-term goal of the organisation is to accelerate the access of patients to innovative medicines through the collaboration of all healthcare stakeholders, collaborations which include considerable contributions from patients either through active participation and input or the use of clinical data.

It is a time-consuming process to map the patient journey during the course of a disease, compiling information from multiple sources such as physician and patient/caregiver interviews and secondary research to gain a broad perspective on each key topic. But as **Robin Evers**, *Vice President, Worldwide Regulatory Strategy – Primary Care, Pfizer,* explained, the research allows companies to compile a deep understanding of their customers, the patients and their long-term goals and motivations and apply this knowledge to research and development efforts for new pharmacologic interventions, thereby creating value for the patient the payer, the regulatory authority and the companies themselves in terms of long-term sustainable investment.

Francesco Pignatti, *Head of Section Oncology Safety & Efficacy of Medicines, European Medicines Agency (EMA)* outlined the role of patients at the EMA, where today they are members of the EMA Management Board, responsible for governance and budget approval within the agency and also act as members of Scientific EMA Committees, advisors to the Committee for Medicinal Products for Human Use (CHMP), Scientific Advisory Groups and the Scientific Advice Working Party. However, whilst regulators are changing the ways in which decisions are made at the agency, examining the tools necessary to make all types of explicit and transparent decisions and seeking consensus as to the best methods for achieving collaboration among all stakeholders including patients, optimal methods for eliciting patient preferences without bias are yet to be determined and EMA regulators must continue to adapt to the use of variable methods and values in their decision making.

Discussing stakeholder collaboration in the precompetitive space, **Dr Frank W. Rockhold**, *Senior Vice President, Global Clinical Safety and Pharmacovigilance, GlaxoSmithKline* said that the methods for obtaining information about medicines and about the perspectives of patients living with disease and the ways to assess the information and communicate that assessment to patients should be considered in a non-competitive environment. All stakeholders would benefit from the alignment of these inputs and methodologies. Shared benefit-risk information could help industry create and regulate medicines and provide product information that more directly address patients' concerns. Shared information about medicines' benefits and risks could allow patients along with their healthcare providers to make decisions for their own health and wellness needs, based on a better understanding of the impact of disease and its treatment.

Patricia Pellier, *Vice President, EMA Regulatory Affairs, Celgene International* described the three objectives that industry has in their interaction with patients: understanding, support and involvement. To understand patients, the developers of medicines must obtain deep insight and learn the disease from patients' viewpoints. To support patients, industry must develop tools to facilitate understanding, interaction and awareness. To be better involved with patients, industry should continually provide information about the safe and effective use of its medicines throughout their development and life cycle and provide funding for disease advocacy and patient support organisations.

SESSION: WHAT ARE THE KEY METHODOLOGIES BEING ADVOCATED AT THE PRODUCT LEVEL TO ENSURE THAT THE PATIENT'S VOICE IS BEING HEARD IN CLINICAL DEVELOPMENT?

There are two methods for involving patients in the evaluation of benefit-risk in the development of new medicines currently being used by pharmaceutical companies, conjoint analysis, a survey-based method for determining the relative importance that individuals place on a defined set of disease or treatment outcomes and patient-reported outcomes, tools to collect

direct patient responses regarding treatment effects, health-related quality of life or other characteristics. **Dr Jamie Cross**, *Program Director Regulatory Affairs, Genentech Inc.* suggested other methods for industry to achieve a patient-centric operational model including the incorporation of formal opportunities for patient review of protocols prior to finalisation, the inclusion of the patients of community physicians in clinical trials and the enabling of community-based clinicians to participate in trials in remote locations through the use of video conferencing. Additionally, it is hoped that that using new technologies such as wearable devices to provide a feedback loop between patient and doctors, wireless digital imaging and micro-chipped pills to gather information from natural settings as opposed to the artificial construct of a traditional clinical trial will allow decision making that is informed by a more complete understanding of a product's real-world benefits and risks.

Prof Steffen Thirstrup, *Former Director of Licensing Division, Danish Health and Medicines Authority*, described patient involvement at the EMA, where significant inroads have been made in the involvement of consumers in decision making and where the agency liaises with representatives of 34 organisations who represent the interests of European patients and consumers. European legislation has specified that patients must be represented on the EMA Management Board, the Committee for Orphan Medicinal Products, the Paediatric Committee and the Committee for Advanced Therapies and the Pharmacovigilance Risk Assessment Committee. However, although there is regular patient participation in the Committee for Medicinal Products for Human Use (CHMP) as part of Scientific Advisory Groups and ad hoc expert meetings, there is no permanent patient representation in this group.

The value judgements that are part of the benefit-risk evaluation of new medicines are currently made by clinicians and regulators, who have received no special training that renders them more qualified to perform these evaluations than any other stakeholder in public health. In fact, it might be argued that patients rather than physicians or regulators are the best judge of their own welfare. **Dr. Reed Johnson**, *Distinguished Fellow and Principal Economist, Health Preference Assessment Group, Research Triangle Institute* detailed the differences, strengths and weaknesses of three different methods for eliciting patients' values and preferences: analytic hierarchy process, best-worst scaling and discrete-choice experiments, also known as conjoint analysis.

Dr Neil McAuslane, *Director, CIRS*, presented the results of a small CIRS survey to elicit information regarding the contribution of patients to the benefit-risk assessment of medicines from the perspective of pharmaceutical companies, regulatory agencies and patient organisations. From the company's perspective, the hurdles to patient participation centred on methodologic uncertainty regarding how the input would be used and accepted. Proposed solutions included patient engagement guidelines, alignment on feasible and flexible methodologies and models for benefit-risk assessment. From the agencies' perspective, hurdles centred on finding representative, informed patients without unresolved conflicts of interest, methodological issues in terms of synthesising the experience from a large number of patients into a cohesive message and extrapolating clinical trial data to general patient populations. Solutions that were proposed included developing patient-centred conflict of interest guidelines, direct engagement with patient groups and clear communication of the regulator's role. From the patient's perspective, a lack of understanding is a major hurdle, in terms of the language and statistical methods that may be poorly understood. Additional issues include a lack of experts in some rare disease area, a lack of funding and the exclusion of patients who are more difficult to treat from clinical trials. Proposed solutions include the expansion of patient involvement, education and patient workshops and the development of a pool of experts in rare diseases

Day 2 Chair, Prof Sir Alasdair Breckenridge, *Former Chairman, Medicines and Healthcare products Regulatory Agency, UK*, introduced the Workshop Syndicate Rapporteurs who presented summaries of the discussions in their groups on two topics: "What are the critical success factors that will enable the involvement of the patient's perspective on benefits and harms to contribute to the future success of research and development of new medicines?" and "What are the critical success factors for the assessment of the patient's perspective on benefits and harms to contribute to the regulatory review?"

SESSION: THE PATIENTS' VOICE IN DEVELOPMENT: THE RECOMMENDATIONS

AstraZeneca is using cutting-edge technologies and services to increase and improve the flow of information to patients in the clinical development and post-approval settings, to track how a medicine is impacting the patient's healthcare outcome in real time and to gain insights regarding a patient's experience and how they use their medicine. **Moira Daniels**, *Vice President, Regulatory, Policy, Intelligence and Labelling, AstraZeneca, UK* discussed a new application being developed at her company for use by a treating physician on clinical trial visits that will encourage the physician to employ the recommended treatment algorithm in order to retain patients in the study so that they could achieve the long-term benefits of treatment.

This application contains links to all the reference documents applicable to a particular patient and his treatment in order to manage the patient interaction, enter the data electronically and aid in clinical decision making.

The Therapeutic Goods Administration, Australia has been conservative in its use of social media because of concerns about resource requirements, a loss of control over information, legal liability for non-removal of inaccurate or discriminatory comments, the need to ensure a consistency of message disseminated through many channels, advertising on social media sites and commercial confidentiality. However, the agency does employ the use of *Twitter* accounts to rapidly alert stakeholders rather than as a two-way communication, with micro-blogs linked to web pages. In addition, **Dr John Skerritt**, *National Manager Therapeutic Goods Administration, Australia* identified multiple opportunities for communication through social media for regulators and other stakeholders including *Facebook* and *YouTube* videos to explain risk, the pharmaceutical registration processes, the appropriate use of medicines and to encourage adverse events reporting and *Twitter* and *Facebook* to communicate the registration of major new medicines and medicine and medical device recalls and to report adverse events.

Achim Kautz, *Policy Director, European Liver Patients Association* related several cases illustrating the impact of social media, including one instance in which an online survey affected the revision of treatment guidelines. The German Liver Aid Society conducted two sequential online surveys among patients with hepatitis C, the results of which confirmed that although patient quality of life improves with successful treatment, it may deteriorate if treatment is unsuccessful. In addition to scientific publication, the results were discussed at the German Hepatitis C Guidelines Conference. As a result of publicising the patient input contained in the surveys, the current German Hepatitis C Guidelines specify that a patient's wish for or against treatment must be respected and treatment must be offered to all patients who do not have contraindications upon their request.

Recommendations from across the Syndicates

1. Interview patients enrolled in phase 1 and 2 studies to develop methodologies to improve phase 3 study design, including the evaluation of benefits and risks and recommendations for patient-reported outcomes.
2. Hold routine focus groups with patients at the earliest stages of development to establish dialogue and provide ongoing feedback.
3. Conflict of interest requirements need to be revisited and updated to reflect real-world needs rather than political expediency.
4. Use new technologies such as smartphones and electronic case report forms to collect real-world data from patients and also to communicate the results of clinical trials to participants, providing a greater motivation for participation and completion among diverse cohorts of patients.
5. CIRS should organise a roundtable to bring together key stakeholders to identify hurdles, propose solutions and gain consensus regarding what is needed to develop better cooperation throughout a product life cycle.
6. Conduct a comprehensive survey on the major hurdles today for including patient information in the evaluation of benefit-risk.
7. Review one or two important disease-specific guidelines for drug development (possibly a PhD research topic) to determine if they are appropriate to incorporate patient input by:
    - Exploring the methodology that would enable patient groups to contribute to the review of these guidelines
    - Identifying the patient groups relevant to the disease area in order to engage them in the process
    - Using a structured approach
    - Obtaining patient views on the value of the current guidance(s)
8. Examine benefit-risk methodologies to see if they are applicable to support post-marketing activities.
9. Raise the profile of the issues relative to patient input in benefit-risk decision making that were raised during this Workshop through publication.

Workshop Programme

SESSION: THE INCLUSION OF PATIENTS' PERSPECTIVES IN UNDERSTANDING THEIR NEEDS IN TERMS OF BENEFITS AND RISKS AT THE DISEASE AND PRODUCT LEVEL	
Chairman's welcome and introduction	**Dr Mary Baker**, *President, European Brain Council*
Keynote Presentation – Can patients contribute to the benefit-risk assessment of new medicines?	**Prof Michel Goldman**, *Executive Director, Innovative Medicines Initiative*
How do patients currently inform and companies and agencies identify needs at the disease level in order to influence research and early development?	
Regulatory Viewpoint	**Robin Evers**, *Vice President, Worldwide Safety and Regulatory, Pfizer, UK*
Industry Viewpoint	**Dr Franceso Pignatti**, *Head of Section Oncology Safety & Efficacy of Medicines, European Medicines Agency*
Is a collaborative model for identifying patients' perspective on benefits and risks at the disease level a precompetitive area?	**Dr Frank Rockhold**, *Senior Vice President, Global Clinical Safety and Pharmacovigilance, GlaxoSmithKline, USA*
How useful is it for patient groups to collaborate to ensure that their voice is heard by companies, agencies and payers and what are the opportunities and hurdles?	**Patricia Pellier**, *Vice President Regulatory Affairs EMEA, Celgene, Switzerland*
Reflection from the patient's perspective **Jean Mossman**, *Policy Lead, European Federation of Neurological Associations, UK* **Achim Kautz**, *Vice President, European Liver Patients Association* **Jeremiah Mwangi**, *Policy and External Affairs Director, International Alliance of Patients' Organizations, UK*	
SESSION: WHAT ARE THE KEY METHODOLOGIES BEING ADVOCATED AT THE PRODUCT LEVEL TO ENSURE THAT THE PATIENT'S VOICE IS BEING HEARD IN CLINICAL DEVELOPMENT?	
What are the key methodologies being used in clinical development to identify patients' views and what are the pros and cons in how these can inform the Benefit Risk decision by individual stakeholders? Viewpoints on the current methodologies available	
Industry viewpoint	**Dr Jamie Cross**, *Program Director, Product Development Regulatory, Genentech Inc, USA*
Regulatory viewpoint	**Prof Steffen Thirstrup**, *Former Director of Licensing Division, Danish Health and Medicines Authority*
Academic viewpoint	**Dr Reed Johnson**, *Distinguished Fellow and Principal Economist, Health Preference Assessment Group, Research Triangle Institute, USA*

Introduction to the syndicates	**Dr Neil McAuslane**, *Director, CIRS*
Syndicate Discussions	
Syndicate A: What are the critical success factors that will enable the involvement of the patient's perspective on benefits and harms to contribute to the future success of research and development of new medicines?	
Chair	**Dr Thomas Lonngren**, *Strategy Advisor*
Rapporteur	**Frederic Ivanow**, *Senior Director, Janssen, UK*
Syndicate B: What are the critical success factors for the assessment of the patient's perspective on benefits and harms to contribute to the regulatory review?	
Chair	**Prof Robert Peterson**, *Executive Director, Drug Safety and Effectiveness Network, Canadian Institutes of Health Research*
Rapporteur	**Dr Louise Gill**, *Senior Director, Global Regulatory Affairs, GlaxoSmithKline, UK*
SESSION: THE PATIENTS VOICE IN DEVELOPMENT: THE RECOMMENDATIONS	
Chairman introduction	**Prof Sir Alasdair Breckenridge**, *Former Chairman, MHRA, UK*
Panel Discussion *This session is to have a reaction from different stakeholders to the ideas suggested by the Syndicates*	
Payer viewpoint	**Victoria Thomas**, *Associate Director: Patient and Public Involvement Programme, National Institute for Health and Care Excellence, UK*
Patient groups viewpoint	**Jean Mossman**, *Policy Lead, European Federation of Neurological Associations, UK*
Industry viewpoint	**Dr Isabelle Stoeckert**, *Head, Global Regulatory Affairs Europe/ Canada, Bayer Pharma AG, Germany*
Regulatory viewpoint	**Prof Steffen Thirstrup**, *Former Director of Licensing Division, Danish Health and Medicines Authority*
The utilisation of social media and new technology to gain a better understanding of patients' needs: How could it be appropriately harnessed for clinical development?	
Industry viewpoint	**Moira Daniels**, *Vice President, Regulatory, Policy, Intelligence and Labelling, AstraZeneca, UK*
Agency viewpoint	**Dr John Skerritt**, *National Manager Therapeutic Goods Administration, Australia*
Patient viewpoint	**Achim Kautz**, *Vice President, European Liver Patients Association*

Section 2: Syndicate Discussions

Two Syndicate Discussion Groups were asked to discuss aspects of bringing the perspective of patients into the development and regulation of new medicines.

Syndicate Discussion A

What are the critical success factors that will enable the involvement of the patient's perspective on benefits and harms to contribute to the future success of research and development of new medicines?	
Chair	**Dr Thomas Lonngren**, *Strategy Advisor*
Rapporteur	**Frederic Ivanow**, *Senior Director, Janssen, UK*

Background

As companies and agencies develop frameworks for the benefit-risk evaluation of new medicines and for communicating this evaluation to stakeholders, there has been a growing awareness that the patient's voice is a critical component. Moreover, the patients' role is central throughout a medicine's life cycle. In the development phase, patient input allows companies to ensure that they are developing medicines of value to their primary stakeholder, whilst during the regulatory review of new medicines patients can provide a perspective on the maximum acceptable risk and minimum acceptable efficacy that may differ from that of regulators.

At a CIRS Workshop held in April 2012 there was a consensus that patients should be involved in the benefit-risk evaluations in the development and regulation of medicines. However although industry and agencies are in agreement regarding the high value that they place on patient input, there are challenges such as the industry funding of patient groups, which results in public criticism of real or perceived bias. There is also the question around appropriate methodologies and whether a single patient can provide a representative opinion and if the needs of individual patients may unduly influence decision making. Finally, it is recognised that patient input to decision making needs to be credible and the lack of technical knowledge of the average layperson represents a significant obstacle to that credibility.

The objectives of this Syndicate group were to discuss:

- The current situation among companies in obtaining information regarding benefits and harms directly from patients as part of the research and development process
- The challenges to companies to obtain benefits and harms information from patients that will be of value to the research and development process
- A future landscape in which information or data directly from patients on benefits and harms would be central to informing the decisions made in the research and development of new medicines
- Short- and long-term recommendations regarding how the environment needs to change for patient information or data on benefits and harms to inform the research and development process

Questions for consideration

1. The Syndicate was asked if they agreed with the following premise and if not to suggest what substantial changes should be made. Premise: the next generation of research and development will be patient centred – A key component of this will be based on information or data on the benefits and harms being obtained directly from patients that will be of value to inform research and development decision making, both at the disease level as well as for specific products.
2. The Syndicate was asked to consider the current environment in regard to patient involvement in providing information on benefits and harms in the research and development process and to consider the

following questions:

- When do companies routinely elicit patients' views on benefits and harms?
- At what stage do you think patients' views should be sought?
- What typical methodologies are used by your company for eliciting patients' views?
- What are the key challenges from a company and patient perspective?

3. What do you think the future landscape is for patient involvement in drug development in terms of possible interactions among regulators, industry, patients, payers, clinicians and government in matters of policy strategy, quality, trust, regulation, society, technology and methodologies?

Results

Critical issues

What is the current situation among companies in obtaining benefits and harms directly from patients as part of the R&D process?

Currently there is no standardised methodology within industry for obtaining information from patients regarding the benefits and harms of medicines in development. In fact, there are few formalised incentives for industry or regulators to consider the perspectives of patients. Accordingly, many healthcare stakeholders feel that research and development seems to be driven by the needs of industry rather than those of patients and regulators do not consistently solicit information regarding patients' needs in their evaluation of submissions.

What are the current challenges to companies to obtain benefits and harms information from patients that will be of value to the R&D process?

Political agendas are averse to patient and industry interaction because conflict of interest considerations can get in the way of the common interests of patients, regulators and industry. The identification of experts and patient advocates in specific diseases who can advise regulators has been complicated by restrictive conflict of interest requirements governing these interactions and this difficulty is likely to increase as industry moves toward the development of more targeted medicines. Likewise, regulatory guideline development does not adequately incorporate patients' views or disease considerations. Although patients are well placed to determine what they need and can live with, they often lack a formal place or forum to express their views.

A lack of reporting or feedback to patients who are part of clinical trials discourages patient participation and contributions.

Strategies

Patients want their needs to be integrated into research and development, regulatory and post-authorisation processes. This Syndicate agreed that proper methodologies are required that would allow the right questions to be asked of patients early in the development process. The methodologies would need to be adapted to therapy areas and product specificity and should incorporate adequate incentives to make them a viable piece of the research and development process.

In addition, patients should organise in a structured way to demonstrate the societal benefit of early and continuous dialogue between patients, regulators, industry and payers. More widely available training and education need to be developed for patients to increase their awareness and knowledge of the research and development and regulatory decision-making process and of optimal methods for interaction with industry and regulators. Additionally, the development of new communications technologies or the better use of existing innovations is needed to capture and communicate patient interactions and data.

Joining forces, industry and patients' organisations need to speak against traditional, conservative guideline development and confirm that the benefits of including the patient's voice in research and development and decision-making processes outweigh any real or perceived risk of conflict of interest. Patients and industry also need to come together to show the value of their partnership in making the right drug available to the right patients while allowing industry to sustain a viable innovative business model. Routine roundtable discussions among structured patients' groups, regulators, industry and payers should allow progressive development of the future landscape for patient-informed research and development, regulatory and payer decision-making processes.

Although conflict of interest is a reality, the political environment and regulator mindset need to evolve to include an acceptable level of patient and industry interaction to develop a framework providing for optimised research and development efficiency, better regulatory

oversight and fair and equitable incentives, pricing and reimbursement for innovative patient-focused drugs that will serve the interests of all parties. Legislators and regulators who are informed of patients' needs could better balance economic, health and litigation considerations into laws and regulations that will allow society to benefit from a system where industry innovation is encouraged and regulatory and payers decisions will be aligned with patient and society needs.

Recommendations

1. Interview patients enrolled in phase 1 and 2 studies to develop methodologies to improve phase 3 study design, including the evaluation of benefits and risks and recommendations for patient-reported outcomes.
2. Hold routine focus groups with patients at the earliest stages of development to establish dialogue and provide ongoing feedback.
3. Conflict of interest requirements need to be revisited and updated to reflect real-world needs rather than political expediency.
4. Use new technologies such as smartphones and electronic case report forms to collect real-world data from patients and also to communicate the results of clinical trials to participants, providing a greater motivation for participation and completion among diverse cohorts of patients.
5. CIRS should organise a roundtable to bring together key stakeholders to identify hurdles, propose solutions and gain consensus regarding what is needed to develop better cooperation throughout a product life cycle.

Syndicate Discussion B

What are the critical success factors for the assessment of the patient's perspective on benefits and harms to contribute to the regulatory review?	
Chair	**Prof Robert Peterson**, *Executive Director, Drug Safety and Effectiveness Network, Canadian Institutes of Health Research*
Rapporteur	**Dr Louise Gill**, *Senior Director, Global Regulatory Affairs, GlaxoSmithKline, UK*

Background

Applying the same background information as Syndicate A, this Syndicate also had the same objectives, except that they were asked to consider aspects of applying patient input into the regulatory review of new medicines from the perspective of regulators. That is, their objectives were to discuss

- The current situation **within agencies** in obtaining information regarding benefits and harms directly from patients as part of the **review process**
- The key challenges to **agencies** to obtain benefits and harms information from patients that will be of value to the **review process**
- A future landscape in which information or data directly from patients on benefits and harms would be central to informing decisions made in the **review** of new medicines
- Short- and long-term recommendations regarding how the environment needs to change for patient information or data on benefits and harms to inform the r**egulatory review process**

Questions for consideration

1. The Syndicate was asked if they agreed with the following premise and if not to suggest what substantial changes should be made. Premise: the next generation of research and development will be patient centred – A key component of this will be based on information or data on the benefits and harms being obtained directly from patients that will be of value to inform the regulatory review process, both at the disease level as well as for specific products.
2. The Syndicate was asked to consider the current environment in regard to patient involvement in providing information on benefits and harms in the regulatory review process and to consider the following questions:
   - Regarding opinion or information on benefits or harms, perspectives on the relative importance of benefits and harms and the understanding of potential tradeoffs:
     - From whom and when is the information normally collected?
     - Do you think patients' views should be sought directly?
     - What are the typical methodology(ies) used at this stage for eliciting patients' views?
     - What are the key challenges from an agency and patient perspective?
3. Like Syndicate A, this Syndicate was asked what they thought the future landscape for patient involvement in drug development might look like in terms of possible interactions among regulators, industry, patients, payers, clinicians and government in matters of policy strategy, quality, trust, regulation, society, technology and methodologies.

Results

Critical issues

It was the consensus of this Syndicate that patients can broaden regulator, industry and HTA understanding of a disease. Accordingly, an assessment should be made of current benefit-risk methodologies to determine if any are appropriate for the incorporation of patient input and then these methodologies should be included as a routine part of regulatory assessments.

Current methodologies for evaluating benefit-risk have focused on pre-approval and there is a need to extend these methodologies for benefit-risk assessment after regulatory approval.

In fact, it was further agreed that patient input should span the product life cycle and should be sought to develop disease-specific guidelines for drug development, before phase 2, at the time of marketing application review and after approval. There was particular discussion regarding whether it should be necessary for a regulatory agency to first seek patient views on risk on those occasions when it becomes necessary to withdraw an approved product.

Ensuring appropriate patient representation to derive input is critical, however, and as patient organisations frequently have constrained resources, regulators may need to ensure that patients receive the necessary education and training to fulfil this mission.

In addition to seeking the input of patients, the Syndicate concluded that the industry should broaden its reach and request input from regulatory agencies other than the US FDA, EMA and PMDA and all stakeholders should take better advantage of social media in their interactions with each other. Finally, regulatory agencies should recognise that methodologies, input and results of patient input may change with the advent of personalised medicine.

Strategies

The group agreed on five critical success factors for the assessment of the patient's perspective on benefits and harms to contribute to the regulatory review.

1. A structured approach for the assessment of both benefit and harm is required.
2. Identification of the appropriate representation of patient perspectives is needed and may necessitate education and training, possibly leveraged through the work of other organisations such as European Patients Academy on Therapeutic Innovation (EUPATI).
3. Regulators need to have confidence in the methodologies in order to have confidence in the data.
4. Take advantage of multiple opportunities to engage the patient, not just during the review of the marketing application.
5. Collaborate: patient input should be shared by regulators, health technology assessment agencies and industry.

Recommendations

1. Conduct a comprehensive survey on the major hurdles today for including patient information in the evaluation of benefit-risk.
2. Review one or two important disease-specific guidelines for drug development (possibly a PhD research topic) to determine if they are appropriate to incorporate patient input by:
   - Exploring the methodology that would enable patient groups to contribute to the review of these guidelines
   - Identifying the patient groups relevant to the disease area in order to engage them in the process
   - Using a structured approach
   - Obtaining the patient views on the value of the current guidance(s)
3. Examine benefit-risk methodologies to see if they are applicable to support post-marketing activities.
4. Raise the profile of the issues relative to patient input in benefit-risk decision making that were discussed during this Workshop through publication.

Panel Discussion of Syndicate Results: Key points

A panel discussed the Syndicate presentations from the perspective of a payer, patient, industry member and regulator

Victoria Thomas, *Associate Director: Patient and Public Involvement Programme, National Institute for Health and Care Excellence*

- Beginning on 1 April 2013, the remit of the National Institute for Health and Clinical Excellence (NICE) was expanded to include social care in addition to clinical and public health. Ms Thomas explained that this does not mean that patients have been forgotten but rather that the Institute's evaluations must also include considerations of a wider society. To this end, the NICE Citizens Council aims to speak on behalf of society and taxpayers, whilst a separate programme supports patients, carers, service users and other members of the public.
- Information is obtained from patients and carers by NICE through a systemised and formal part of the process by which new drugs are assessed and appraised for the UK National Health Service. Ms Thomas agreed that patients should be involved as early as possible in drug development and stay involved throughout the product life cycle. Furthermore, because it is important to obtain as much information about patients as possible, NICE would welcome patient information from industry that they have gleaned from this continual patient interaction as well.
- The adoption of a standardised approach to obtaining patient input would ensure that patients are asked the right questions early in the process and lead to better shared decision-making between patients and clinicians at the consultation stage.
- The perception of conflict of interest has always been inherent in patient-industry interactions. A number of Canadian cancer patient organisations have dealt with this issue by developing a self-governing model that includes a code of conduct that specifies their relationships with industry, the funding that they receive and how it is used as well as the restrictions that are in place.
- Collectivism amongst patient organisations is incredibly important and should be further explored as the collective voice can exert a very powerful influence.
- Training and education for patients and patient organisations about drug development, regulation and health technology appraisal, such as is available through EUPATI (page 18) is critically important, but it should be recognised that education can be obtained through patient experience and expertise as well. The point that was raised in Syndicate discussions about the breadth of understanding that patients bring to the regulatory and drug development process is important to remember and is something that is continually revisited as part of the systematic patient engagement at NICE. To gain a full and real picture of the important issues surrounding a new medicine, patient perspective should be part of the triangle of evidence along with clinical and economic data.
- Although it is important to ask patients about the risks they are willing to take to achieve the potential benefits of a medicine, it should also be understood that individual patients may each make a different decision based on the same benefit and risk information.
- To support and guide patients to provide the type of information that would be useful to assessors in their decision making, such as the consequences of living with a disease or of taking a particular drug, NICE is developing a formal interaction template

Jean Mossman, *Policy Lead, European Federation of Neurological Associations, UK*

- As it may be unrealistic for every company to expect to engage patients and patient organisations at every step in the drug development, regulatory and reimbursement processes for every new medicine in development, the development of a standardised approach for patient engagement that includes clarity of objectives and perhaps sharing of findings is key.
- Finding the best treatments for diseases does not represent a conflict of interest but rather an opportunity to work for the common interest of patients, governments, industry and society in general. As discussed by Ms Thomas, many patient groups currently have very clear guidelines that are freely available on their websites and elsewhere as

to where they receive funding and how they use that funding. Ms Mossman noted that Dr Baker indicated that the establishment of trust rather than simply a discussion of transparency is at issue and rebuilding that trust among healthcare stakeholders is absolutely essential. Unfortunately, although a publication from patient groups on this topic would be worthwhile, most patient organisation resources are expended delivering direct services to people living with an illness or their caregivers.

- Many patients and patient organisations do not understand how, for example, the EMA can say a medicine is effective enough to use and NICE can say it is not effective enough to be reimbursed. More effort must be made to educate patients and patient organisations about the drug development process, that is, the journey of a medicine from new molecule to its access and use by the patient.
- One of the challenges surrounding benefit and risk of therapy is that a patient's perception of these factors changes as their disease progresses. However, we should not be paralysed by the challenges, but rather seek the methodology that will allow us to better understand how to reflect these changing needs throughout a disease.
- Ms Mossman concluded with the wish that some of the recommendations from the 2012 CIRS Patients Workshop such as the development of regulatory guidelines around patient engagement and the commitment of legislative bodies to eliminate potential legal barriers to patient involvement in benefit-risk decisions would be implemented so that real progress in inserting the patient perspective into the heart of the development and regulation of medicines could be observed.

Dr Isabelle Stoeckert, *Head, Global Regulatory Affairs Europe/Canada, Bayer Pharma AG, Germany*

- It is undeniable that industry needs a structured approach to benefit-risk assessment and patient preference input into this structure, before and after approval is essential. One of the hurdles to this goal is the need for cross-functional collaboration within companies. Until fairly recently, almost all patient preference research has been done through marketing teams. This needs to be expanded to more exposure of developmental groups and the data gathering and results could be better shared.
- It is not necessary to invent new codes to control conflicts of interest. Companies each have codes of ethics in place to provide guidelines for appropriate, ethical interactions with patients and patient organisations. Interactions should be transparently defined in terms of content and setting and this transparency will help to increase trust.
- A structured and scientific approach such as the methods discussed by Drs Cross (p 28) and Johnson (p 32) may bring more respect and visibility to patient input. Good guidelines from regulatory agencies on what would be acceptable evidence may also help meet some of the challenges that surround this uncertainty. Possible sources for these guidelines might emerge from the Innovative Medicines Initiative (IMI) Research or EMA Initiatives or the currently ongoing US FDA indication-related workshops.
- There should be science-based guidance for the use of social media to gather patient input, such as qualifying specific patient organisations and tools for participation.
- To achieve patient-centric development, it is important to gather patient information regarding a product's benefits and risks as early as possible in development. The tools to rank treatment outcomes prior to using them in pivotal clinical trials should involve patients' perspective. Such tools should then be consistently applied throughout a product's life cycle, perhaps becoming more quantitative as development progresses and more data become available.

Prof Steffen Thirstrup, *Former Director of Licensing Division, Danish Health and Medicines Authority*

- Although it is true that some regulators feel uncomfortable when addressing how best to address advice from patients, there are examples of regulators who do solicit patient input such as when the CHMP held hearings on the withdrawal of the multiple sclerosis drug Tysabri because of concerns regarding the drug's association with progressive multifocal leukoencepholapathy. At these hearings, patients convinced regulators that for them, the risk of PML was worth the benefits of treatment and the drug was returned to the market. With this as an example of effective patient-regulator interaction, regulators should take the next

step and involve patients in decision making on a more regular basis.

- To make needed updates and changes to guidelines to best incorporate patient input, regulators must increase their knowledge about current research in bringing patients into decision making such as that surrounding patient-reported outcomes and measurement of utilities.
- The regulatory environment must change so that evaluations of clinical relevance incorporate patient judgements.
- Transparency does not just entail the public provision of information – the information must be made publicly understandable, particularly information regarding the rationale behind regulatory decisions.
- New methods for handling conflict of interest must be developed. In addition to patient-industry interactions, conflict of interest issues also concern the use of external experts in regulatory decisions, which is becoming more common globally.
- Finally, it should be remembered that just as patients are not a homogenous group, regulators too, vary in their approaches and viewpoints on benefit and risk and decision making.
- There are no fixed patient representatives at the CHMP. Patients are involved in supporting committees and scientific advisory groups and patient representatives are invited on a case-by-case basis to provide input, but are not formally involved in final decision making.

Section 3: Presentations

Can patients contribute to the benefit-risk assessment of new medicines?

Dr Michel Goldman

Executive Director, Innovative Medicines Initiative

With an annual budget of 2 billion Euros, the Innovative Medicines Initiative (IMI) is the largest public-private partnership in life science today. In addition to regulators, patient organisations and academia, IMI projects are conducted by consortia of pharmaceutical companies collaborating in the precompetitive space. The long-term goal of the organisation is to accelerate the access of patients to innovative medicines through the collaboration of all healthcare stakeholders.

The initial focus of IMI was to develop new models to accelerate drug development but this agenda was broadened in 2011 to also include the later phases of drug development and address challenges in society and healthcare (Figure 1). Forty projects have been launched to date, involving approximately 4,500 researchers. This total includes representatives from 18 patient organisations, a number that IMI is committed to increasing in future. Collaborative activities and related influential publications have increased exponentially each year since 2007.

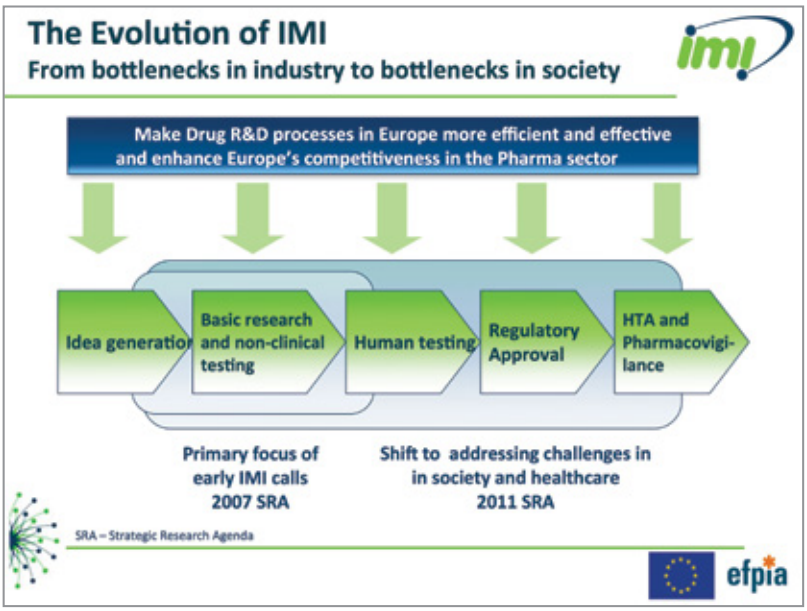


Figure 1. In 2011, IMI shifted the focus of its programmes to include later stage pharmaceutical development and issues in public healthcare.

Key challenges addressed by IMI projects include disease heterogeneity, the lack of predictive biomarkers, outdated clinical designs and regulatory processes, insufficient incentives for the pharmaceutical industry and biotechnology companies and the need for a shift in the mindset among stakeholder communities. Dr Goldman provided several examples of IMI programmes to address these critical challenges, which include considerable contribution from patients either through active participation and input or the use of clinical data.

The Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (PROTECT) Consortium is coordinated and managed by the European Medicines Agency and is focused on new ways to address benefit-risk assessment. In one of the group's five Work Packages, eight methodologies for benefit-risk assessment were tested for natalizumab, the drug that was approved for relapsing and remitting multiple sclerosis, withdrawn due to concerns regarding progressive multifocal leukoencepholapathy and reintroduced because of patient demand. Using multi-criteria decision analysis, the group was able to graphically show that the characteristic of the medicine that most influenced its benefit-risk assessment was it ability to prevent relapse.

In addition to four programmes for professional education, IMI has also funded an important project for patients, the European Patients Academy on Therapeutic Innovation (EUPATI). EUPATI develops and disseminates accessible, well-structured and user-friendly information and education on medicines research and development, builds competencies among well-informed patients and the public and develops expert capacity in patient advocates. In addition the organisation has created the leading public library on patient information in the six most common languages, established a widely used, sustainable infrastructure for objective, credible, correct and up-to-date knowledge and facilitates patient involvement in research and development to support industry, academia, authorities and ethics committees.

EUPATI develops and disseminates accessible, well-structured and user-friendly information and education on medicines research and development, builds competencies among well-informed patients and the public and develops expert capacity in patient advocates .

Programmes in development in the IMI pipeline include those that will develop a framework for rapid assessment of the benefit-risk of vaccines, incorporate real-life clinical data into drug development and leverage emerging technology for pharmacovigilance. It is envisioned that like existing IMI projects, these future public-private partnerships will contribute to move medicine forward by addressing key scientific challenges, developing tools to translate scientific advances into regulatory guidelines, considering new pathways to accelerate patient access to innovative therapies and providing a neutral platform that fosters collaboration between stakeholders.

How do patients currently inform and companies and agencies identify needs at the disease level in order to influence research and early development?

Robin Evers[†]

Vice President, Worldwide Regulatory Strategy – Primary Care, Pfizer

The patient voice at pharmaceutical stage gates

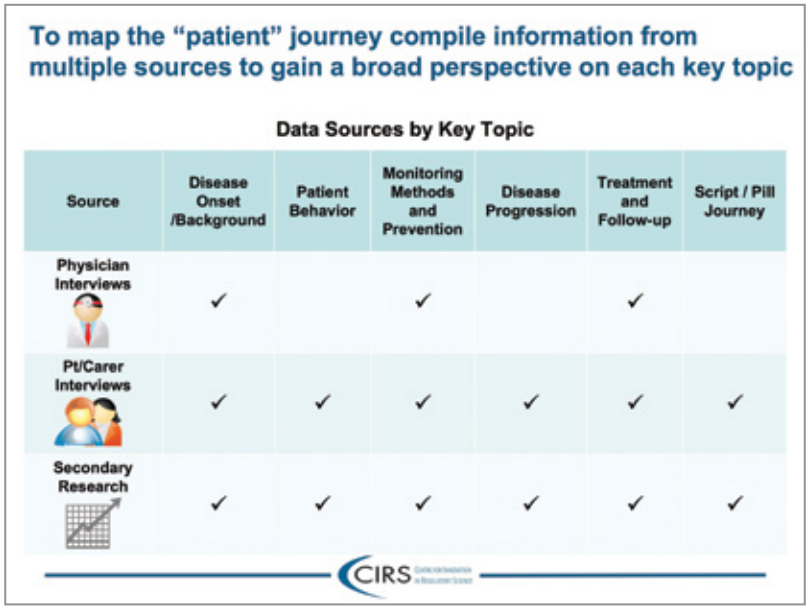
The pharmaceutical industry looks to bring the voice of the patient into early drug development through the use of patient group input, social media, focus groups and physician-mediated interviews. At this time point, a large wealth of data is gathered at the disease area level to develop ideal product profiles that are used to identify candidates for development.

Later in development, at the time of "proof of concept" and value proposition, companies solicit patient involvement and input into the development of clinical trial endpoints, clinically meaningful effects and potential patient-reported outcomes (PROs). However, in addition to traditional methods to collect patient-level data for clinical trials such as PROs and utilities, companies also need to develop novel methodologies such as the use of social media and advanced data mining.

Patient input may also be involved in the regulatory submission and review of new medicines through patient meetings with sponsors and participation in regulatory advisory committees. Industry and agencies should ensure a structured, organised and informed forum for either direct or physician or association patient participation in this phase of development.

It is a time-consuming but important process to map the patient journey during the course of a disease, compiling information from multiple sources such as physician and patient/caregiver interviews and secondary research to gain a broad perspective on each key topic (Figure 2). These topics include background on the disease and its onset, methods for monitoring and prevention, changing patient behaviour through the course of the disease and for individual follow-up and care, causes for relapse, reasons for secondary treatment and changes in treatment paradigms. Other topics include which medicines are currently used, their

Figure 2. Patient input regarding their experience with disease and treatment becomes critical background information for pharmaceutical company teams.



. . . industry should be aware that this empowerment may permanently change the nature of discourse between industry and patients.

benefits and harms, how they are prescribed and whether patients actually fill and take their prescriptions. This information must all be distilled into summaries for a broad spectrum of pharmaceutical company individuals from the clinical research statistics, development, pharmacometrics and regulatory teams.

The research allows companies to compile a deep understanding of their customers, the patients and their long-term goals and motivations and apply this knowledge to research and development efforts for new pharmacologic interventions, thereby creating value for the patient the payer, the regulatory authority and the companies themselves in terms of long-term sustainable investment.

Increasing patient participation

Industry is aware that the rate of patient participation in clinical trials is low and patients themselves are telling pharmaceutical companies that they need better sources of information and better methods of engagement for those trials. In their 2008 Clinical Trial Awareness Campaign, the American Association for Cancer Research cited a 5% rate of participation of adult cancer patients in clinical trials versus 75% who would participate if possible.

Pfizer has undertaken one potential method for increasing patient participation with its "clinical trial by telephone" testing of an approved product. In this study, patients were recruited via the Internet and able to self diagnose their condition and medication was sent directly to their home. The study was implemented in a regulated environment approved by the US FDA. Stringent enrolment criteria ensured that only appropriate patients were tested and patients had access to appropriate healthcare support during the course of their treatment. Implementing this innovative pathway involved multiple challenges such as those inherent in the mail delivery of IND-registered products, prescription legislation restrictions and obtaining all necessary information for reporting adverse events, but the programme stands as an example of an innovative method to increase patient participation in clinical trials.

Patient control of data

In an another novel pilot programme, in an effort to transform the concept of study subjects, or those who are the subject of an investigation, into study participants, those who take part in a research activity, Pfizer partnered with the Center for Information and Study on Clinical Research Participation (CISCRP) to translate the outcomes of clinical trials into summaries written in patient-understandable language. These summaries were then shared with the study participants so they could appreciate the value that they brought through their participation, not only to themselves but to the scientific community and to other patients. This programme was also faced with challenges, such as the potential loss of precision in the adaption of the language of technical scientific outcomes of studies to ensure that it was broadly understandable.

There are a wide variety of data collected from patients resulting from both the research in which they participate and real-world experience; this includes not only primary clinical information, but often detailed information about the prescriptions they fill and pay for as well as for their doctor visits, hospital stays and laboratory results. One recent study found that 91% of patients surveyed were willing to share this information for scientific research;[1] however, industry should be aware that this empowerment may permanently change the nature of discourse between industry and patients. Patient forums that act as information and access gateways for disease states already exist and industry should be mindful of the need to adapt traditional research methods to accommodate these new paradigms while maintaining rigorous research standards and guarding against bias.

Mr Evers concluded his presentation by suggesting two additional pathways for patient engagement in medicine development: the potential value of patient participation in data monitoring committees and the establishment of a partnership with regulatory agencies to provide structured information about the patient experience throughout the course of a disease and treatment.

[†] Views expressed in this summary are those of the author and do not necessarily represent the view of Pfizer.

Reference

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How to include patients' perspectives in the decision-making process

Dr Francesco Pignatti

Head of Section Oncology, Safety & Efficacy of Medicines, European Medicines Agency

Patient perspective at the EMA

Although the focus of the European Medicines Agency (EMA) has always centred on patients, hands-on patient involvement in EMA activities is a relatively recent phenomenon. The remit of the Agency has shifted to include more public involvement in decision making, gradually evolving from the sharing of the rationale for regulatory decisions to active public participation in the regulatory process through the provision of insight and opinion.

Today, patients are members of the EMA Management Board, which has a supervisory role with general responsibility for budgetary and planning matters, the appointment of the Executive Director and the monitoring of the Agency's performance. They also play an institutional role as members of Scientific EMA Committees such as the Committee for Orphan Medicinal Products (COMP), the Paediatric Committee (PDCO), Committee for Advanced Therapies (CAT) and the Pharmacovigilance Risk Assessment Committee (PRAC)

Patients are also occasionally involved as experts advising the committee responsible for the approval of medicines, the Committee for Medicinal Products for Human Use (CHMP) and also act as experts in the Scientific Advisory Groups and Scientific Advice Working Party. In fact it has been calculated that in approximately 50% of requests for protocol assistance in which patients are involved, their input ultimately influenced the outcome. The overall number of patients and consumers involved in EMA activities has increased from 76 in 2007 to 423 in 2011 and patients are particularly well represented as advisors concerning treatments for orphan diseases.

. . . in approximately 50% of requests for protocol assistance in which patients are involved, their input ultimately influenced the outcome.

Patients and benefit-risk decisions

EMA decision makers have traditionally used the framework of expected utilities to make benefit-risk decisions, in which data and uncertainties for a medicine equals the probability of positive or negative events for that medicine. That probability is multiplied by the values or utilities that are associated with those events, taking into account risk attitudes. This calculation was formerly performed implicitly, but recently, the EMA has explored the use of qualitative methodologies such as the effects table, which allows the decision maker to simply build a compact display of effects and information to be used for a more transparent, explicit assessment of the benefit-risk balance. The effects table can be generally applied and used as the basis for quantitative methods such as multi-criteria decision analysis (MCDA). Although MCDA allows higher precision analyses, it requires more substantial effort to build and may not be needed in clear-cut benefit-risk decision making (Figure 3).

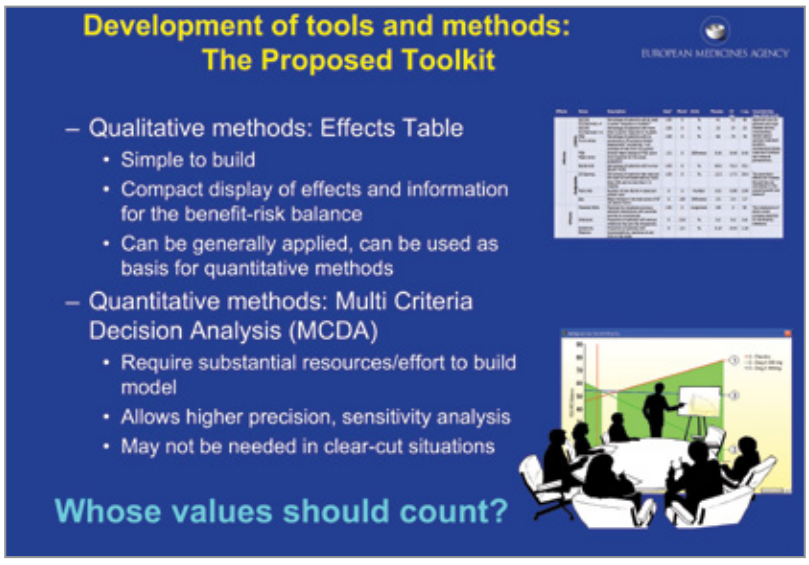

Figure 3. Qualitative and quantitative methodologies for benefit-risk analysis.

Regardless of the choice of decision model, the values that are applied in the evaluation are typically those of the regulator, even though some research has shown that regulator values can be poor surrogates for those of patients. However, whilst the use of patient preferences in benefit-risk decision making is expected to increase the transparency and openness and possibly even the quality of decision making, it is also associated with challenges such as the fact that patients may not be fully informed about all aspects of a product's benefits and risks, their perspectives can be seen as anecdotal, their

preferences may evolve, and these opinions may be difficult to obtain reliably and without bias.

It has been recognised that flexible decision frameworks may be required to handle all types of evaluations at the EMA and regulators are exploring the ways in which decisions are made at the Agency, examining the tools necessary to make all types of explicit and transparent decisions. They are seeking consensus as to the best methods for achieving collaboration among all stakeholders including patients, but optimal methods for eliciting patient preferences without bias are yet to be determined and EMA regulators will continue to explore the use of different methods and values in the decision making process.

Patients' perspectives on benefits and risks as a precompetitive area

Dr Frank W. Rockhold

Senior Vice President, Global Clinical Safety and Pharmacovigilance, GlaxoSmithKline

Dr Marilyn A. Metcalf

Senior Director, Global Clinical Safety and Pharmacovigilance, GlaxoSmithKline

Alignment of benefit-risk assessment and communication

Healthcare stakeholders frequently work simultaneously to meet different but overlapping needs. Pharmaceutical and biologics companies developing new therapies gather data from clinical trials in what they hope is a representative sample of patients with a particular disease and use methods such as focus groups to obtain patient perspectives on that disease and its treatments. Regulators meanwhile, evaluate information about new medicines from multiple sources, including clinical trial results, spontaneous reports and observational data to understand how such interventions may affect morbidity, mortality and disease incidence and prevalence and also try to obtain the patient perspective through mechanisms such as patient meetings and advisory groups. For their part, patients try to obtain as much information as possible to help them decide what therapy best fits their needs and to determine if they will be among those that are helped or harmed by a new drug. Although each of these groups may have different points of view, they are all working toward the same goal: better outcomes for patients. Whilst data that are gathered and assessed about specific drugs are competitive, the methods for obtaining information about medicines and the perspective of patients living with disease and the ways to assess the information and communicate that assessment to patients is non-competitive. Therefore, all healthcare stakeholders would benefit from shared standards for levels of evidence and the systematic collection and reporting of information.

Figure 4. Patients' expectations for benefit and tolerance for risk for a medicine may be based on the nature and stage of their disease.

Working in this precompetitive space, it should be decided what information could be shared among stakeholders. This information could include the impact of disease on the lives of patients as well as the potential positive and negative impact of a therapy for that disease. It may be extremely useful to consider the potential division of patients into subgroups according to factors such as activity level, lifestyle, genetics or demographics and the variability of the impact of disease and the desired outcomes from treatment according to those subgroups.

Rationale for sharing benefit-risk information

Shared benefit-risk information could help industry create medicines and vaccines and provide product information that more directly address patients' concerns. For example, endpoints in clinical trials for migraine therapies would include effectiveness measured against factors that patients have indicated were of primary importance such as pain, lack of sleep, anxiety and the ability to drive, work or function socially. Drug information provided to patients would explore how to balance these concerns versus potential adverse events.

This shared information could also assist regulators in making and articulating decisions that respond directly to those same patient concerns. It could incorporate evidence of the impact of untreated versus treated migraine on patients' well-being as well as evidence of the impact of migraine treatment side effects under circumstances of typical use. Information about daily functioning for individuals with migraine and their families, their productivity, and the short- and long-term outcomes of treatment, for example, would allow regulators to understand more about the impact of both the disease and therapy.

Once a drug is approved, shared information about benefits and risks could allow patients along with their healthcare providers to make decisions for their own health and wellness needs, based on better understanding of the impact of disease and its treatment. The benefit-risk tradeoffs that patients make may depend on whether the drug they are evaluating is preventative, curative, for acute or chronic treatment or end-of-life palliation of symptoms (Figure 4). The decision to use a new drug might be centred on their own personal experience of living with the daily impact of disease, sorting through which symptoms and effects are likely to be addressed by the medicine and understanding what side effects the medicine may cause and what can be done about them. The decision could also be founded on the input of others such as formal and informal data from healthcare providers, drug pamphlets, websites and other patients.

Shared benefit-risk information could help industry create medicines and vaccines and provide product information that more directly address patients' concerns.

Developers and regulators of medicines should provide information to patients and their caregivers that is needed to develop these trade-offs relative to the duration, intensity and probability of potential benefits and harms associated with using a therapy (Figure 5). However, communicating the probability of the occurrence of positive and negative effects to patients with little background in quantification often proves challenging.

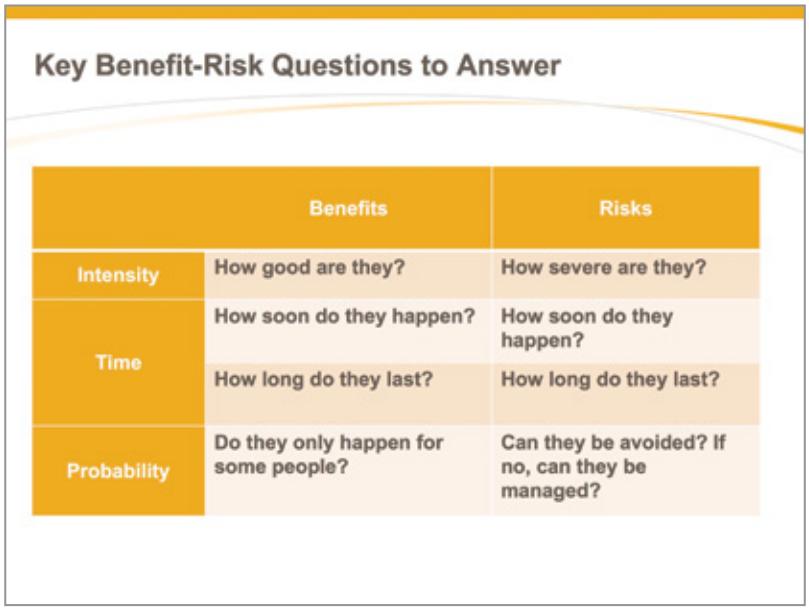

Figure 5. Developers and regulators of drugs should provide information to patients in order to develop benefit-risk trade-offs relative to the duration, intensity and probability of potential benefits and harms associated with using a therapy.

Moving forward

All healthcare stakeholders should seek to uncover how and where to access more patients' views as early in development as possible. The field will continue to gain from improved methodologies to obtain this information. However, once patient input has been provided, it will remain important to recognise which patients have been represented and which were left out. It may be unrealistic for developers and regulators to determine the benefit and risk balance for a new medicine for individual patients and these parameters may be more accurately estimated within "clusters" of patients with similar characteristics. Industry members and regulators should set standards for the characterisation of treatments in the precompetitive space and then determine how individual treatments meet those standards during competitive research.

Patients groups: Collaboration, opportunities, challenges

Patricia Pellier

Vice President, EMA Regulatory Affairs, Celgene International

The improvement of patient health is the common goal of all healthcare stakeholders and today's patients have assumed a much more active role in the achievement of that goal. Patients now have access to a wide range of information about diseases and their treatment and the amount of information is likely to increase in the future. Patients become responsible and compliant with their treatment when they are informed and are active participants in that treatment, making patient involvement mandatory to the improvement of health.

Industry has three objectives in their interaction with patients: understanding, support and involvement.

To understand patients, the developers of medicines must obtain deep insight and understand the disease from patients' viewpoints. This understanding will result in positive impact for clinical development, post-approval studies and for the development of more personalised treatment choices.

To support patients, industry must develop tools to facilitate understanding, interaction and awareness. Supported by public funds, patient organisations and pharmaceutical companies including Celgene RareConnect is a successful example of such a tool. This online project enables people affected by rare diseases to form communities across languages and geographic barriers, promotes awareness and understanding and provides a source of credible disease-specific information and a method for those with rare diseases and their families to share experiences, support and information with each other. In another example of the development of tools to facilitate understanding, Celgene recently conducted a workshop to examine a patient leaflet for utility, readability and understanding and to provide suggestions for change.

To be better involved with patients, industry should continually provide information about the safe and effective use of its medicines throughout their development and life cycle.

The ideal patient organisation partner for industry should possess three criteria: transparency, independence and expertise.

Matthew Herper of Forbes called Biogen Idec and Elan's efforts to develop a test to identify patients who can use the multiple sclerosis drug Tysabri without risk of developing progressive multifocal leukoencephalopathy and communicating that information to patients "the model for facing a drug safety crisis."[1] One method employed by Celgene for patient involvement is the funding of Life Beyond Limit, a coalition of advocacy groups for patients with myelodysplastic syndromes and their families.

The ideal patient organisation partner for industry should possess three criteria: transparency, independence and expertise. That is, the origin of funding for the organisation must be clear, there must be diversification among its stakeholders and the group should bring its own well-defined values to the discussion.

Challenges

The primary challenge to industry and patient interaction is the fact that regulators and pharmaceutical companies are both looking for interaction with the same patient groups. This challenge, however, may be met by establishing guidelines and frameworks for interaction for all stakeholder groups. Similarly, rules for industry contracts for support with patient organisations must be defined appropriately and include the expected services (if any), which are expected from the patient groups. In addition, as demands for transparency continue to increase, industry must decide if they will provide all product data to patients both before and after approval and to what extent to provide the means of interpretation of that data.

Patient organisations too, are faced with multiple challenges including the need to find a balance between acting as spokesperson organisation yet representing specific patient needs. Despite these challenges, it must be realised that patients are key players in healthcare and open discussion is required to find the best way to work together and to ensure trust among all stakeholders.

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REFLECTION FROM THE PATIENT'S PERSPECTIVE

Achim Kautz, *Vice President, European Liver Patients Association*

- The results of industry or regulatory patient questionnaires may be skewed because of a lack of clarity. That is, when technical, non-patient-friendly language is used, the objectives of the questions may be clear to the designer but not to the patient and therefore not accurately reflect patient responses.
- Real-world patient input at the development, review and post-approval phases is critical. Clinical trials of new therapies may be very well designed, monitored by experts and thoroughly reviewed by regulators but still not be able to replicate real-world circumstances and therefore may miss issues or adverse events that occur when patients manage their own treatment. Likewise, physicians without sufficient experience in a particular therapeutic area may not prescribe or manage new medicines appropriately. Because of these circumstances, post-approval evaluations of new medicines should continue to take place at pre-defined (eg., six-month, yearly) intervals to "fine tune" any management issues as required.

Jeremiah Mwangi, *Policy and External Affairs Director, International Alliance of Patients' Organizations, UK*

- Since 2010, the International Alliance of Patients' Organizations (IAPO) has participated in the Patient and Public Involvement Working Group of the IMI PROTECT initiative. IAPO brings in patient perspectives into understanding or characterising the benefits and risks of a particular product. Mr Mwangi explained that the group has particularly discussed the communication of benefits and risks to patients and patient groups.
- It is important to differentiate between the two types of patient involvement in benefit-risk decision making; that is, participation in the governance, review and overall decision making in medicines through for example, membership in an EMA Working Group versus participation in the generation of data through for example, taking part in a patient preference survey. There are methodological as well as philosophical challenges to the management of both types of participation such as ensuring appropriate representation.
- Although there have been many organisations such as the EMA who are setting influential examples of patient participation, much work remains to be done to bring other organisations on board to drive this work forward globally. Stakeholders should draw on the experience of other ongoing works such as that of the European Commission which has funded projects on reflexive governance.
- Patient involvement requires significant resources and we must investigate appropriate sources to generate necessary funding.
- Access to patient views is an ongoing challenge. Patients who have participated in trial design and who are themselves enrolled in clinical trials are an excellent ongoing resource for the generation of benefit-risk data required by regulators and others.

Jean Mossman, *Policy Lead, European Federation of Neurological Associations, UK*

- It has been recognised for some time that many patients are willing and interested in clinical trial participation. In a paper co-authored by Ms Mossman in 1995, it was reported that only 10% of patients with cancer were not willing to take part in clinical trials. However, despite this knowledge, the rate of participation has not significantly improved.

Audience Question

When I talk to our people who are trying to recruit patients for cancer clinical trials, they tear their hair out trying to find patients, and so there seems to be a bit of a disconnect. Are the protocols too complex or enrolment criteria too stringent? Do you have any idea of what that disconnect is?

Response

Although there are often issues around eligibility criteria it is possible to increase enrolment. Patient characteristics are not the only barrier. It might be the time required to participate, the required outlay of financial resources or clinician attitudes toward the study. In the UK there has been great emphasis on enrolling patients into clinical trials, particularly in oncology and patient

organisations are involved in the National Cancer Research Network in the design of clinical trials as well as in improving patient access. The result is that currently, approximately 20% of patients with cancer become part of clinical research.

There is very good research in oncology that demonstrates that healthcare professionals are poor surrogates for patients. It is essential that all healthcare stakeholders understand what it is like to live with a potentially terminal illness on a day-to-day basis, and only the patients and their caregivers can really provide that understanding.

Audience question

Do you think we need to go a step further and involve family members for the surrogate perspective — in other words, family-reported outcomes?

Response

The impact of illness on the family is much broader than we anticipate and understanding these effects from all points of view is important. Furthermore, we need to do more to understand the impact on the people living with the illness, not in just the six months or year of the trial, but two, five and ten years down the line. No consistent mechanisms are yet in place to fully appreciate the impact of a therapy on caregivers.

Audience question

What are the considerations for which we must be mindful regarding interactions with patient organisations, especially in Europe?

Response

- There was a very heated debate in the European Parliament when the information to patient legislation was being reviewed and addressed.
- Conflict of interest issues represent a barrier to patient input. A recent policy directive from the EMA stated that all patient representatives of the EMA who are active in scientific committees or meetings concerning decisions about medicines are not permitted to participate in advisory board meetings organised by pharmaceutical companies, even if they are transparent and disclose their associations. As a result, a company trying to incorporate the patient perspective into its research and development activities will not be able to benefit from the contributions of a patient representative who, because she is very knowledgeable about her illness and skilled at expressing important issues is also engaged with the EMA and vice versa.
- Patient groups can be an incredibly robust source of information that is far broader than clinical trials. One such group was noted to have received as many as 35 thousand inquires a year from patients and their caregivers.
- Regulators should speak more directly with patient groups at meetings. They are precluded from coming to meetings sponsored by a single pharmaceutical company, but if there are multiple patient groups at that meeting, that represents a significant opportunity to educate patients about the regulatory process and how they can contribute.
- Some pharmaceutical companies believe that regulators are not supportive of engaging patient groups in the design or conduct of clinical trials. If the EMA and US FDA made more public statements of their support for patient inclusion, this might provide additional support for an ongoing industry-patient engagement.

Audience comment

We are aware of course pf what is happening in the United States at the moment, where the FDA have engaged in a very positive initiative over the next five years to arrange 20 workshops which will include patients and examine how and when patients should be involved in drug development and the regulatory review. Hopefully, this will move the whole patient voice initiative forward.

General audience questions and comments

Audience comment

Even though technology is empowering patients, the practice medicine and investigation of new medicines is still through a licensed medical professional. What is the role of the healthcare professional in these research interactions?

Audience response

Patient groups work very closely with physicians and see them as key advocates for patient organisations, but they are not the only representatives of the voice of the patient. From the patient group perspective one might hear less about the doctor because these organisations have spent many years ensuring

that the role of physicians is expanded from that of gatekeeper to pharmaceutical companies and regulatory and reimbursement bodies to strong patient advocates with these organisations.

Audience question

Could a patient group representative share any experiences that they may have had with regard to informing HTA decisions, for example, providing evidence to develop a clearer understanding of the drug's value that can then be communicated to HTA agencies, or other interactions at the HTA level?

Audience response

Patient organisations have had the opportunity to appeal successfully to NICE resulting in the reversal of a non-coverage decision, so there is experience where an HTA body has listened to the patient perspective. Although previously, NICE appraisals never referred to patient evidence, there is often now an acknowledgement of the patient and healthcare professional's input.

Many patient organisations are committed to equipping their members to contribute to HTA activities, and an educational tool kit has been developed for patient organisations which is available on the Health Technology Assessment International website in Spanish, English, Mandarin, Polish, Swedish, and Greek. We've also run training courses with the London School of Economics for health technology for patient groups from across Europe so their voice can be heard.

Patient involvement in benefit-risk assessment during drug development: What are the methods currently being used?

Dr Jamie Cross

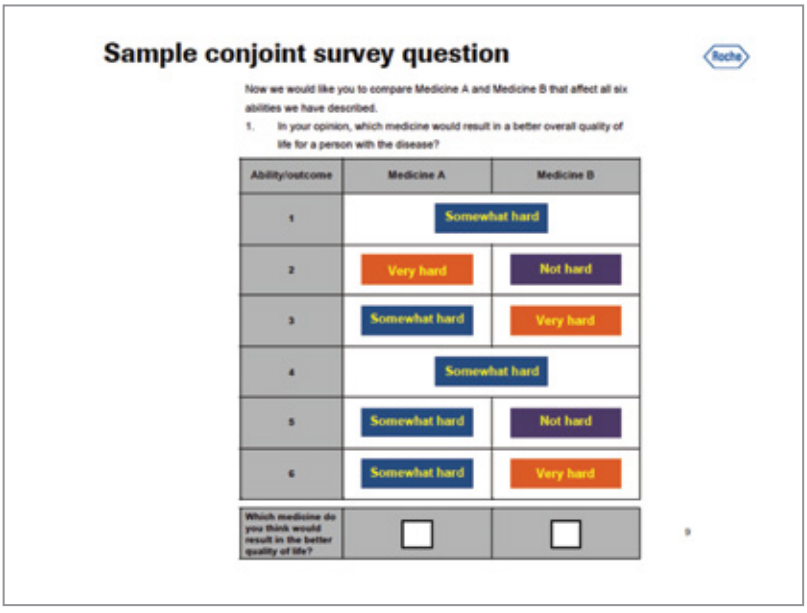
Program Director Regulatory Affairs, Genentech Inc.

1 New opportunities: Conjoint analysis

There are two main methods currently being used by pharmaceutical companies for involving patients in the evaluation of benefit-risk in the development of new medicines, conjoint analysis and patient-reported outcomes (PROs). Conjoint analysis is preference research conducted to better understand which treatment features or disease outcomes are of greatest clinical value to patients (or care-givers). This could help to understand what effect sizes might be clinically meaningful to these stakeholders. This type of research provides an opportunity to approach patients early in drug development to learn what matters to them in the course of treating their disease, creating a feedback mechanism to influence study design and development decisions. Genentech has recently applied such an approach to gain feedback from caregivers who care for patients afflicted with Fragile X Syndrome.

Conjoint analysis is a survey-based method for determining the relative importance, that is, the preferences that individuals place on a defined set of disease outcomes or treatment features. At a high level using this methodology, survey participants (e.g., patients) first answer a series of screening and demographic questions. Then, they answer "ramp-up" questions that explain different features of two treatments and establish respondents' preferences for these features. Finally, respondents are asked several overall trade-off questions such as "In your opinion, which of these two medicines would result in a better overall quality of life for a person with the disease?" (Figure 6) Once the treatment feature or disease outcome that is most preferred by respondents is calculated, the value of the other endpoints relative to the most preferred can be established. This thereby establishes patient preferences for an array of outcomes. Using this methodology, endpoints can be selected for clinical trials that are most relevant to patients and their caretakers.

Figure 6. Conjoint survey questions can be used to calculate treatment preferences among patients.



Conjoint analysis limitations and positive features

All survey-based methodologies have inherent limitations in terms of their sources of potential bias and these limitations are often used to discredit their application. However, it should be recognised that traditional clinical trials have many sources of potential bias, which are nonetheless used to establish the efficacy and safety of medicines. Understanding of a given method to collect data on patients is key to reducing the potential for bias. Limitations to the use of conjoint analyses include the fact that their reliability is a function of both the responder and the survey design. In addition, the treatment attributes that are included in the survey cannot represent an exhaustive list of those associated with a disease or treatment. Also, researchers must endeavour to ensure that respondents are representative of the intended population for treatment.

Industry's use of conjoint analysis at phase 1 and 2 development has been limited despite the fact that obtaining benefit-risk perspectives from patient respondents can provide benchmarks for pharmaceutical development decisions and can help industry understand the overall clinical value of a product, that is, its benefit-risk tradeoffs. An understanding of the tests that can be performed to reduce bias and confounding may increase acceptance and uptake of this methodology.

. . . obtaining benefit-risk perspectives from patient respondents can provide benchmarks for pharmaceutical development decisions and can help industry understand the overall clinical value of a product . . .

2 Status quo: Patient-reported outcomes

Patients can be better evaluators than clinicians of certain therapeutic outcomes and clinician-assessed endpoints may not include outcomes of relevance to patients. PROs, tools to collect direct patient responses regarding treatment effects, health-related quality of life or other characteristics, represent an opportunity to characterise the benefits or risks of a new medicine directly from a patient without interpretation by a clinician. Although there has been only limited use of PROs to support product approvals and labelling to date, there are at least two examples of the impact that the use of these outcomes has had in medicine development. The initial US product label for vinorelbine for treatment of stage 4 non-small cell lung cancer did not contain information related to PROs. However, after a questionnaire evaluated the effect of vinorelbine on health-related quality of life compared with fluorouracil (5-FU) and leucovorin among persons with the disease, labelling was approved to state that quality of life, distress and functioning was not adversely affected by use of vinorelbine when compared with the control.[1]

The Ruxolitinib in Myelofibrosis Symptom Assessment Form evaluated the effect signs and symptoms of importance to patients with myelofibrosis. This PRO instrument included concept elicitation to determine what disease and treatment parameters were important to patients as well as a cognitive debriefing to confirm the relevance of the survey instrument to patients. As a result of this assessment, a PRO endpoint was developed for use in the registration trial that measured the proportion of patients with a >50% decrease in a Total Symptom Score from baseline to Week 24, and resulted in corresponding claims being included in the US prescribing information.[2]

PROs limitations and positive features

As previously mentioned, patients may be more appropriate evaluators of some outcomes. Moreover, PROs represent an opportunity for greater patient engagement and provide a patient perspective in addition to clinical endpoints. However, in order for a patient-reported outcome to be qualified for regulatory use, a developer must ensure content and construct validity; reliability, sensitivity, respondent burden; translation into relevant languages and cultural adaptation of the tool. These qualifications can be labour intensive and even when outcomes are validated, it may be unclear how to interpret the results. At least in the US, few product labels that are approved actually contain information on patient reported outcomes, with the exceptions being products like ruxolitinib.[3]

Despite their current limited use, both conjoint analysis and PROs provide opportunities for improving patient-centric benefit-risk assessment, including increased awareness around the disease, unmet treatment needs and the impact of the disease potential treatment for patients. They provide an opportunity to better incorporate patients' perspectives into research hypotheses, build patient feedback into study protocols and to enlarge the proportion of patients represented in clinical trials.

3 Looking ahead: A patient-centric operational model

Various components of a patient-centric operational model are being implemented or have been planned for future implementation at Genentech; this includes considering the use of these inputs at key life cycle points; that is, at time of trial development design, feasibility study development and start-up, conduct and closeout. For example, it is envisioned that the current industry developmental model that features the use of key opinion leader clinician advisory panels and advisory boards to understand unmet medical needs can be adapted to benefit from information representing the patient's perspective.

It is further hoped that the planned Genentech Patient Pathway programme will allow researchers to gain insights into patient behaviours, whilst the Patient Voice curriculum will increase patient involvement in trials by incorporating formal opportunities for patient review of protocols prior to finalisation. In addition, the use of electronic health records for trial recruitment is being investigated. In this activity, timely and targeted trial awareness activities would be targeted to healthcare professionals so that they might consider presenting the option for trial enrolment to their appropriate patients at the time of diagnosis. This could allow the inclusion of the patients of community physicians who may not be tied in with large, highly recognised academic

research centres. Similarly, Telemedicine, which is used in clinical practice to reduce healthcare costs and deliver care to remote patients, could enable community-based clinicians to participate in trials in remote locations through the use of video conferencing with primary trial investigators. Remote patient oversight including early intervention, therapy adherence and safety oversight in clinical trials could be provided through the use of wearable devices to provide a feedback loop between patient and doctors

Genentech is also interested in finding ways to make greater use of innovations in mobile technology that will allow the use of wireless digital imaging and greater use of existing technology such as biosensors. For example, micro-chipped pills might allow investigators to understand the patterns of drug use during clinical trials. These technologies will allow a move from clinic-based static snapshots of patient health to a more dynamic stream of patients' physiologic data. It is hoped that that gathering information from natural settings as opposed to the artificial construct of a traditional clinical trial would allow decision making that is based on a more complete understanding of a product's real-world benefits and risks.

Challenges

Challenges remain to the incorporation of the patient voice. Clinical development must be adapted so that rather than being a gatekeeper of patient information, the clinician is seen as a patient partner. To affect these adaptations, however, healthcare providers must be included in the discussions surrounding necessary changes in policy.

It is also vital that industry understands both the opportunities and requirements for going directly to patients for data collection. They must address existing barriers to enable the use of patient feedback to inform clinical development decision making, which currently relies on clinical trial data, clinician feedback and regulatory precedence. In addition, stakeholders must act to optimise the use of technological innovation and develop standards to enable the timely uptake of devices that capture information in a more patient-centred setting.

Finally, as the use of patient preference research and patient-reported outcomes becomes more widespread, industry must ensure that information regarding product research, evaluation and use is available and relevant and understandable to patients.

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Patient involvement: A regulator's view on current activities

Prof Steffen Thirstrup

Former Director of Licensing Division, Danish Health and Medicines Authority

Regulators of medicines following a traditional paternalistic decision-making paradigm may be challenged in their interactions with today's informed and empowered patient. To overcome this challenge it is essential that they gain a better understanding of patients' perceptions and value judgements concerning the elements of benefit-risk evaluation and evaluate the traditional established endpoints of efficacy and safety for new medicines in light of the patent perspective together with their real-world relevance.

Additionally, regulators should understand that patients are not homogenous groups of people suffering from a disease but rather are individuals among whom only a subset may be appropriate candidates for new medicines, each with views on issues such as appropriate trial endpoints that may differ according to factors such as age and disease state. It is likely, for example, that a young person may be less willing to accept the risk of a serious adverse event in exchange for the relief of disease symptoms than would a person of advanced age with a more advanced disease.

The EMA has made some significant inroads to patient involvement in decision making. The agency has devoted a section on the EMA website to patients and carers at http://www.ema.europa.eu/ema/index.jsp?curl=pages/audience/alp_audiencetype_000001.jsp&mid=

This site contains news and information about medicines in the European Union for patients and consumers including the names of 34 organisations who represent the interests of European patients and consumers through their liaison with the EMA.

The EMA Human Scientific Committee's Working Party with Patients and Consumer Organizations 2013 Work Plan contains sections for the development of information to patients, pharmacovigilance and risk management, transparency and dissemination of information, interactions with healthcare professionals and other activities such as ad hoc participation in Scientific Advisory Group meetings and scientific advice, involvement in medications shortages and EMA geriatric medicines strategy, implementation of legislation on falsified medicines and participation in EMA workshops.

European legislation has specified that patients must be represented on the EMA Management Board, the Committee for Orphan Medicinal Products, the Paediatric Committee and the Committee for Advanced Therapies and the Pharmacovigilance Risk Assessment Committee. Although there is regular patient involvement with the Committee on Herbal Medicinal Products or the Committee for Medicinal Products for Human Use (CHMP), there is no permanent representation. This has been a point of criticism for the EMA, as the CHMP is the originator of final benefit-risk decisions for new medicines. However, patients do participate in CHMP activities as part of Scientific Advisory Groups and ad hoc expert meetings where, just as any other external advisor, they are required to comply with directives to resolve potential conflicts of interest.

The 2011 EMA Annual Report specified the numbers of individual patients and consumers who have been involved as experts in CHMP-related activities: 22 as participants in Scientific Advisory Groups; 13 as participants in scientific advice consultation; 4 as participants in the Committee for Orphan Medicinal Products; 27 in the review of Questions and Answer documents for safety, 38 in the review of European Public Assessment Report (EPAR) summaries; 71 in the review of package leaflets and 25 in the annual EMA training session, with a total of 200 experts.

However, although the majority of patients surveyed in 2011 regarding their EMA participation thought of it as a positive experience, half of surveyed regulators did not regard this involvement as beneficial. Admittedly, the survey only represents a small fraction of regulators but these results may indicate that although the paradigm is shifting, much work remains to be accomplished. Patients should be encouraged to participate in regulatory activities at the national and EMA levels to more fully participate in the pan-European agency.

The 2011 Annual Report specified the numbers of individual patients and consumers involved as experts in CHMP-related activities . . . with a total of 200 experts.

Methodologies to identify patients' views in clinical development: An academic viewpoint

Dr. Reed Johnson

Distinguished Fellow and Principal Economist, Health Preference Assessment Group, Research Triangle Institute

The need for patient value judgements

Whether patients can contribute to the benefit-risk assessment of new medicines depends on whether they are given an effective voice and whether anyone is listening to that voice. One method for the provision of the patient viewpoint is the collection of patient preference data. Throughout the life cycle of a medicine, these data can help to establish unmet medical needs, ascertain the relative importance of clinical trial endpoints and determine the maximum acceptable risk for a given benefit.

Regulators have indicated that simple evaluations of the benefits and risks of new products can be accomplished through the use of qualitative or semi-quantitative models such as the FDA Benefit-Risk Framework or the EMA Effects Table, whereas more complex evaluations involving associated adverse events that may be irreversible, difficult to treat or fatal might require quantitative analyses, in which treatment and disease attributes are weighted. However, establishing the relative importance of attributes such as elevated liver enzymes, symptom relief and severe events such as myocardial infarction or progressive multi-focal leukoencephalopathy, or general disease progression remains a subjective value judgement.

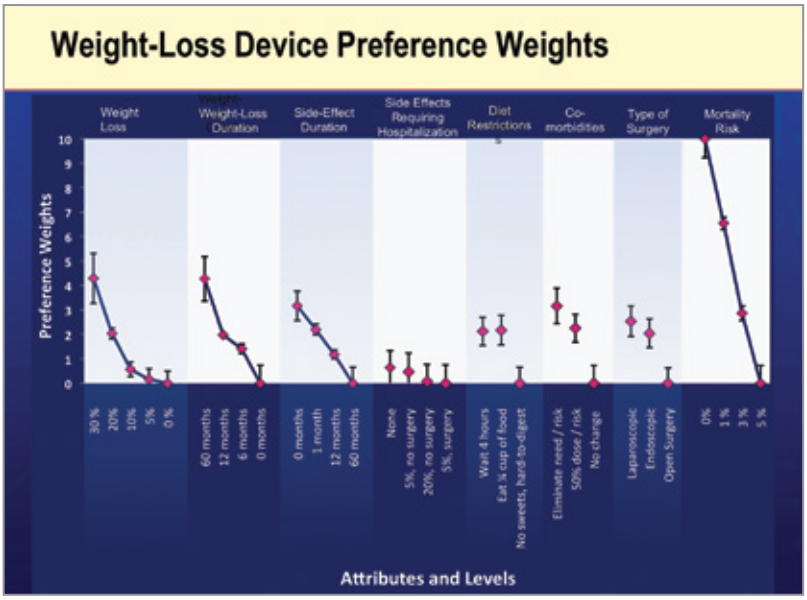


Figure 7. In a discrete choice experiment in weight loss device preferences, the importance of weight loss relative to potential adverse events increased significantly at 60 pounds.

As the EMA Guidance Document on the Co-Rapporteur Day 80 Critical Assessment Report there is a clear distinction between the factual data and value judgements that are both contained within benefit-risk assessment:

"The benefit risk assessment … contains a mixture of factual data and interpretation of the data through value judgements . . . A clear distinction between facts and interpretation is also a prerequisite to allow the reader to evaluate the intellectual processes and criteria that lead from the findings to the interpretation and conclusions on the benefit risk balance."[1]

Whereas the factual data in these evaluations comes from clinical trial results, the value judgements are made by clinicians and regulators, who have received no special training to render them more qualified to perform these evaluations than any other stakeholder in public health. In fact, it might be argued that patients rather than physicians or regulators are the best judge of their own welfare.

In the generation of the evidence of patients' value judgements, however, well-established criteria for acceptability or validity must be met. Respondents who are making the evaluations must be well informed, that is, they must evaluate relevant clinical endpoints with a common understanding of the benefits and risks. The research must be performed as a controlled experiment with randomised experimental stimuli and basic standards for rational preference measurement must be employed. The research sample size must be large enough to encompass the heterogeneity of preferences among patients that is due to condition severity, treatment outcome experience and socio-demographic characteristics. Finally, complex statistical analyses must be performed to evaluate the quality of the data, correct statistical modelling and test hypotheses.

Methodology differences, strengths and weaknesses

In the use of stated preference methods, treatment alternatives are characterised by combinations of features or attributes and the preferences among treatment alternatives depend on the relative importance of those features. Respondents state preferences among constructed alternatives and preference weights are calculated or estimated consistent with observed responses. These preference weights

. . . value judgements are made by clinicians and regulators, who have received no special training to render them more qualified to perform these evaluations than any other stakeholder in public health . . . patients rather than physicians or regulators are the best judge of their own welfare.

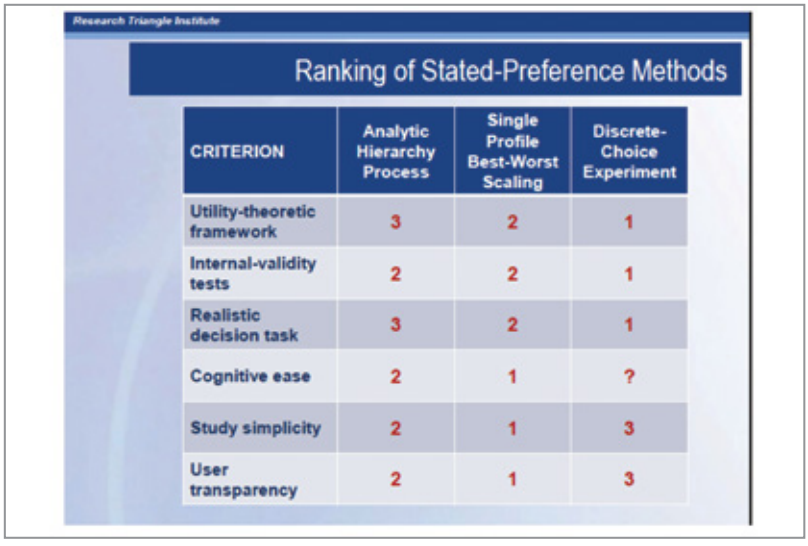
quantify relative importance as the willingness to accept tradeoffs among attributes. Stated preference approaches include analytic hierarchy process (AHP), best-worst scaling (BWS), discrete-choice experiments (DCEs) or conjoint analysis and multi-criteria decision analysis (MCDA).

In the AHP evaluation of medicines, two types of attributes of a disease or treatment are compared against one another at a time and scored, that is, efficacy attributes are rated against tolerability attributes, then efficacy attributes are also rated against risk attributes and finally, tolerability attributes are rated against risk attributes resulting in an overall "score" for a choice. In BWS, respondents rate individual disease or treatment attributes or complete disease or treatment profiles as "least important" or "most important." As discussed by Dr Cross (p 28), in DCE, respondents indicate their preferences for the individual attributes of two treatments and after the most preferred treatment feature is calculated, the value of the other attributes relative to that preference can be established and an overall choice question is posed to respondents.

Dr Johnson presented an illustration of the results of DCE in which respondents rated the attributes of weight loss surgery, which showed that the importance of weight loss increased significantly for respondents relative to the risk of adverse events as the amount lost reached 60 pounds (Figure 7). Similarly, Wong and colleagues demonstrated that DCE respondents with advance renal cell carcinoma indicated that they were willing to tolerate a 2% risk of liver cancer to achieve an increase in progression-free survival from five to ten months.[2]

Ranking the three stated choice methods, Dr Johnson found that DCE was superior to AHP and BWS in terms of consistency with a well-defined theory, internal validity and the ability to be presented to respondents as a realistic decision task. BWS and AHP, however, could both be considered more cognitively easy and simpler to administer and the results easier to explain compared with DCE (Figure 8).

Figure 8. Discrete choice experiments may be considered superior to both analytic hierarchy process and best-worse scaling according to three out of six criteria.



Challenges

There are challenges, however, to the use of all stated choice methodologies, including their potential for hypothetical bias, despite the fact that they are designed to be as plausible to respondents as possible. In addition, the surveys can be difficult to understand and interpret by many participants. To compensate for these challenges, researchers at Research Triangle Institute attempt to present options to survey participants in unique ways: graphically, numerically and as percentages. And although stated choice methodologies may appear to be simple to administer, they all require expertise in qualitative and quantitative survey methods. Moreover, the use of BWS and DCE also necessitates experience in experimental design, whilst DCE designers and administrators must have experience in advanced statistical analysis. Finally, the acceptability of stated choice research is often challenged by stakeholders, particularly regulators and payers.

Dr Johnson concluded with a quote from Professor Amriam Gafni, which points to the need to overcome these challenges and to use the most appropriate methodology to elicit patient preferences: "When asking the public to assist in determining health priorities, we should use techniques that allow people to reveal the true preferences. If not, why bother asking them at all?"[3]

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Syndicate introduction and pre-Workshop survey results

Dr Neil McAuslane

Director, Centre for Innovation in Regulatory Science

CIRS conducted a small survey to gain a perspective on patient involvement in the research and development and regulation of new medicines from participants from three patient organisations, seven regulatory agencies and six pharmaceutical companies. The survey covered the purpose and current scope of activities for patient involvement, thoughts on precompetitive collaboration, current challenges and ideas regarding the future landscape. It was envisioned that the results of this small sample would provide perspectives from these three stakeholder groups to help position the Syndicate discussions of the Workshop, which were designed to parallel the main parts of the survey

Disease state information – Company viewpoint

Results of the survey showed that clinical development and commercial teams from all six responding companies collect information from physicians regarding disease states routinely or on an ad hoc basis to meet specific information requirements. Two of the six companies also obtain this information from patients. Other groups from which some companies indicated information was collected included healthcare workers, payers, carers, patient advocacy groups, spouses and families.

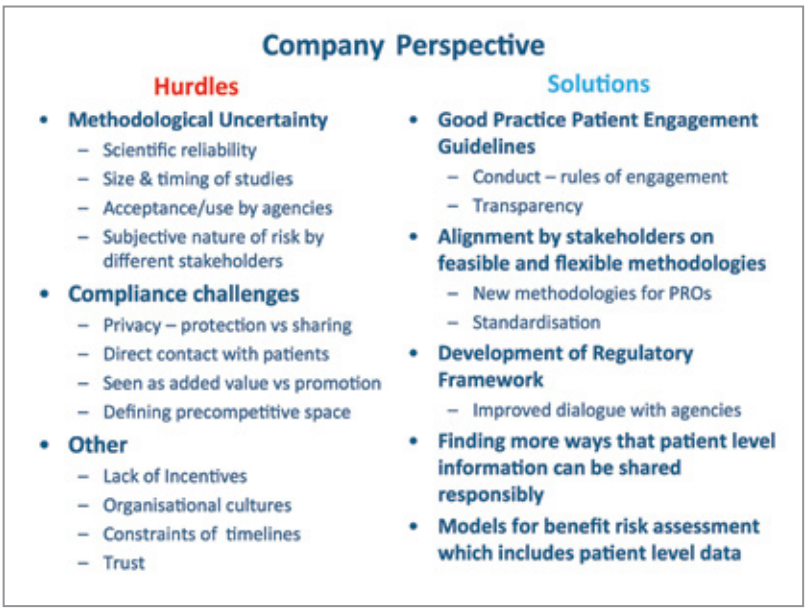

Figure 9. Perspectives of company respondents to CIRS survey on hurdles and solutions to patient input into benefit-risk decision making.

Companies specified that the primary reason that this information is collected is to inform the therapeutic product profile of a new medicine prior to initiation of development. The secondary reasons given were to make an informed decision on potential new treatments required and to decide on the benefit-harm/risk profile that new treatments should have. Companies also indicated, however, that the rationales were not so much primary and secondary as chronologic, with varying reasons at different developmental stage gates and various reasons for the use of the information among the functional teams.

All respondents specified that their companies collaborate to collect information on patients needs at the disease level; however, although the majority are working together with academics, patient groups and healthcare providers, only three companies indicated collaboration with regulatory agencies, two payers and one collaborating with other companies working in the same disease area.

Groups that are collecting information regarding patients in the precompetitive space included

- IMI PROTECT in Work Package 5
- Developers of regulatory authority guidelines
- The FDA through its patient network and disease area meetings
- The European Patients Academy on Therapeutic Innovation (EUPATI)

In addition, information is also obtained through specific patient group meetings, interviews with patients and healthcare professionals, online patient communities, focus groups, blinded market research, anthropometric research and thought leader and patient advisory boards.

Precompetitive space – Company and agency viewpoints

All responding companies and the majority of agencies agreed that the companies should collect and share precompetitive, disease-level data. Five of seven agencies also felt that agencies should be involved in this activity as well. Survey respondents indicated that the primary topic for data collection is the tradeoffs that patients at different stages of disease progression would be willing to make in terms

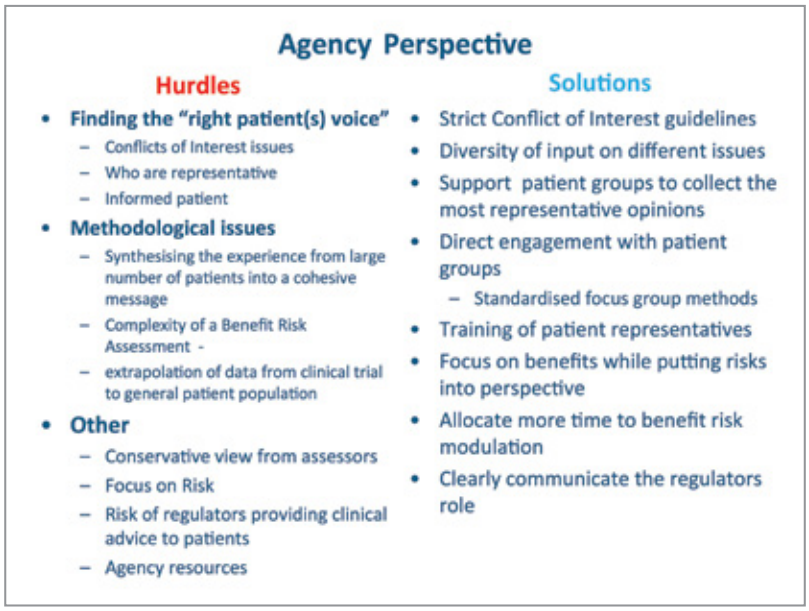

Figure 10. Perspective of agency respondents to CIRS survey on hurdles and solutions to patient input into benefit-risk decision making.

of benefits and risks. Secondary topics were diseases that require new or better treatments and detailed information around the benefits that patients with the disease or their carers are looking to have as part of a new treatment. It was also suggested by participants that priorities rather than tradeoffs might be better terminology to use for patients, especially for those experiencing the early stages of a disease.

Development- and product-specific approaches – Company viewpoint

Although the majority of company respondents felt that their company should routinely elicit patient views on the benefits and harms of a medicine throughout its lifecycle, most were unsure if this occurred in their company any time other than during phase 2b/3. Four companies indicated that they routinely provide patients with information on the results of clinical trials and for two of those companies, information was provided solely through publication. Three companies provide information on benefits and risks that have been identified for new products and again, two of those companies only provided the information via publication. Half of companies informed patients of the methodologies employed for evaluating benefits and risks. However, patient group respondents specified that benefit and risk information was only occasionally or rarely forthcoming from companies.

Companies collect information about a product's benefits and harms from physicians, patients undergoing treatments via patient-reported outcomes and other means, patient groups, carers and non-physician healthcare providers. The results from the outcome of the clinical trials in terms of efficacy and safety were given the most weight by companies in their development of a benefit-risk profile for a new medicine followed by the views of treating physicians and finally, the views of patients.

Agency viewpoints

Three of seven agency respondents include or invite direct patient input with regard to benefits and harms from patients during the review process. Two of those respondents also indicated that this viewpoint was a part of the decision-making process while one specified that the input was an aid. Two agencies involve individual patients in this process, three involve patient groups and one, patient advocates. Two agencies solicit patient opinion regarding a product's benefits, three regarding its harms and three regarding the relative importance and tradeoffs for benefits and harms and disease- or treatment-level opinions.

In fact, all respondents thought that regulators should solicit information regarding the relative importance or tradeoffs of benefits and harms directly from patients although only a limited number of agencies are currently doing so. Individual comments indicated that regulators should obtain this information from patients as their ultimate customer, to balance the risk awareness of the regulatory agency and to ensure that regulatory decisions are aligned with patient preferences and willingness to trade benefits for risks. It was also remarked that although it is difficult to solicit information directly from individual patients, is it appropriate to use patient group representatives in forums that include experts, healthcare professionals and regulators.

Six of seven agency participants indicated that the usefulness and contribution of patient-reported outcomes (PROs) is very dependent on how the PRO instrument has been developed and validated. One respondent said that PROs were critical to informing regulatory decisions,

. . . good regulatory decision making needs to be supported by substantiated clinical data for efficacy and safety and by objective science-based assessment approaches based on knowledge and experiences

two said they provide some useful information and four said they are currently of limited use to reviewers.

Patient organisation viewpoints

All three patient organisations have been invited to give direct patient input by pharmaceutical companies or regulatory agencies, two in aid of the design and conduct of a clinical trial. All three have been asked about the benefits for which patients are looking, whilst one was asked occasionally by agencies and two were asked occasionally by companies about the harms about which patients are concerned. Two participants were asked for their perspective on relative importance or their understanding of tradeoffs occasionally by agencies and three participants occasionally by companies.

Regarding the communication of benefits and harm for medicines to patients, one respondent felt that companies' performance was satisfactory and two that is was poor. All three participants felt that regulators communicated benefits and risks poorly. One respondent felt that healthcare professionals communicated this information very well and two satisfactorily. Finally, two participants felt that publicly available documents communicated the benefits and harms of new medicines satisfactorily and one indicated that this communication was poor. Individual comments were that healthcare communication in general was poor with the use of unclear and jargon-laden language. It was also commented that patients are the experts living with the illness and their views are focused and relevant.

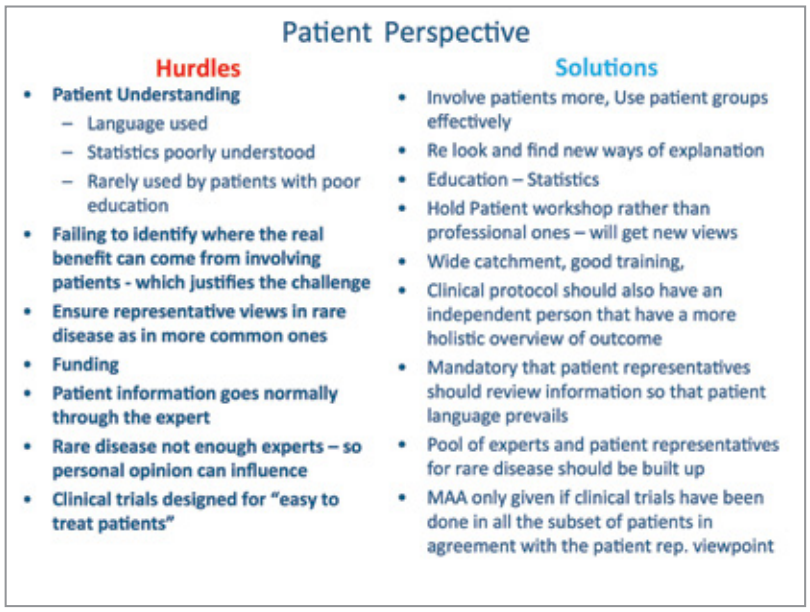

Figure 11. Perspectives of patient organisation respondents to CIRS survey on hurdles and solutions to patient input into benefit-risk decision making.

Hurdles and solutions

From the company's perspective, the hurdles to patient participation centred on methodologic uncertainty regarding how the input would be used and accepted. Other challenges included compliance, organisational culture, timing constraints in development and lack of incentives and trust. Proposed solutions included patient engagement guidelines, alignment on feasible and flexible methodologies and models for benefit-risk assessment (Figure 9).

From the agencies' perspective, hurdles centred on finding representative, informed patients without unresolved conflicts of interest, methodological issues in terms of synthesising the experience from a large number of patients into a cohesive message and extrapolating clinical trial data to general patient populations, conservative assessors with a focus on risk and a lack of agency resources. Solutions that were proposed included conflict of interest guidelines, direct engagement with patient groups and clear communication of the regulator's role (Figure 10).

From the patient's perspective, a lack of understanding is a major hurdle, in terms of the language and statistical methods that may be poorly understood. Additional issues include a lack of experts in some rare disease areas, a lack of funding and the exclusion of patients from clinical trials who are more difficult to treat. Proposed solutions include the expansion of patient involvement, education and patient workshops and the development of a pool of experts in rare diseases (Figure 11).

Dr McAuslane concluded by asking Syndicate participants to discuss the prospective landscape for this issue through the discussion of the critical success factors that will enable the involvement and assessment of patients' perspectives on benefits and harms to contribute to the future successes of the research and development and regulatory review of medicines.

The utilisation of social media and new technology to gain a better understanding of patients' needs: How could it be appropriately harnessed for clinical development?

Moira Daniels

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AstraZeneca is using cutting-edge technologies and services to increase and improve the flow of information to patients in the clinical development and post-approval settings, to track how a medicine is impacting the patient's healthcare outcome in real time and to gain insights regarding a patient's experience and how they use their medicine. Other companies are also investigating the use of these technologies to improve patient outcomes, and clinical trials are currently ongoing worldwide to investigate the use of informatics such as "smart phone" applications to promote medication adherence and achieve a positive benefit for patients.

There are currently two billion people worldwide using the internet and five billion, or 72% of the world's population have access to information via mobile telephones. Health is the most common web topic and although more than 85% of patients use a technology to obtain information on health-related topics there is no quality control governing this information. Potential applications for new technologies that could be targeted to these technology users include improved treatment adherence, clinical decision making through the monitoring and analysis of clinical investigation data such as measurements of blood pressure, cholesterol and lung function as well as the occurrence of adverse events. Clinicians could use the technologies to make adjustments to treatments and analyse trends and patterns in clinical investigation data in real time. Technologies could also optimise the use of patient-reported outcomes and enable effective clinical trial recruitment.

Today's digital home may contain multiple electronic devices such as glucose meters, scales, pedometers and blood pressure cuffs that could be used to link stakeholders and move healthcare communication to a new paradigm. Accordingly, AstraZeneca has formed a project team with various external partners called Intelligent Pharma that seeks to enable some of these devices to improve the level of disease and treatment information in healthcare records and make that information available to family caregivers and healthcare providers. Technologies that can potentially be used include mobile phone alerts, specially developed applications or devices, email alerts, iPads, web-based programmes and everyday appliances such as watches with specific design features.

However, although it is currently possible for healthcare providers to access some patient data and to provide limited information to patients and simple medication reminders, technology is not yet being fully utilised, in part due to legislation constraints that require paper sources for patient information. Sophisticated medication reminders, additional disease management, healthcare services and outcome reporting and the use of data to tailor interventions to maximise the benefit of treatment on overall health outcomes remains in the future (Figure 12).

Errors in key variables in clinical trials include violations of inclusion or exclusion criteria, the interpretation of efficacy phenomena as adverse events (AEs) and vice versa and incorrect interpretation of AEs or attribution of their causality. When AEs are inappropriately managed they can develop into serious events and lead to errors in titration or inappropriate withdrawals from trials and ultimately, frequent occurrence of

Figure 12. Only limited use has been made of healthcare informatics technology to date.

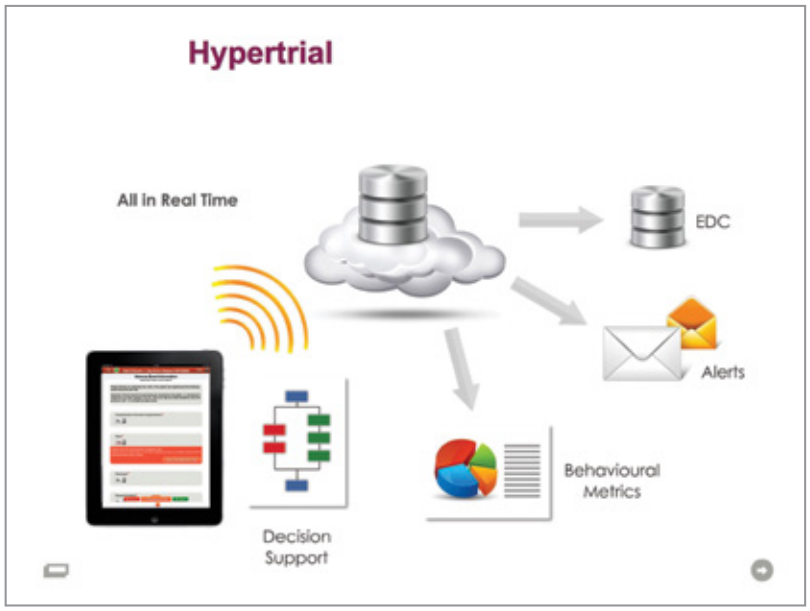


Figure 13. AstraZeneca is piloting the use of new technology to aid in treatment decision making and record keeping.

this type of error may compromise the integrity of a clinical study. For example, there was a high rate of withdrawal in a recent oncology trial because the occurrence of a controllable rash among treated patients was not being adequately managed. To meet this important challenge, AstraZeneca worked with an external developer to design an application for use by the treating clinician during study visits that will encourage the physician to employ the recommended treatment algorithm in order to retain patients in the study so that they could achieve the long-term benefits of treatment. This application contains links to reference documents applicable to a particular patient and his treatment in order to manage the patient interaction, enter data electronically and aid in clinical decision making. It additionally allows the company to compile insights as to the behavioural metrics of clinicians (Figure 13).

. . . [as a result of new technology] patients are able to take control of their illness, take the right dosage at the right time, receive evidence that a treatment is having the desired effect, improve outcomes to their health and manage side effects . . .

This type of application yields several important benefits to patients. In addition to promoting an awareness of clinical trials, patients are able to take control of their illness, take the right dosage at the right time, receive evidence that a treatment is having the desired effect, improve outcomes to their health and manage side effects in real time. It also is a source of individualised data and tailored support that should improve the quality of physician and patient conversations, providing patients with needed information on their disease and its treatments.

The use of new technologies is not without its challenges. In the United States, applications that contribute to or make a clinical decision are considered by the FDA to be the equivalent of medical devices, which need to conform to relevant device regulations; however, their regulatory status in Europe is unclear. What is clear is that the use of new technology in healthcare will continue to grow, which is perhaps reflected in the fact that on the day of this presentation, the National Health Service in the UK released publicly an application library for managing health, which can be found at http://apps.nhs.uk/.

How can new communication technologies help a regulator better understand patients' needs?

Dr John Skerritt

National Manager Therapeutic Goods Administration, Australia

TGA transparency review

The Therapeutic Goods Administration (TGA) of Australia regulates therapeutic goods including prescription, over-the-counter and complementary medicines, medical devices, biologicals, blood and blood products. It evaluates these goods before they are marketed and monitors products once they are on the market, assessing the suitability of medicines and medical devices for export with a focus on safety, efficacy and quality. The agency does not regulate professional practice, reimburse for the cost of medicines nor evaluate their cost effectiveness.

In 2010, a transparency review was conducted, resulting in a number of key recommendations. These recommendations included that the Australian Therapeutic Goods Advisory Council be established. To strengthen its communications, it was further recommended that the TGA develop and implement a comprehensive communication strategy; work with other key providers of information more systematically; ensure that information on the TGA website is current, accurate, relevant, timely and meets audience needs; provide user-friendly information on the risk-based framework under which TGA operates. There were a number of other transparency recommendations related to product regulation, such as a recommendation to conduct a feasibility study into an early post-approval risk communication scheme for therapeutic goods.

To provide transparency in its regulation of therapeutic goods, the TGA was advised to provide explanations on its regulatory processes; adopt publication principles on the outcomes of application assessments; publish a policy on disclosure of commercially confidential information; assess the feasibility of developing an on-line system for submission and tracking of applications for assessment; educate the public that listed (complementary) medicines are not evaluated for effectiveness by TGA prior to market; improve medicines labelling and packaging to assist consumers and health practitioners to make informed decisions and maintain the currency of Consumer Medicines Information and Approved Product Information.

Regarding important information about adverse events, alerts and recalls it was recommended that the TGA facilitate the recognition and reporting of adverse events by health practitioners and consumers and make an Adverse Events Database available to and searchable by the public; improve the visible management of adverse events from immunisation; improve timely communication of alerts and recalls. Finally, in matters of advertising the transparency review recommendations were to improve the access to and quality of information on the processes for regulation of advertising of therapeutic goods, including complaint processes and outcomes and develop and implement a system to publish the outcomes of investigations and compliance actions taken.

Figure 14. The TGA has established a a recalls and safety alerts portal and early warning system to inform about potential safety issues

TGA Communication and Education Framework

As a result of these recommendations, a public TGA Communication and Education Framework was established. The framework outlines the roles and responsibilities of the TGA and how new activities will be implemented and existing activities enhanced. It also provides the specifics regarding interactions with other information providers, communication and education priorities including communicating about the role of the TGA and the benefit versus risk approach of the TGA and projects to be conducted from 2013 through 2015. These projects include the development of

- a publicly available adverse events database

Figure 15. The Department of Health uses Twitter to rapidly alert stakeholders rather than as a two-way communication.

- a recalls and safety alerts portal and early warning system to inform about potential safety issues (Figure 14)
- procedures for complaints about therapeutic goods and advertising
- explanations of benefit-risk assessment of new prescription and over-the-counter medicines, processes used to evaluate generic medicines for registration and the listing process for complementary medicines
- publication of post-market reviews of complementary medicines
- information about TGA enforcement powers, procedures and outcomes of enforcement activities and regulatory processes and agency roles in the food /registration interface.

The TGA recognises that "old-fashioned" approaches still have a place in communications, including the use of mass media – TV, newspaper and radio extensively draw on the TGA website and Rich Site Summary (RSS) feeds. Other channels of communication include patient and consumer representatives on the Advisory Committee for Prescription Medicines and the Advisory Committee for the Safety of Medicines, face-to-face meetings involving consumer representatives and the TGA Public Contact Team.

TGA, including through its Public Contact Team receives 41,000 phone and 150,000 email inquiries annually and customer service standards have been established for the consistency, timeliness and nature of TGA replies. Depending on the nature of the call, the team can also refer callers to the TGA website, TGA specialist professional staff or other information as required. Medicine-related queries from patients and consumers include those concerning personal importation of medicines and travelling overseas with medicines; complaints about medicine performance, quality and side effects and questions regarding whether a particular product is available for use for a condition. The nature of these queries also contributes to informing TGA's future communication priorities.

TGA and social media

The TGA employs the use of Twitter accounts managed by partners at the Department of Health and Ageing (@HealthAgeingAU); Australian Prescriber (@AustPrescriber) NPS (@NPSmedicinewise) and the Australian Consumer Health Forum (@OurHealthAus) in a limited way. However, most of these partners use Twitter to rapidly alert stakeholders rather than as a two-way communication (Figure 15). Micro-blogs are often linked to web pages and patient or consumer feedback is usually sought through email or phone. RSS feeds are used in a similar way.

The TGA has been conservative in its use of social media because of concerns about

- resource requirements for active participation in social media and moderation of posts;
- a loss of control over information, which is a challenge when the accuracy of regulatory information provided by TGA can be a factor in legal proceedings;
- legal liability for non-removal of inaccurate or discriminatory comments;
- the need to ensure a consistency of message disseminated through many channels;
- presence of advertising on social media sites, and
- commercial confidentiality, because details of medicines being considered for registration are not publicly disclosed in Australia.

In addition, TGA does not wish to discourage consumers from seeking advice from a healthcare professional, for which social media is not a substitute.

However, it is recognised that there are multiple opportunities for communication through social media for regulators and other stakeholders. Facebook and YouTube videos can be used to explain risk, the pharmaceutical registration processes, the appropriate use of medicines and

to encourage adverse events reporting. Twitter and Facebook can be used to communicate the registration of major new medicines and medicine and medical device recalls and to report adverse events, although the legal issues surrounding content must be carefully considered. Other media can be used to gather input to inform medicines development and regulatory priorities, for recruitment for clinical trials, to identify indications that need to be addressed, to address demands for off label use and to communicate the benefits and risks for new medicines at the disease level. The US FDA interactive video "Medicines in My Home" (http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingOver-the-CounterMedicines/ucm092139.htm) is an example of the appropriate and thoughtful use of social media for communication.

Communicating regarding TGA activities and obtaining feedback from stakeholders using traditional and new media is particularly critical for the TGA during 2013/14 when they will be engaging in reforms in prescription medicines, medical devices, medicines labelling and packaging, complementary and over-the-counter medicines regulation, therapeutic goods advertising, medicines compounding and post-marketing reforms in adverse events, safety signals and product recalls.

Facebook and _YouTube_ videos can be used to explain risk, the pharmaceutical registration processes, the appropriate use of medicines and to encourage adverse events reporting.

Dr Skerritt concluded by stating that stronger consumer and patient communications is central to his vision for TGA, with strong science-based internationally harmonised regulations relative to the level of risk and consistent decisions based on the national Act and Regulations. TGA is currently modifying its processes and procedures through a pathway involving consultation and transparency and will continue to strive to achieve a greater predictability of regulatory processes and timeframes and to attract and retain excellent and committed staff and to improve communications with industry and consumers including the time- and resource-efficient use of new technologies.

The utilisation of social media and new technology to gain a better understanding of patients' needs: How could it be appropriately harnessed for clinical development?

A patient perspective

Achim Kautz,

Policy Director, European Liver Patients Association

Why use social media?

Because the general public is 90% more likely to trust the recommendations of someone they know and 70% more likely to trust independent as opposed to institutional recommendations, the use of social media is an important method for patient communication as well as a resource to obtain patient data. However, the landscape of social media changes rapidly and varies vastly from country to country, with consumer preferences for specific media channels also varying according to age and demographics:

- *Facebook* and *Twitter* are of primary importance worldwide, with 100,000 uses or "tweets" on *Twitter* every minute.
- *LinkedIn* has grown in popularity in the United States where its use currently outstrips that of *Facebook*.
- In China, meanwhile, the top-ranking social channel changes every week.
- *YouTube* has emerged globally as a viable, portable platform for non-written education.
- Web pages are considered to be the most stable media tool.
- *SurveyMonkey* is a quick and easy method for obtaining data. In fact, there is enormous potential to rapidly acquire useful patient data from almost all of these media although the trend toward the use of close communication circles such as those in *Google+*, which is currently popular in Germany, are not easily penetrated by industry, regulators or even

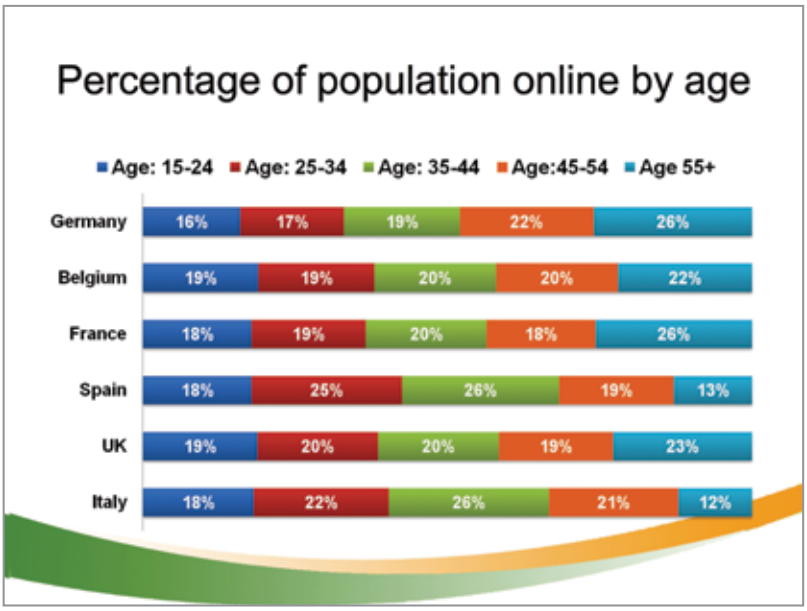


Figure 16. In Europe, people of all age groups are using the internet.

patient representatives, since personal invitations are required for access.

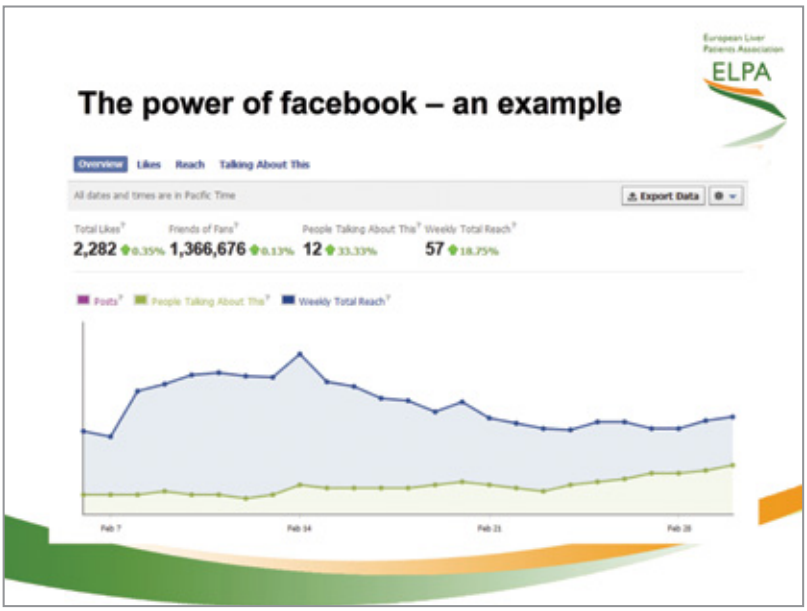
- Contrary to popular assumption, people of all ages are online and in several countries in Europe, use by those 55 years and older is greater than that of people aged 15 to 24 years and is growing (Figure 16).

Using social media for research

To gain a better understanding of patients' needs, communication should occur on the different levels of social media. The use of *Twitter* and *Facebook*, online questionaires through *SurveyMonkey* or online tests allows the collection of many answers to specific questions in a short timeframe. For example, the German Liver Aid Society (Deutsche Leberhilfe E.v.; http://www.leberhilfe.org) has developed an online test to determine an individual's likelihood of becoming a liver patient that is taken by 60,000 people each month at www.lebertest.de.

In addition, in 2012, the Society tested the power of *Facebook* communication to raise awareness of the link between receiving a tattoo under unsterile conditions and the development of hepatitis. Well-known tattoo artists were asked to promote a one-question survey: "Have you ever received a tattoo under unsterile conditions or do you know someone who has?" The total of those who "liked" or promoted the question was 2,282 people, who had a total of 1,366,676 friends, all of whom were exposed to the question and its message. Within seven days the Association received 60,000 answers from people who could be added to a database and sent subsequent requests for information multiple media forms (Figure 17).

Figure 17. Over one million people were exposed to a hepatitis awareness message posted on Facebook.



It is important to understand, however, that for the results of social media research to have scientific validity, specific requirements must be fulfilled. There should be a minimum of 500 valid responses from a good cross section of a population. The results must be compared with results obtained from non-chronically ill people and the survey must be repeated to identify trends.

Maximising the effect of communication

Only a minority of patients are aware that social media are used as platforms for scientific research and patient organisations should learn to promote this type of use on their web pages and integrate it into their social media toolkits. In an example of the successful promotion of social media research, the German Liver Aid Society conducted two sequential online surveys in hepatitis C patients in two years, the results of which indicated that hepatitis C has a negative impact on quality of life and social well-being. The survey additionally found that although patient quality of life improves with successful treatment it may deteriorate if treatment is unsuccessful. In addition to being published in the journal Zeitschrift für Gastroenterologie, the results were discussed at the German Hepatitis C Guidelines Conference. As a result of publicising the patient input contained in the surveys, the current German Hepatitis C Guidelines specify that a patient's wish for or against

It is important to understand, however, that for the results of social media research to have scientific validity, specific requirements must be fulfilled.

treatment must be respected and treatment must be offered to all patients who do not have contraindications upon their request.

Finally, it is important to remember that face-to-face meetings should also be considered to be a form of social media. The European Liver Patients Association routinely invites industry representatives to its Advisory Board meetings and scientific roundtables to discuss patient needs and questions about new drug safety and efficacy that have been elicited from surveys and live meetings. Other issues that are discussed include the optimal setting for clinical trials; that is, inclusion and exclusion criteria and the compassionate use of new medicines. Mr Kautz invited regulators and members of the pharmaceutical industry to consider the use of the power of patient organisations to obtain the input of these important stakeholders in medicines development and regulation.

Appendix: Workshop Attendees

Patient representatives		
Dr Mary Baker	President	European Brain Council
Achim Kautz	Vice President	European Liver Patients Association
Jean Mossman	Policy Lead	European Federation of Neurological Associations, UK
Jeremiah Mwangi	Policy and External Affairs Director	International Alliance of Patients' Organizations, UK
Regulatory and health technology agencies		
Prof Sir Alasdair Breckenridge	Former Chairman	Medicines and Healthcare Products Regulatory Agency, UK
Dr Petra Dörr	Head of Management Services and Networking	Swissmedic
James Leong	Senior Regulatory Specialist	Health Sciences Authority, Singapore
Dr Jan Mueller-Berghaus	Head, Major Policy Issues, International Relations Unit	Paul-Erlich-Institut, Germany
Prof Robert Peterson	Executive Director	Drug Safety and Effectiveness Network, Canadian Institutes of Health Research
Dr Francesco Pignatti	Head of Section, Oncology. Haematology & Diagnostics	European Medicines Agency
Sinan Bardakci Sarac	Senior Medical Officer	Danish Health and Medicines Authority
Dr Eyal Schwartzberg	Head of Pharmaceutical Division	Ministry of Health, Israel
Dr John Skerritt	National Manager	Therapeutic Goods Administration, Australia
Prof Steffen Thirstrup	Former Director of Licensing Division	Danish Health and Medicines Authority
Victoria Thomas	Associate Director, Public Involvement Programme	National Institute for Health and Clinical Excellence, UK
Pharmaceutical companies, public/private partnerships, research groups and consultancies		
Lill-Brith von Arx	PhD thesis employee	Novo Nordisk A/S, Denmark
Dr Jamie Cross	Program Director, Product Development Regulatory	Genentech Inc, USA
Moira Daniels	Vice President, Regulatory Policy, Intelligence and Labelling	AstraZeneca, UK
Robin Evers	Vice President, Worldwide Safety and Regulatory	Pfizer, UK
Dr Louise Gill	Senior Director, Global Regulatory Affairs	GlaxoSmithKline, UK
Prof Michel Goldman	Executive Director	Innovative Medicines Initiative, Belgium
Dr Surendra Gokhale	Head, EU/RoW CT Regulatory Management	F. Hoffmann-La Roche AG, Switzerland
Dr David Guez	Director of R&D Special Projects	Recherches Internationales SERVIER, France
Dr Sanjay Gupta	Executive Director and Head of Health Economics and Outcomes Research	Daiichi Sankyo, USA
Zalmai Hakima	Associate Director, HEOR	Astellas Pharma Global Development, The Netherlands
Dr Ansgar Hebborn	Head, GPMA Market Access Policy	F. Hoffmann-La Roche AG, Switzerland
Moira Howie	Director, Global Advocacy and Professional Relations	Eli Lilly & Co, UK
Frederic Ivanow	Senior Director	Janssen, UK
Dr David Jefferys	Senior Vice President	Eisai Europe, UK
Kim Johnson	Senior Director, Regulatory Affairs	Celgene Europe Ltd, UK

Dr Reed Johnson	Distinguished Fellow and Principal Economist	Health Preference Assessment Group, Research Triangle Institute, USA
Dr Thomas Lonngren	Strategy Advisor	
Dr Christine Mayer-Nicolai	Senior Director, Head Regulatory & Science Policy Europe	Merck KgaA, Germany
Ana Oliveira	Associate Director, Global Regulatory Affairs	Takeda, UK
Taisa Paluch-Kassenberg	Senior Regulatory Affairs Manager	Astellas Pharma Europe B.V, The Netherlands
Dr Patricia Pellier	Vice President, Regulatory Affairs EMEA	Celgene, Switzerland
Dr Frank Rockhold	Senior Vice President, Global Clinical Safety and Pharmacovigilance	GlaxoSmithKline, USA
Dr Stefan Schwoch	Senior Director, GRA-EU Oncology and CV	Eli Lilly & Co Ltd, UK
Dr Isabelle Stoeckert	Head, Global Regulatory Affairs Europe/ Canada	Bayer Pharma AG, Germany
Maggie Tabberer	Director, Respiratory PRO, Global Health Outcomes	GlaxoSmithKline, UK
Mary Uhlenhopp	Senior Manager, Advocacy and Ally	Amgen (Europe) GmbH, Switzerland
Dr Liia Vaichtein	Associate Director, Global Medical Affairs	Takeda, UK
Dr Kristin Van Goor	Senior Director, Scientific and Regulatory Affairs	PhRMA, USA
John Way	Director, Regulatory Affairs	Biogen Idec Limited, UK
Academic institutions		
Professor Bruno Flamion	Professor of Physiology and Pharmacology	University of Namur, Belgium
Kimberley Hockley	PhD Student	Imperial College, London
Prof Sam Salek	Director, CSER	Cardiff University, UK
Centre for Innovation in Regulatory Science		
Nicola Allen	Research Fellow	
Patricia Connelly	Manager, Communications	
Art Gertel	Senior Research Fellow	
Lawrence Liberti	Executive Director	
Dr Iga Lipska	Senior Research Fellow	
Dr Neil McAuslane	Director	
Prisha Patel	Manager, Emerging Market Programme	
Professor Stuart Walker	Founder	