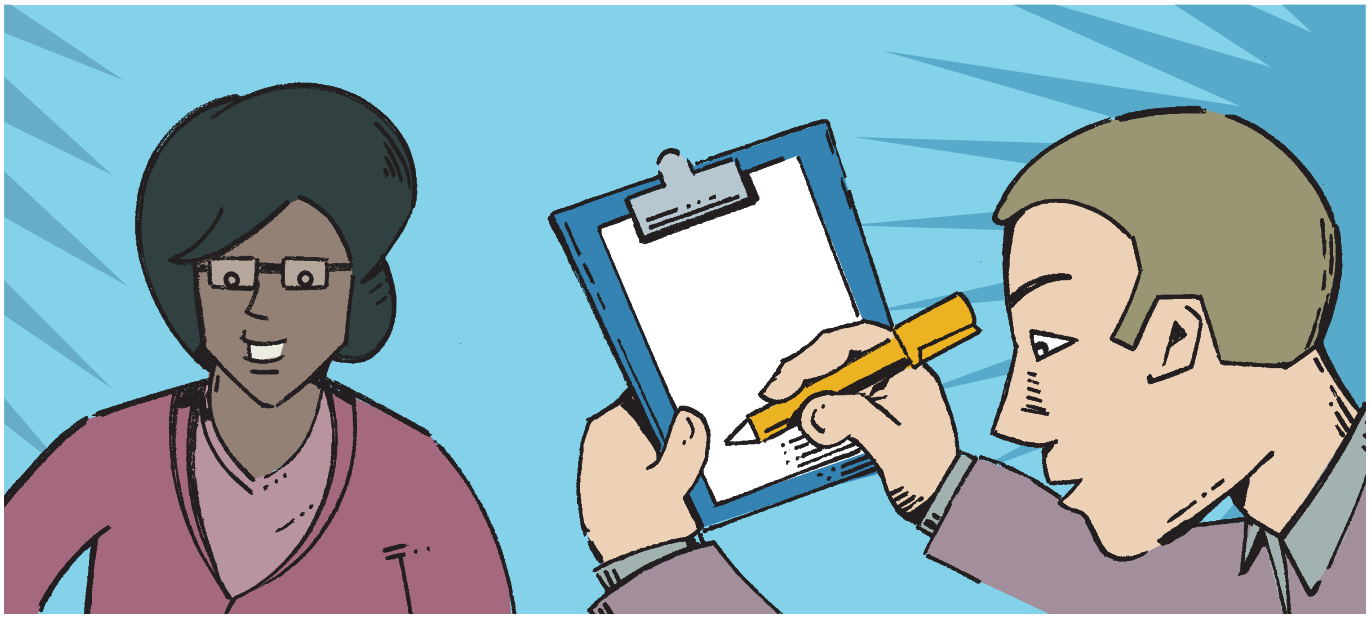

THE ASSESSMENT OF BENEFITS AND HARMS AND THEIR RELATIVE IMPORTANCE FOR PATIENTS, INDUSTRY AND AGENCIES:

HOW SHOULD THEY BE CAPTURED?

2-3 APRIL 2014
SURREY, UK

WORKSHOP REPORT

CIRS Centre for Innovation in Regulatory Science

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CIRS - The Centre for Innovation in Regulatory Science - is a neutral, independent UK-based subsidiary company, forming part of the Intellectual Property and Science business of Thomson Reuters. The mission of CIRS is to maintain a leadership role in identifying and applying scientific principles for the purpose of advancing regulatory and HTA policies and processes. CIRS provides an international forum for industry, regulators, HTA and other healthcare stakeholders to meet, debate and develop regulatory and reimbursement policy through the innovative application of regulatory science. It is governed and operated for the sole support of its members' activities. The organisation has its own dedicated management and advisory boards, and its funding is derived from membership dues, related activities and grants.

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Section 1: Executive Summary

Background to the Workshop

Patients' perspectives on benefits and harms are critical to the development and review of medicines. The question for agencies, companies and patients is not whether the incorporation of those perspectives should occur but how. Aside from the data generated directly from clinical trials, patients and patient groups are only occasionally engaged in discussions of benefits and harms and how these can be considered in regard to their relative importance in their lives. The challenges for patient participation from a company's perspective centre on how best to integrate patient values into clinical development, the methodology to capture their input and on the uncertainty regarding regulatory agency acceptance of the input. The challenge for regulatory agencies, meanwhile, lies in how to extrapolate patients' viewpoints on benefits and risks to the general patient population.

The key questions for discussion are

- When patients', agencies' and companies' perspectives on benefits, harms and relative importance differ, how should this be reconciled?
- Should patients' perspectives (apart from highly objective clinical trial data) be collected?
- What influence will such information have on both company and agency decision-making processes?
- How should this information be elicited?
- Can there be development of simple methodologies that meet both the agencies' and companies requirements?

This Workshop focused on the potential differences among stakeholders and whether there could be a way of simply collecting patients' views on benefits and harms and their relative importance that can allow patients' perspectives to inform company and agency decision making.

Workshop Objectives

- **Review methodologies** for capturing benefits and harms and their relative importance
- **Identify** differences in the relative importance of benefits and harms among stakeholders
- **Make recommendation**s for different approaches that patients can take to inform companies and agencies of their needs

Key points from presentations

Day 1 Chair, Professor Robert Peterson, *Executive Director, Drug Safety Effectiveness Network, Canadian Institute of Health Research* initiated the Workshop by emphasising its focus: the patient perspective on the uncertainties that remain regarding the benefits and harms of a new medicine following its extensive and expensive drug development programme and regulatory authorisation. As the terminology in this area continues to evolve, it is important for all stakeholders to recognise that the users of a new therapy incur not only the risk that may be associated with the product's safety but the risk that may be associated with its efficacy; that is, the risk that a benefit will not be derived.

The keynote presentation by **Dr John Skerritt**, *National Manager, Therapeutic Goods Administration, Australia* set the stage through the identification of important issues for examination at the Workshop: Consumer survey information is valuable in challenging assumptions and identifying priorities for healthcare communication. Regulators are increasing their engagement with patient groups but it has still been a challenging to capture detailed and broad input from patients into medicines authorisation. Some excellent initiatives are underway to help understand patient perspectives better but pre-market input from patient groups is often sought and received by regulators too late in the product review process. Finally, patients and patient groups have an equally important role in pharmacovigilance.

Researchers have written that one of the main challenges in the assessment of the benefits and

harms of new medicines relate to the selection of health outcomes that are important to patients. **Jean Mossman**, *Policy Lead, European Brain Council* pointed out that patient-reported outcomes should be those with an impact on disease and on aspects of daily living with implications for the patient's future. Ideally, these outcomes should also be individualised, as they are likely to vary over the course of a disease and changing personal circumstances. In addition, patients and caregivers should be involved in deciding the metrics of collecting the outcomes at times the patient deems appropriate, which may vary by patient, by illness and by the stage of the disease.

All stakeholders acknowledge the need to take into account the patient's experience with a disease and its treatment and integrate this parameter into the evaluation of medicines. **Dr Isabelle Moulon**, *Head of Patients and Healthcare Professionals, European Medicines Agency (EMA)* explained that the EMA involves patients along the life cycle of the medicine as experts in their disease and its treatment. The EMA interacts with patients and patient groups in two different aspects: first, as people representing themselves or people like themselves with a certain disease or condition, through dialogue with patients' organisations and patient participation in EMA Patients' and Consumers' Working Party and workshops and second, as people representing the general patient community through membership in scientific committees evaluating new medicines.

Since 2011, the benefit-risk team at GlaxoSmithKline has assisted internal product teams in the development of systematic presentations of the evaluation of the benefit-risk of medicines. **Dr Marilyn Metcalf**, *Senior Director, Benefit Risk Evaluation, GlaxoSmithKline, USA* reported that the number and diversity of products for which the benefit-risk team's services have been employed has grown each year and now includes mature and over-the-counter products. GSK is also involved in a number of projects that seek to improve the level of research and development success through patient-inclusive multi-stakeholder collaboration. The company has made a commitment to work toward developing a better understanding of disease processes and a holistic view of patients through the measurement and characterisation of their actual experience in disease management, their views on benefit-risk tradeoffs and their goals for treatment. They plan a focus on diseases and disease endpoints, improving measures of efficacy and safety and learning how to collect more information on effectiveness. Progress has been made in the incorporation of patient perspective but additional learning is both anticipated and welcomed.

Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (PROTECT), led by the European Medicines Agency and consisting of 31 public and private partners, aims at strengthening the monitoring of the benefits and risks of medicines. As **Kimberly Hockley**, *Research Assistant, Imperial Clinical Trials Unit, Imperial College, London* related, within PROTECT, Work Package 5 sought to find methods for continuous benefit-risk monitoring by integrating data on benefits and risks from multiple, different data sources. WP5 additionally strove to bring patient and public involvement forward earlier in this decision-making continuum, particularly at the level of regulatory decision making, making the process that produces the summary benefit-risk statements in regulatory public assessment reports more transparent and more defensible. Results of the Work Package indicated that many different formal methods of benefit-risk assessment can be used to elicit patient preferences, each with its own unique features, strengths and weaknesses but further exploration is needed to more fully assess these methods.

Because PROTECT WP 6 aimed to validate the methodologies for eliciting patient preferences explored in WP 5, the VALue and Utilities among European Patients (VALUE) study was conducted to evaluate the use of the Measuring Attractiveness through a Categorical Based Evaluation (MACBETH) software to gather those preferences. **Andrea Beyer**, *Senior Researcher, University of Groningen, The Netherlands* reported that in this study, 62 patients with multiple sclerosis evaluated several MS treatment outcomes, rating the difference in attractiveness between two different outcomes, such as having no relapses in the next five years compared with one relapse in the next five years. The patient interface collected qualitative data and MACBETH converted these data to quantitative scores to build a treatment decision model. Results of the study in the form of value function curves indicated that the majority of patients assigned the highest weight to the treatment outcome *reduction of disability due to disease progression* and the ability to walk was a strong predictor of values or risk attitudes toward

treatment side effects. The WP 6 study Visualizing Uncertainty Among Laypersons and Experts (VISUALize) will be launched in a larger number of patients (5600) across different disease areas in eighteen questionnaires across the United Kingdom, the Netherlands and France and involve patients, healthcare professionals and regulators.

Patient and public involvement is a fundamental, integral part of the business of National Institute for Health and Care Excellence (NICE). **Lizzie Amis**, *Senior Public Involvement Adviser, Public Involvement Programme, NICE* explained that patients and their carers participate throughout the process of NICE appraisals, from scoping through publication, overseen by a centralised, dedicated team that operates under a formal board-level policy with the support of senior management. Each NICE HTA committee has three full-time paid lay members with full voting rights, who are openly recruited through the NICE website. Additionally, national patient groups concerned with specific diseases can attend scoping workshops, comment on draft documents, provide written submission of evidence, nominate patient experts and appeal recommendations and any member of the public can comment on draft recommendations. Committee members have indicated; however, that the impact of patient involvement is primarily in the decision-making process rather than in the decision-making outcome.

When working to incorporate the perspectives of patients into benefit-risk decisions, rather than ask these key stakeholders how important the effects of the medicine are to them, researchers should inquire how big the effect differences are and how much the patients care about them. Deciding how much those differences matter, however, requires that a judgement be made that cannot be independent of a range of comparisons. **Dr Lawrence Phillips**, *Emeritus Professor of Decision Sciences, London School of Economics and Political Science, UK* discussed swing-weighting, a simplified method to quantify the importance of an effect difference to an individual, which can be accomplished in several steps. First, criteria are defined so that they are comprehensible to people without a medical or scientific background. Next, scales with plausible ranges are created and participants arrange the swings between those ranges in their rank order according to their therapeutic value. Finally, swings are weighted against one another to determine added value.

Because patients are experts on the diseases they have **Dr Pierre Démolis**, *Vice Chairman, CHMP, ANSM, France* feels that they may be helpful in regulatory decision making; however, it should be recognised that from a regulatory perspective, there is currently no single, simple method for eliciting patients' views on the benefits, harms and relative importance of treatment. The appropriate time for eliciting patients' views on the benefits and risks of medicines depends on the disease under study. It also relates to the phases at which the patients have a clear understanding of the benefits they expect, the relative importance of any risks and the outcomes they are expecting or have experienced. For migraine, patient insights might be most valuable after the migraine crisis has ended. In MS patients insights might be most useful once the disease has reached a plateau. For end-stage renal disease, patient insights might be most important once disease progression is evident. In breast cancer: Patient insights could be most informative throughout the interval between diagnosis and long-term follow-up and patients who have survived over the long term could have special insight into the benefits and risks of treatment.

Dr Jamie Cross, *Regulatory Program Director, Genentech Inc, USA* specified the properties required for simple methods to collect patient benefit-risk input: understandability to the patient, interpretability to all, encompassment of all relevant outcomes and flexibility for different decisions. Potential simple methods for the acquisition of patient input include qualitative survey research conducted by industry and medical and patient organisations and the use of online media and "big data" analysis. Among challenges to the realisation of simple methods to assess patients' views of benefit-risk include are a lack of resources to systematically engage medical and patient organisations and questions about the applicability of big-data methods to benefit-risk decision making. In addition, the value added by these methods is currently unknown and it remains to be determined if the incorporation of patients' views on benefit-risk would decrease the number of type 1 or type 2 errors in regulatory decision making.

Dr Yatin Shivkar, *Medical Director, Safety & Benefit-Risk Management, Biogen Idec, USA* reported that Biogen Idec recently evaluated the effectiveness of its benefit-risk communication to patients in the context of the TYSABRI® Outreach: Universal Commitment to Health (TOUCH®) programme, a US risk management

system for Tysabri (natalizumab), which is indicated for relapsing multiple sclerosis. Responses from 700 participants in the TOUCH Stakeholder Project revealed that most patients are interested in receiving information about risks that is balanced by information on benefits. To this end, medication guides are a useful source that can be improved by highlighting new information and including information on the benefits of treatment. The front line of benefit-risk communication, however, is the healthcare provider, who must be educated and supported if benefit-risk communication to patients is to be successful.

Barbara Sabourin, *Director General, Therapeutic Products Directorate, Health Canada* outlined the initiatives that Health Canada has implemented, developed and planned to improve the communication of benefit-risk to patients. The Plain Language Initiative involves the use of language, layout and design techniques; short, simple sentences; the active voice; common words and simple expressions; white space and a question-and-answer format. A draft version of a *Best Practices Guide for the Design of Safe Health Product Labels and Packages* has been created to increase the clarity and readability of information presented on inner and outer labels and packages and to identify information to be given most prominence on the main drug panel. The revised Look Alike/Sound Alike Guidance provides industry with more detailed information on the assessment process and the submission requirements to demonstrate that a proposed name for a new medicine is not likely to be confused with another name authorised for use in Canada. Consumer Medication Information enhancements include revised guidance for industry on the format and content of consumer information in part III of the product monograph. A pilot study for patient communication is also being conducted, which, it is hoped, will systematically gather patients' perspectives on unmet medical need, anticipated benefits and risk tolerance; will determine methods and test internal Health Canada processes for incorporating patient input into real-time submission reviews and will identify areas where patient education and/or reviewer training are required.

The Welsh Institute for Health and Social Care in collaboration with the Genetic Alliance recently conducted research into patient involvement in benefit-risk decision making in a two-phase project. **Prof Marcus Longley**, *Director, Welsh Institute for Health and Social Care, University of South Wales, UK* related that participants agreed that regulators and pharmaceutical companies should work more closely to encourage the measurement and assessment of a broader framework of benefits. It was further understood that regulatory decisions should be more transparent and decision processes should be clearly articulated to reduce misunderstandings and to improve patients' confidence in the system and that further work should be undertaken to explore differences in decision making between regulators and patients. Additionally, there was consensus that changes should be made to improve the way in which patients are involved in regulatory processes and that the process should be more flexible for rare and serious conditions, involving patients and clinicians in an additional decision-making step if it looks as though a new medicine is going to be denied. Finally, it was agreed that better evidence on social factors can help inform the decision-making processes at the health technology assessment and prescribing level.

Patients should be involved in the medicine development continuum, from the targeting of research areas through the development of medicines to the marketing of a final product and its post-launch management. **Moira Daniels**, *Vice President, Head Global Patient Safety Services, PAREXEL International, UK* observed that currently, patient involvement is occurring much earlier in the medicine development process in disease areas and has revealed insights and helped to shape clinical research activities. Patient insight activities are being conducted within project teams in research and development and patient views have shaped patient-reported outcome tools and influenced the type and frequency of invasive test procedures. Patient involvement has been especially important in geriatric and paediatric clinical research. Industry supports the creation of a "health citizen" responsible for making their own healthcare decisions.. To that end, it is providing structures and resources that empower the people of the European Region to make use of their own assets, be active participants in shaping health policy, respond to health challenges by improving health literacy, ensure that their voices are heard in patient-centred health systems and participate in community and family life.

In his second presentation, **Dr Pierre Démolis**, *Vice Chairman, CHMP, ANSM, France* provided the regulatory viewpoint as to the role of the patient in the future, saying that it is likely that

patients will have an established role in the EMA Committee for Medicinal Products for Human Use (CHMP) by the end of this decade. The evolution of the patient's role will encompass individual patients with specific diseases and disease-specific patient associations such as those for breast cancer and multiple sclerosis. Patient involvement in pharmacovigilance will also be very important and will include access to agency website portals.. This transformation will be based on the principle that if regulators build patient confidence in the regulatory process, patients will trust in regulatory decisions and in the ability of regulators to include their perspectives in their decision making.

The patient voice is important at every stage of medicine development, including post-marketing research and the role of patients should be equal with other stakeholders, with their perspective on benefit-risk assessment actively elicited. A recent collaboration between the Genetic Alliance UK and the University of South Wales in the assessment of medicines for serious conditions provides an example of the value of this active elicitation **Christopher Friend**, *Trustee, Genetic Alliance, UK & Medical Advisory Service* agreed with Dr Démolis, that patients will have an important role in pharmacovigilance by 2020, saying that during a time of personalised/stratified medicine and economic pressures, formal collaboration with academia, regulators and industry will be the hallmark of patient involvement in medicine development, including involvement in pharmacovigilance and the provision of formalised HTA input. This involvement will hopefully be accompanied by a greater understanding by all parties of the most appropriate therapies for serious, rare and long-term conditions.

Recommendations from across the Syndicates

1. **Produce guidelines for regulators surrounding the collection of patient input for information and education.**
2. **To improve the framing of decision questions, systematically use methods to structure input from all perspectives.**
3. **To gain maximum benefit from patient and regulatory resources, select one (or more) model(s) and systematically work through the steps for involving patients.**
4. **Adapt key sections of the CIRS summary benefit-risk framework to capture patients' insights throughout a product lifecycle.**
5. **Collaborate with CIRS, patients and other stakeholders to develop a meaningful, relevant patient query framework.**
6. **Keep patient interaction simple, leveraging existing processes if possible, valuing progress over perfection and embracing technology.**
7. **Analyse the current structure of patient information such as drug monograph sections and propose amendments to better reflect the benefits, risks, consequences and uncertainties of taking medications in easy-to-understand language.**
8. **An evaluation framework needs to be established for the new and revised patient and healthcare professional educational materials in order to validate their utility.**
9. **Develop a stepwise approach to the dissemination of these educational materials to include current technologies and media.**
10. **As part its activities, the Consortium for Benefit-Risk Assessment (COBRA) should develop a template for public assessment reports to include elements of the benefit-risk framework.**

Workshop Programme

DAY 1: 2 APRIL 2014	
SESSION: COLLECTION OF PATIENTS' PERSPECTIVES ON BENEFITS, HARMS AND RELATIVE IMPORTANCE	
Chairman's welcome and introduction	**Prof Robert Peterson**, *Executive Director, Drug Safety Effectiveness Network, Canadian Institute of Health Research*
Keynote presentation – Why understanding patient perspectives on benefits and harms of therapeutic products is critical to the future of regulatory agency decision making	**Dr John Skerritt**, *National Manager, Therapeutic Goods Administration, Australia*
Patient organisation viewpoint	**Jean Mossman**, *Policy Lead, European Brain Council*
Regulatory viewpoint	**Dr Isabelle Moulon**, *Head of Patients and Healthcare Professionals, European Medicines Agency*
Industry viewpoint	**Dr Marilyn Metcalf**, *Senior Director, Benefit Risk Evaluation, GlaxoSmithKline, USA*
What has been the experience of IMI PROTECT in the collection of patient views and how can this be used directly in the assessment of benefit-risk?	**Kimberly Hockley**, *Research Assistant, Imperial Clinical Trials Unit, Imperial College, London*
Providing patient preferences into the regulatory discussions: What are the pathways being explored?	**Andrea Beyer**, *Senior Researcher, University of Groningen, The Netherlands*
How do other decision makers collect information from patients and how does this influence decision making? HTA agency viewpoint	**Lizzie Amis**, *Senior Patient Advisor, Public Involvement Programme, NICE*
SESSION: SIMPLE METHODOLOGIES TO CAPTURE PATIENTS' VIEWS ON BENEFITS, HARMS AND RELATIVE IMPORTANCE - WHAT COULD THEY LOOK LIKE?	
What simple methods could be used to elicit patients' views on benefits, harms and relative importance?	
Academic viewpoint	**Dr Lawrence Phillips**, *Emeritus Professor of Decision Sciences, London School of Economics and Political Science*
Regulatory viewpoint	**Dr Pierre Démolis**, *Vice Chairman, CHMP, ANSM, France*
UK industry viewpoint	**Dr Jamie Cross**, *Regulatory Program Director, Genentech Inc, USA*

Syndicate sessions	
Syndicate A: Collection of benefits, harms and relative importance information from patients: Current methodologies – can these be simplified?	**Chair: Dr Thomas Lönngren**, *Independent Strategy Advisor, Pharma Executive Consulting, Sweden* **Rapporteur: Maggie Tabberer**, *Director, Patient Focussed Outcomes, GlaxoSmithKline, UK*
Syndicate B: New methods for the collection of benefits, harms and relative importance from patients: Can these be synergistic with the benefit-risk framework?	**Chair: Dr John Skerritt**, *National Manager, Therapeutic Goods Administration, Australia* **Rapporteur: Dr Linda Scarazzini**, *Vice President, Medical Safety Evaluation, AbbVie Inc, USA*
Syndicate C: Communication of benefit-risk: What should be in the public domain?	**Chair: Dr Petra Dörr**, *Head of Communication and Networking, Swissmedic* **Rapporteur: Nancy Pire-Smerkanich**, *Educational Liaison, Doctoral Candidate, International Center for Regulatory Science, School of Pharmacy, University of Southern California, USA*
DAY 2: 3 APRIL 2014	
SESSION: COLLECTION AND COMMUNICATION OF PATIENTS' VIEWS ON BENEFITS, HARMS AND THEIR RELATIVE IMPORTANCE: THE RECOMMENDATIONS	
Chairman's introduction	**Dr Mary Baker**, *Immediate Past President, European Brain Council*
Feedback from Syndicate sessions	
The communication of benefits and harms to patients: How well are we doing and what needs to be improved?	
Industry viewpoint	**Dr Yatin Shivkar**, *Director, Safety and Benefit-Risk Management Biogen Idec, USA*
Agency viewpoint	**Barbara Sabourin**, *Director General, Therapeutic Products Directorate, Health Canada*
Patient viewpoint	**Prof Marcus Longley**, *Director, Welsh Institute for Health and Social Care, University of South Wales, UK*
Future perspectives – Looking forward to 2020: What will be the role of the patient?	
Industry viewpoint	**Moira Daniels**, *Vice President, Head Global Patient Safety Services, PAREXEL International, UK*
EMA viewpoint	**Dr Pierre Démolis**, *Vice Chairman, CHMP, ANSM, France*
Patient viewpoint	**Christopher Friend**, *Trustee, Genetic Alliance UK*

Section 2: Syndicate Discussions

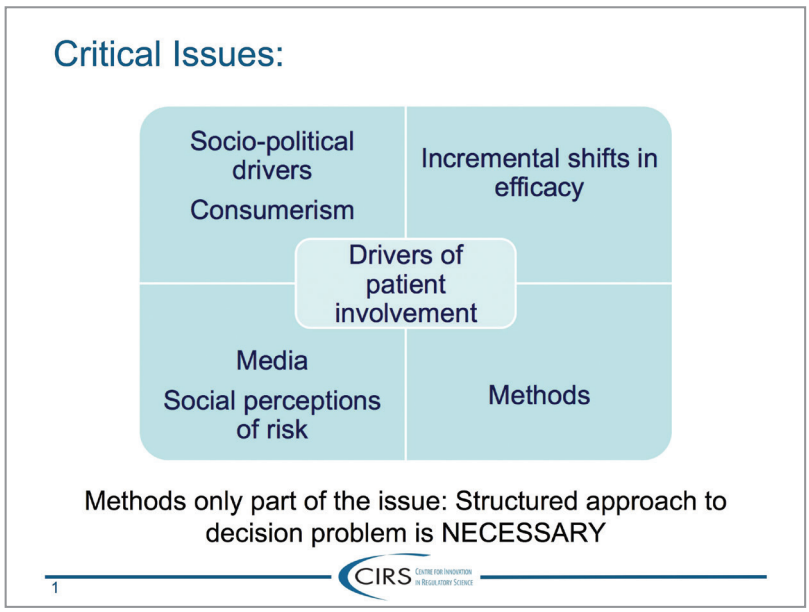
Syndicate Discussion A

Collection of benefits, harms and relative importance information from patients: Can current methodologies be simplified?	
Chair	**Dr Thomas Lönngren**, *Independent Strategy Advisor, Pharma Executive Consulting, Sweden*
Rapporteur	**Maggie Tabberer**, *Director, Patient Focussed Outcomes, GlaxoSmithKline, UK*

Background

Patients' perspectives on benefits and harms and their relative importance are critical to the development and review of new medicines, both at the disease and therapy level. Current methodologies are criticised as either being too complex and expensive or as being problematic regarding scientific reliability or regulatory acceptance. In addition, regulatory agencies must determine how to extrapolate patients' viewpoints on a medicine's benefits and harms to the general patient population. However, all stakeholders, including patients, industry and agencies agree that patients need to be engaged in a discussion of benefits and harms and their relative importance in their lives. Therefore, an alignment by stakeholders on feasible and flexible methodologies seems critical.

Figure 1. There are multiple factors that impact patient involvement in benefit-risk decision making.



This Syndicate was asked to discuss the potential simplification or modification of current methodologies for their effective utilisation in the clinical development and review of new medicines.

Objectives

The objectives of this Syndicate group were to:

- Identify current methodologies that are robust enough to be utilised in both development and regulatory decision making
- Discuss the key challenges and potential opportunities for these methodologies to be simplified or modified without losing any regulatory strength
- Recommend how current methodologies can be used to obtain patients' perspectives on benefits, harms and tradeoffs, which can be used to inform regulatory decision making

Questions for consideration

It was hoped that this group would provide feedback on:

- The current methodologies and their place in the toolkit for acquiring robust data that are valuable in assessing patient benefits, harms and tradeoffs
- How these current methodologies could be simplified for wider use and what the challenges and opportunities are for developing simpler methods for use in the regulatory setting

Critical issues

Methods that this Syndicate considered for capturing patient input into the importance of benefits and risks included conjoint analysis, multi-criteria decision analysis, patient-reported outcomes and health outcomes modelling. The group noted, however, that the last two of

these methods cover a multitude of approaches. Moreover, methodology selection is only one driver for patient involvement in benefit-risk decision making (Figure 1) and regardless of the method selected, a structured approach to the decision problem is still necessary.

Different structured approaches have been developed, notably Problems, Objectives, Alternatives, Consequences, Tradeoffs, Uncertainty, Risk tolerance, Linked Decisions (PrOACT-URL); the CIRS Benefit-Risk Action Team (BRAT) framework and the CIRS Universal Methodology for Benefit-Risk Assessment (UMBRA). However, identifying which are the key benefits and risks to evaluate through these frameworks can be challenging. Moreover, this Syndicate felt that in the current regulatory environment, structured decision-making frameworks remain largely unused although there are ongoing pilot projects such as the Innovative Medicines Initiative Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (IMI PROTECT) project, which should be encouraged.

It should also be recognised that current methods for framing and structuring decision making do not mandate patient involvement throughout the process. Additionally, although there is increased patient participation in regulatory benefit-risk decision making, it is not typically well-structured nor does it involve quantitative input. However, therapeutic area guidelines are evolving to include patient-centric outcomes and there is increasing pressure from health technology assessors, for example, to build patient-focussed measures into the evaluation of medicines.

Decisions about benefit-risk profiles are becoming more complex because of such issues as ageing populations, increasing co-morbidities and changing economic climates and admittedly, the methods for acquiring and integrating patient input into decision making are not simple. But it is more important to simplify the interface for the acquisition than the methodology. In fact, all methods to acquire patient input may be appropriate in some situations and tailoring approaches to fit particular decision problems and improving the questions that patients are asked will improve the selection and use of these tools in decision making.

Strategies

Providing information and education to improve understanding of the methodologies used to collect patient input regarding the benefits and harms of new medicines will increase transparency in decision making. Additionally, the proactive uptake of structured decision-making metrics should also improve the quality of regulatory decisions. Finally, continued patient involvement in the development of therapeutic area guidelines, particularly in the areas of inclusion and exclusion criteria and the identification of primary and secondary endpoints will ensure patient-centric outcomes are part of quality decision making.

Recommendations

1. Produce guidelines for regulators surrounding the collection of patient input for information and education.
2. To improve the framing of decision questions, systematically use methods to structure input from all perspectives.
3. To gain maximum benefit from patient and regulatory resources, select one (or more) model(s) and systematically work through the steps for involving patients.

Syndicate Discussion B

New methods for the collection of benefits, harms and relative importance from patients: Can these be synergistic with the benefit-risk framework?	
Chair	**Dr John Skerritt**, *National Manager, Therapeutic Goods Administration, Australia*
Rapporteur	**Dr Linda Scarazzini**, *Vice President, Medical Safety Evaluation, AbbVie Inc, USA*

Background

There is good agreement across the agencies developing benefit risk frameworks that there are four key stages to benefit-risk evaluation: Framing the decision; Identifying the benefits and risks; Assessing the benefits and risks; and Interpretation and recommendation. Underpinning these is an overarching eight-step framework (Figure 2).

All the benefit-risk methodologies currently being developed by pharmaceutical companies and regulatory agencies incorporate these steps explicitly or implicitly. This overarching framework provides the basis for a common agreement on the principles for assessment and the type of questions regulators have to consider in the evaluation of a medicine.

This Syndicate was asked to discuss if the UMBRA framework could form the basis of a simple methodology to gather input and insight from patients regarding the benefits and harms of new medicines and their relative importance.

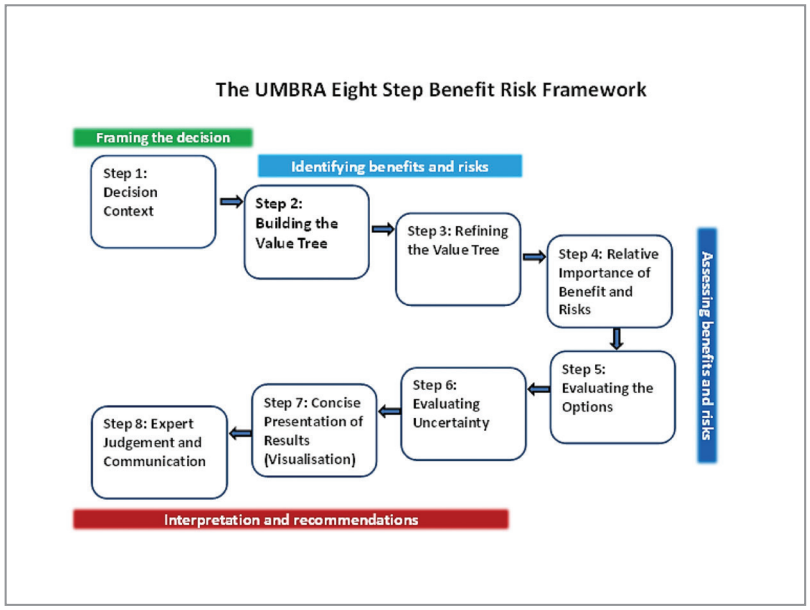


Figure 2. The Universal Methodologies for Benefit-Risk Assessment (UMBRA) framework for benefit-risk evaluation.

Objectives

The objectives of this Syndicate group were to:

- Discuss the key challenges and potential opportunities for collecting information from patients using a systematic, structured approach that mirrors the UMBRA framework
- Identify the elements of the framework for which patient information could be of the most value in informing decision making in clinical development and regulatory review
- Recommend ways in which the framework could potentially be used to seek information from patients and discuss the barriers and possible solutions for such an approach.

Questions for consideration

The Syndicate was provided a draft template, which follows the UMBRA steps and is being used to enable agencies to document their benefit-risk decisions in a systematic structured way. It was envisioned that suggested feedback might include:

- Whether it would be of value for patients to complete some or all of the suggested sections of the benefit-risk summary template, thus providing information in a way which is in line with the framework that companies and agencies are using
- To identify the critical elements that need to be contained is such a methodology and opportunities and hurdles for such an approach to be utilised in a regulatory setting

Critical issues

This Syndicate was in agreement with a theme that emerged from the Workshop; that is, patient input should be incorporated as early in development as possible and that input should concern their perceptions and acceptance of both benefits and harms. In addition, international alignment should occur among industry and agencies for the collection of patient input during the entire drug lifecycle assessment plans rather than just at the time

of regulatory submission. The US FDA has established a model for the accrual of patient perspective on disease states rather than on medicines through its Patient-Focused Drug Development programme. Although more of a challenge because of the perception of conflict of interest, sponsors can and should follow that model in the pre-competitive space, establishing patient-relevant endpoints for clinical trials.

The group was asked to evaluate the template developed by CIRS for benefit-risk evaluation that is currently being evaluated by international regulators. It was recognised that to avoid creating an additional burden on resources, any framework must be able to be adapted to be employed at specific milestones in parallel with existing templates or procedures to avoid duplicative efforts.

There are significant sources for patient data in social media sites and reports of some pilot efforts that have sought to use this information but industry as a whole has yet to take advantage of these data sources because of concerns regarding their integrity as well as regarding resulting obligations to report results.

Strategies

The Syndicate agreed that the background section of the CIRS Summary Template for the Benefit-Risk Assessment could be adapted to capture patient insight. This section is particularly suited for that purpose as it details the decision context for the evaluation; that is, it contains information regarding the proposed indication, the treatments evaluated and the unmet medical need.

The identified benefits and risks section of the template is the key area where meaningful and relevant questions could be posed to capture relevant patient information. It was suggested that benefits and risks could be recast as advantages and disadvantages here. Although some members of the Syndicate questioned whether patients should be relied upon to provide weights for benefit and risk parameters in the summary section of the template, most agreed that a ranking system would be useful.

Exit interviews for participants in clinical trials were suggested as a particularly useful methodology for collecting patient benefit-risk perceptions. Adding structured questions to the template to determine patient perspectives on risk evaluation and mitigation strategies (REMS) would also be useful in the development of patient-centric tools that are helpful rather than burdensome to the system. These elements of the Summary Template could be adapted now and a small pilot study initiated. It should be remembered, however, that communication is vital and we should always report back to patients the results of their input.

Recommendations

1. Adapt key sections of the CIRS summary benefit-risk framework to capture patients' insights throughout a product lifecycle.
2. Collaborate with CIRS, patients and other stakeholders to develop a meaningful, relevant patient query framework.
3. Keep patient interaction simple, leveraging existing processes if possible, valuing progress over perfection and embracing technology.

Syndicate Discussion C

Communication of benefit-risk: What should be in the public domain?	
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Background

Transparent communication of the benefit-risk decision is one of the key components of any summary basis of approval or public assessment report that is provided by the regulatory agency licensing a new medicine. This information is critical for both patients and physicians to aid them in understanding the benefits, harms and uncertainty associated with a medicine and how a regulatory agency viewed these elements in their decision making.

As agencies move toward the use of a structured systematic framework in the review of new medicines that requires a more explicit evaluation and documentation of the benefits, harms and uncertainties of medicines, should this change the way the decision is communicated in the summary basis of approval or public assessment reports?

As has been detailed in the background for Syndicate B, there is good agreement across the agencies developing a benefit-risk framework that there are four key stages: Framing the decision; Identifying the benefits and risks; Assessing the benefits and risks; and Interpretation and recommendation. Underpinning these is an overarching eight-step framework that provides the basis for a common agreement on the principles for assessment and the type of questions regulators have to consider in the evaluation of a medicine.

This Syndicate group was tasked with determining what, if any, of this should be communicated in regulatory public assessment reports for new medicines. In addition, they were to discuss whether structuring the benefit-risk part of the public assessment report or summary basis of approval to reflect the structure of the framework would provide improved clarity on the benefits, harms and uncertainties in such a way that it would enable patients to both understand what the regulatory agency has evaluated and to undertake their own benefit-risk decision based on the same information.

Objectives

The objectives of this Syndicate group were to:

- Discuss the key challenges and potential opportunities for improved transparency, decision making and communication through use of the structure of the overarching benefit-risk framework in public assessment reports and summary bases of approval
- Identify which elements of the framework would be of most value to patients if included in public assessment reports or summary bases of approval
- Recommend how the framework could be used by agencies to communicate their benefit-risk decisions in a way that will enable patients to make an informed decision around the benefits, harms and uncertainties of new treatments

Questions for consideration

- In the future, should the benefit-risk section of public assessment reports be structured so that they mirror a consistent benefit-risk framework?
- What does the group believe are the main challenges and opportunities for aligning the public assessment reports to the benefit-risk framework?
- Could this be of benefit to patients as they make their own therapy decisions (either alone or in conjunction with their doctor)?
- Which elements of the benefit-risk framework does the group think will be of most value to patients and doctors in terms of decision making?
- What would this group recommend and why?

Critical issues

Current information regarding the benefits and risks of new medicines in the public domain primarily consists of product labelling, public assessment reports and a summary bases of approval. These are technical rather

than educational documents, however and they are not being used by the audience for which they were intended; that is, healthcare professionals and "educated" patients. Instead they are typically being used by competitors, media, academia, other regulatory bodies, health technology assessors and the legal profession. In addition, the language currently used in public assessment reports is not suitable for patient use and the awareness and accessibility of these reports continues to be an issue. Public assessment reports could include elements of the benefit-risk frameworks as a tool to better explain decision making.

Additionally, current information rarely employs visualisation tools and contemporary technologies are under-utilised. Although product information is dynamic and changing continuously throughout its lifecycle, the method of communicating it is not and it is not always apparent what is changing about the product's profile.

Specific information on the number needed to treat and number needed to harm is typically not included in product labelling or in public assessment reports; however, no consensus was reached in the Syndicate as to whether it should be included or where that information should reside. It was agreed, however, that education in benefit-risk should be included in healthcare professional curricula.

Strategies

The Syndicate found that what is now lacking is a "document" that captures key messages and communicates benefits, risks, uncertainties and their consequences for patients. If this communication were to be developed, one approach would be for it to be "owned" by industry but reviewed and distributed by regulators. Increased use of the public assessment report summary in a question and answer format in lay language could be achieved by referencing it in the product labelling as well as any other new educational tools that are developed. Additionally, use of visualisation, key points and evolving technologies/media must be considered.

Recommendations

1. Analyse the current structure of patient information such as drug monograph sections and propose amendments to better reflect the benefits, risks, consequences and uncertainties of taking medications in easy-to-understand language.
2. An evaluation framework needs to be established for the new and revised patient and healthcare professional educational materials in order to validate their utility.
3. Develop a stepwise approach to the dissemination of these educational materials to leverage current technologies and media.
4. As part of its activities, the Consortium for Benefit-Risk Assessment (COBRA) should develop a template for public assessment reports to include elements of the benefit-risk framework.

Section 3: Presentations

Why understanding patient perspectives on benefits and harms of therapeutic products is critical to regulatory agency decision making

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The importance of patient communication

In a recent survey of 780 demographically diverse consumers in Australia, although respondents were able to identify the Therapeutic Goods Administration (TGA) as the country's regulatory agency, they were unclear as to the exact role of the agency; that is, they were unsure what the TGA can and cannot regulate and how they assess benefits and harms. Initially, about half of these consumers felt that TGA achieved the right balance of benefits and risks with their assessments while the other half thought that too many or too few risks were being taken. However, once participants were fully informed about the TGA, using language they understood, there was much wider acceptance regarding TGA evaluations and participants who had rated their prior knowledge of TGA as "poor" or "very poor" were much more supportive of TGA's role after receiving information.

Subsequent to this survey, TGA employed consumer focus groups to identify priorities for communication and engagement for the agency and established a public contact call centre and developed a new TGA website and social media content for the issues raised by the focus groups. The identified issues included the role of the TGA, the TGA benefit-risk approach for higher and lower risk medicines, the evaluation of generic medicines and information on travelling with medicines. In addition, there is now a translation service on the TGA search engine for non-English speakers. The TGA also developed teaching materials for universities on regulation and now staffs exhibition booths at non-mainstream conferences such as those for naturopaths, nursing, gym managers and direct sales associations. In 2013, the TGA public call team received 31,790 enquiries, including 11,229 from the general public.

Other organisations are making inroads toward the enhancement of healthcare communications to consumers. A private-public partnership of the EU Commission and the European Federation of Pharmaceutical Industries and Associations (EFPIA), the European Patients Academy on Therapeutic Innovation (EUPATI) was launched in 2012 to facilitate patient involvement in medicines development from research to approval; personalised and predictive medicine; drug safety and the benefit-risk assessment of medicines; pharmacoeconomics, health economics and health technology assessment, the design and objectives of clinical trials and roles of stakeholders and patients' roles and responsibilities in medicines development.

The US FDA has a website dedicated to patient communication at http://patientnetwork.fda.gov, an electronic newsletter that is issued twice monthly with information on product safety and recalls, medicines' discontinuations and shortages, product approvals, consultations on draft guidances, upcoming meetings and blogs. The FDA Patient-Focused Drug Development meetings are being held in 20 disease states such as chronic fatigue syndrome and myalgic encephalomyelitis, HIV, lung cancer and narcolepsy to discuss issues such as disease symptoms and daily impacts that matter most to patients, patient perspectives on treating the disease and incorporating patient input into the benefit-risk assessment of new drugs in these areas.

The value of patient input

In recognition of the importance of the specialised personal experience of living with a disease or condition, patients and patient groups have a growing involvement with regulatory committees and their consultation in pharmaceutical submissions has been well established but issues remain to be resolved:

- How can one collect truly representative patient views?
- Are patient organisations always representative?

- Are there conflicts of interest?
- How can organisations that lobby government on medicine registration or reimbursement also be part of the formal regulatory agency processes?
- What about patient groups that receive pharmaceutical industry funding?

Patient perspectives on benefits and harms should play a part in regulatory agency decision making at two levels, that of market authorisation or removal of specific products and that of regulatory policy initiatives such as provisional or conditional registration. Regulators must continue to be encouraged to accept patient perspectives to ensure that patient preferences are measurable and useful, that clinical trials are designed to optimally capture these events and to help focus on the effectiveness of medicines rather than just their efficacy.

Patient-reported outcome information is vital, especially where objective measurement is challenging, such as in diseases like schizophrenia and depression. Patient input contributes to disease definition and their feedback provides the potential for the identification of new drug targets and better pharmacovigilance. When patient groups are valued by the regulators it contributes to their belief in the scientific rigour under which medicines were developed and instils confidence in the value of new medicines for their condition.

Patient groups can also provide valuable input into meeting some of the challenges for clinical trial development such as the variable quality of predictability of surrogate endpoints compared with actual clinical outcomes. There is also an opportunity for the better use of patient-defined endpoints such as quality of life and family response, when evaluating new antidepressants and antipsychotics. Patients can help ensure that clinical trial populations are representative; that is, that an appropriate age range is represented and that suitable co-morbidities and racial and gender mix are included. The patient voice also reminds developers and regulators that benefit-risk tolerance differs for different populations and individuals.

Innovations in clinical trial design have occurred. Adaptive trial design data enables treatments to be changed midway and comparative effectiveness trials better reflect routine clinical practice but the challenge of personalised medicine – how to achieve adequate statistical power with small patient populations - remains.

Patients can help ensure that clinical trial populations are representative . . . The patient voice also reminds regulators that benefit-risk tolerance differs for different populations and individuals.

While it has been recognised that patients have a key role in helping to ensure that trials are effectively designed, interview-based feedback from trial participants is an underutilised resource for investigators and regulators, with one investigator estimating that only 23% of trial participants surveyed received a summary of the results.[1] In respect for the patient-industry partnership implied in clinical trial participation, it is important that the results of the trials, whether positive or negative, be shared with participants.

Patient involvement will also be critical to the evolving debate for adaptive licensing; that is, the licensing of medicines prior to full phase III trials, which is subject to monitoring of real-life effectiveness and safety. Questions remain, however, such as whether adaptive licensing will lead to lowered evidence standards and who will be accountable if there is a failure associated with a product and the difficulties in withdrawing a medicine once a patient cohort has been established must be understood.

Whether products are approved through adaptive or traditional licensing, greater patient input into pharmacovigilance must be encouraged. Under-reporting is a common global problem. Patient accounts could ensure the collection of important real-life data such as the effects of long-term use and the consequences of co-morbidities.

The reporting of adverse events by patients can be encouraged by keeping it simple and by supporting honest reporting about issues in compliance, co-medications and lifestyles. Automatic use of electronic health records will aid in safety signal detection. Issues to be resolved include the determination of medically useful terminology for adverse events, the methodology for a focus on unexpected rather than known adverse events and the potential use of drug-adverse event pair studies for suspected adverse events. The TGA is encouraging greater consumer reporting of

adverse events through a research project to explore consumers' opinions about experiencing, managing and reporting adverse events, a web-based consumer reporting form and guide and pharmacist dispensing software and training for adverse event reporting.

Having obtained pharmacovigilance data, however, regulators are challenged as to how to communicate it. Risk is often difficult to communicate in simple terms. Regulators must determine if the use of numerical or weighted models of benefit-risk actually influence patients' or prescribers' thinking. Visual or graphical representation is useful with details provided for those who need it.

Patients, regulators and risk

Regulators have been accused of being too conservative while patient groups have been regarded as encouraging too many risks. Regulators, however, must consider if significant off-label prescribing will occur because of the inability of approvals to reflect clinical need or if it actually represents experimentation on patients. They must also be cognisant of the fact that medicines are difficult to withdraw for a lack of effectiveness.

Medicines are withdrawn or highly restricted to correct a Type 1 regulatory error; that is, the withdrawal of an approved medicine for safety reasons where suitable alternatives existed; such as occurred with cisapride, difenfluramine, sibutramine, bromfenac, rofecoxib, lumiracoxib, oral ketoconazole and flunitrazepam. But regulators must also guard against Type 2 errors, that is, the failure to allow beneficial medicines onto the market when there are no good therapeutic alternatives.

The question of how to assess patients' appetite for risk remains problematic. Regulators can be too "one size fits all" in their approach especially when prognosis is poor and few effective treatments exist or a syndrome severity is hard to assess. Patients are often prepared to take greater risks than regulators, such as they were regarding natalizumab for multiple sclerosis despite the associated risk for progressive multifocal leukoencephalopathy, for trastuzumab for metastatic breast cancer despite the risk for associated cardiomyopathy and thalidomide for multiple myeloma despite the risk for associated severe birth defects.

The aim for generating patient benefit-risk data is to provide objective input and represent views of many patients. There are a range of psychology tools and statistical approaches to achieve this objective; for example, preference elicitation such as standard gamble and the threshold technique, generalised weighting such as best-worst scaling and discrete choice and decision support methods such as analytic hierarchy and multi-criteria decision analysis.

Conclusions

Consumer survey information is valuable in challenging assumptions and identifying priorities for communication. Regulators are increasing their engagement with patient groups but it has still been challenging to capture detailed and broad input from patient groups into medicines authorisation. Some excellent initiatives are underway to better understand patient perspectives but pre-authorisation input from patient groups is often sought and received by regulators too late in the product review process. Finally, patients and patient groups have an important role in pharmacovigilance.

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Collection of patients' perspectives on benefits, harms and relative importance: Patient organisation perspective

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Determining whose perspective has been used to drive the regulatory decisions about benefits and harms and whether that perspective is based on knowledge or assumptions is vital to understanding the results. Historically, physicians have been considered representatives of the users of medicine but evidence has shown that they are not typically appropriate surrogates. Therefore, developers and regulators need to involve patients in these decisions and then to be explicit about how the decisions are ultimately derived.

The World Health Organization has stated that patient involvement in their healthcare is a social, economic and technical necessity[1]. Patients' are responsible for many decisions about their health: They decide when to seek medical advice, whether to accept that advice, whether to take the prescribed medicines and whether they will take complementary medicines and adjust their lifestyle. Patient's need for self-management of their illness should not be underestimated. The importance of patient perspective is particularly evident in the complex treatment of some diseases such as cancer and the best way to derive that perspective is through dialogue with patients.

Writing about the personalisation of benefit-risk decision making, Greenhalgh and colleagues stated that

> Conclusions derived from clinical trials (however rigorously conducted) may not apply to individual patients for a host of genetic, physiological, psychological and sociocultural reasons. It will therefore never be possible to legislate for every eventuality at the level of national drug licensing bodies. When drug licensing decisions are overturned, it is generally because existing evidence is reinterpreted—especially in the light of context and personal values. In other words, the evidence base for drug regulatory decisions is to some extent socially constructed.[2]

It is therefore, important that people who use medicines contribute to the context of decision making about them.

The reality is that for patients with a fatal illness that might be amenable to treatment, the outcome is a binary situation: You live or you die. In these circumstances, many – but not all – people will choose the chance to live. Illustrating this point, in a recent workshop for patients with myeloma in Europe, out of seven people, six would take any treatment offered regardless of the side effects, while one had actively opted out of treatment because of the potential for adverse events. The challenge is to represent that range of opinion from the most adventurous to the most cautious. Regulators have been surprised by patients' willingness to incur risk in their treatment. As remarked by UK CHMP member Dr Ian Hudson, "The level of risk patients were prepared to take was quite illuminating . . . it may be that patients' acceptance of risk is higher than the regulator's. . ."

Boyd and associates stated that the main challenges in the assessment of the benefits and harms of new medicines relate to the selection of health outcomes that are important to patients; information asymmetry, with reliable and robust data on benefits and sparse data on harms; problems in the calculation of statistical uncertainty when benefit and harm are put on the same scale using a benefit harm comparison metric and the consideration of patient preferences.[3] However, it is not just important to collect patient-reported outcomes. They should be patient-relevant outcomes or those with an impact on disease and on aspects of daily living with implications for the patient's future. Ideally, these outcomes could be individualised as they are likely to vary over the course of a disease and changing personal circumstances. Patients and caregivers should be involved in deciding the metrics of collecting the outcomes at times the patient deems appropriate, which may vary from patient to patient. Methods to account for patient variables that are unrelated to treatment must still be uncovered.

. . . a future in which patients drive their own care pathways, determine what they want to achieve with treatment, define the potential harms they will tolerate for specific levels of potential benefit

It is important for the end users of medicines to understand what risk means to regulators. The US FDA defines the risk of harm not only as "The possibility of a harmful interaction between the medicine and a food, beverage, dietary supplement (including vitamins and herbals), or another medicine. Combinations of any of these products could increase the chance that there may be interactions" but also as "The chance that the medicine may not work as expected. The possibility that the medicine may cause additional problems."

Ms Mossman envisions a future in which patients drive their own care pathways, determine what they want to achieve with treatment and define the potential harms they will tolerate for specific levels of potential benefit. In this future, patients would not be constrained by protocol-driven care and would be free and able to interpret the data for medicines in the context of their own circumstances.

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Regulatory viewpoint:

Patient's voice in EMA evaluation of medicines

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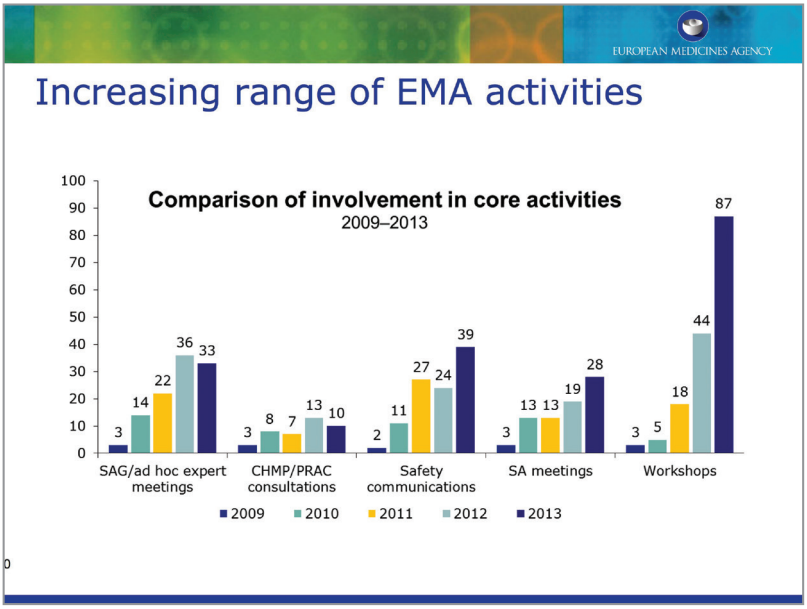
Patients' interaction with EMA: a continuous collaboration

The foundation for the interaction between the EMA and patients was laid at the time when the agency began in 1995, when the Management Board warned of the danger of neglecting partnership with stakeholders, including the public, health professionals and the pharmaceutical industry. Indeed, almost immediately, the EMA initiated dialogue with patients with human immunodeficiency virus on the value of surrogate markers in the approval of anti-HIV drugs, leading to the early approval of protease inhibitors. Today, the real-life experience of patients is routinely embedded in regulatory output at the EMA and a special Patients and Healthcare Professionals Department has been created.

Figure 3. Patients involvement in EMA activities continues to grow in number and scope.



The EMA involves patients along the life cycle of the medicines as experts in their disease and its treatment. The EMA interacts with patients and patient groups in two different aspects –

- as people representing themselves or people like themselves with a certain disease or condition, through EMA dialogue with patients' organisations and patient participation in EMA Patients' and Consumers' Working Party and workshops and
- as people representing the general patient community as members and ad hoc advisors of Scientific Committees evaluating new medicines.

Patient participation in agency undertakings has continued to grow and in 2013, patients were involved in more 550 EMA activities. The range of participation has also continued to evolve (Figure 3). As disease experts, patients provide scientific advice or protocol assistance;

participate in Scientific Advisory Groups (SAG) meetings; review communication material and information on medicines such as package leaflets, European Public Assessment Report (EPAR) summaries, safety communication and other agency documents intended for the public. EMA Committees with patient representation include the Pharmacovigilance Risk Assessment Committee (PRAC) Committee for Orphan Medicinal Product (COMP), Paediatric Committee (PDCO) and Committee for Advanced Therapies (CAT) (Figure 4). A pilot for patients' involvement in Committee for Medical products for Human Use (CHMP) in benefit-risk evaluation is currently ongoing.

After approval, patients can report adverse reactions to medicines through national reporting systems, the results of which are collected in the Eudravigilance database, which is completely open to public access. Patients can participate in post-marketing decisions for new medicines as members of committees, disease experts, public hearing participants and reviewers of post-marketing communication material.

Requirements and expectations for patient participation

Both process and structure must be in place prior to patient participation in specific EMA activities. Patients must make a declaration of interest and sign confidentiality documents. It is expected that patients' organisations may provide personalised support regarding the role of patients in the EMA; the agency, however, is expected to have identified situations where patients' involvement would bring added value and manage both patients' and committee's expectations for that participation.

All stakeholders acknowledge the need to take into account the patient's experience with a disease and its treatment and integrate this parameter into the evaluation of medicines.

Regulators do not expect that the role of patients will be scientific, although it may be. They do expect that patients will provide unique and critical input based on real-life experience and advise on the feasibility of planned investigations. Additionally, regulators hope that patients will reflect on the real-life implications of regulatory decisions, help translate regulatory outcome into meaningful information, identify channels for dissemination of information and add openness, transparency and trust to the regulatory process.

In the benefit-risk evaluation of medicines, the EMA recognises that patients can be consulted on the feasibility of a proposed study, including the relevant patient population, comparator, duration of study, relevant patient outcomes, safety concerns and the feasibility of the risk management plan. As written in the report of an EMA workshop on the patient voice in the evaluation of medicine conducted in 2013 "Because patient views of risk and benefit can differ from those of other stakeholders and may vary between patients and at different stages of disease, this is an important and complex area that may require innovative methodologies".[1]

At this workshop several groups presented models of best practice in patient participation. The European Community Advisory Board (ECAB) – a working group of the European AIDS Treatment Group, detailed their platform for dialogue with pharmaceutical industry and regulators. ECAB is developing models for interaction between regulators and different stakeholders while maintaining the proper independence of each group. The group professes an understanding of the role of patient expert who shares knowledge of other groups.

The European Register for Multiple Sclerosis (EUReMS) is a multinational, multisponsor, partnership between clinical centres and

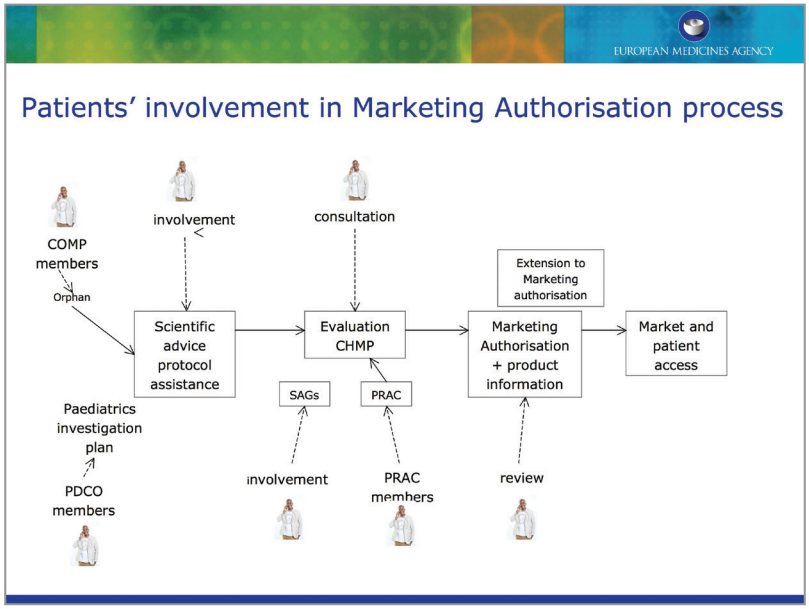


Figure 4. The different capacities of patient involvement in the EMA registration process for new medicines.

patients' organisations to harmonise registers and databases for multiple sclerosis patients in the EU. They have agreed on a common dataset and are developing ways to address variations in access to treatment.

Challenges and caveats

There are challenges in patient involvement in medicines regulation. Regulators must identify appropriate times to obtain input from individual patients versus the patient community. They should develop the means to identify and manage differences of view among patients and between patients and other stakeholders. They need to ensure that patients' views come from independent sources, look at training and support for patients to maximise patient's input, research how to collect and use the wealth of information available from patients and physicians in the post-marketing phase and identify and address all legal, regulatory and financial issues that could give rise to procedural barriers to patients' involvement.

All stakeholders acknowledge the need to take into account the patient's experience with a disease and its treatment and integrate this parameter into the evaluation of medicines. It must be remembered, however that evaluation is at the population level while treatment is at the individual level, values vary among patients and change over the individual patient journey and the role of the healthcare professionals, particularly general practitioners in the patient journey must be acknowledged.

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Collecting patients' perspectives on benefits, harms and relative importance

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Benefit-risk at GSK

Since 2011, the benefit-risk team at GlaxoSmithKline has assisted internal product teams in the development of systematic presentations of the evaluation of the benefit-risk of medicines. The number and diversity of products for which the benefit-risk team's services have been employed has grown each year and now includes mature and over-the-counter products.

As part of this growth and in response to user feedback, a framework was incorporated for benefit-risk evaluation in 2013 and synergies were found with other GSK work such as Periodic Benefit-Risk Evaluation Reports (PBRERs) and Program Safety Analysis Plans (PSAPs). Basic benefit-risk training was also provided for more than 200 staff members and an advanced training programme was planned at the time of this presentation. In 2014, in addition to a growing list of projects, work was initiated on the "rare event" project, which will seek to determine the optimal method for characterising the risks of rare harms that may be associated with either therapies or disease processes.

Benefit-risk decisions: when and what

Benefit-risk decisions should seek to answer basic questions throughout the product lifecycle. In early development, decisions about the molecule in development, its targets, potency, toxicity and animal and in vitro models should be based on the answer to the question *Is this likely to affect the right targets without being too toxic?* In the clinical development phase, decisions about study design, clinical endpoints and outcomes and quality of life should be based on the answers to the questions *Do we have evidence that this is a medicine whose benefits outweigh the harms? Have we identified the key benefits and harms and measured them in meaningful ways?* At launch, decisions about labelling, patient and healthcare professional information and risk management should be based on the answers to the questions *Have we characterized the appropriate patient population for whom the benefits outweigh the harms? Can we manage the harms that occur?* During the remaining life of the product, decisions about long-term follow-up, real-world experience and pharmacovigilance should be based on the answers to the questions *Does the medicine continue to perform when it is used longer and more widely? Do we continue to see more benefits*

than harms? How can we tell?

Benefit-risk decisions and patient input

Benefit-risk decisions should also seek to answer basic questions relevant to patients, albeit with certain caveats. In early development, patient-related decisions should be based on the answer to the question *Where is the unmet medical need?* It is important to keep in mind, however, that although a company can choose therapeutic targets, it has no control over whether a therapy will work; that greater potency usually means greater toxicity and that animal and in vitro models are not completely predictive. Industry should continue to look for more ways to involve patients in early development, especially as knowledge about genetics continues to grow. At the time of clinical development, patient-related decisions should be based on the answers to the questions *Is this clinical trial patient friendly? Are we measuring the right endpoints in the right way? Do we understand the course of the disease and its impact on the patient?* It must be realised that information from patients in clinical trials and health outcomes studies needs to be extrapolated in an effort to determine the right patient population and the right dose and regimen. At launch, patient-related decisions should be based on the answers to the questions *Will this be a medicine that patients want to take? Will it meet their priorities for their health? Have we provided enough information in the right way for patients to make informed decisions?* Industry needs to remember, however, that it is required to communicate some information in specific ways and needs to be more creative and collaborative in the other ways in which information is shared. During the remaining life of the product, patient-related decisions should be based on the answers to the questions *What happens when patients are in an everyday setting rather than a clinical trial? Where do patients go for information? How can we provide the information that is needed and trusted? How can we monitor patients' wellbeing and medicine performance?* The diversity of the post-approval environment creates a number of challenges, however and collaboration with patients is key.

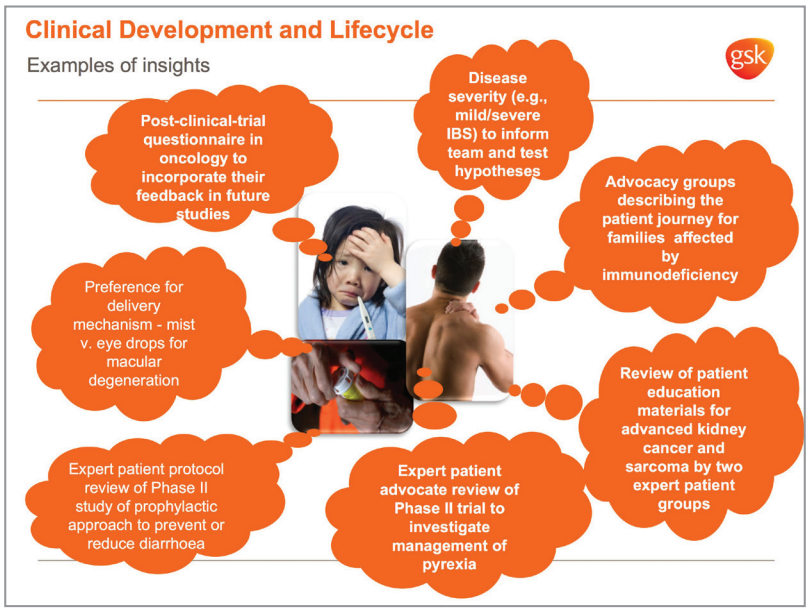

Figure 5. GSK has sought patient input for clinical development and complete product lifecycle issues.

Collecting patient information

Benefit-risk information is collected from patients in a variety of ways. Concept elicitation allows the compilation of data regarding a disease and the impact of its treatment; the definition of treatment benefits and the tradeoffs in benefits and risks that patients are willing to accept. Exit interviews permit the interviewer to explore indications, understand benefits versus risks, substantiate or complement other patient-reported outcome measures, highlight potential issues for adherence to treatment, identify subpopulations with the greatest response or patients unlikely to benefit from treatment. Patient preference utilities facilitates the collection of information that is complementary to clinical and safety data on the benefits and risks of new treatments. They can be used in economic evaluation to inform resource allocation decisions. Conjoint analyses are used to understand patient preferences and benefit-risk tradeoffs and to inform drug development decision making.

Patient involvement in early development

An estimated 90% of compounds entering clinical trials fail to demonstrate the necessary efficacy and safety requirements. GSK is involved in a number of projects that seek to improve the level of research and development success through patient-inclusive multi-stakeholder collaboration. At the Centre for Therapeutic Target Validation, GSK, the European Bioinformatics Institute and the Wellcome Trust Sanger Institute are using big data and genome sequencing to improve the success rates for discovering new medicines. The project aims to address a wide range of human diseases and share data openly to accelerate drug discovery by looking for causal factors across a range of diseases, possibly including rare diseases, oncology and immuno-

inflammation. The Accelerating Medicines Partnership (AMP) was recently launched to identify and validate promising biological targets of disease. The National Institutes of Health, the US FDA, the Alzheimer's Association, the American Diabetes Association, the Geoffrey Beene Foundation, the Lupus Foundation of America, the Pharmaceutical Research and Manufacturers of America, the Rheumatology Research Foundation and USAgainstAlzheimer's, GSK, AbbVie, Biogen Idec, Bristol-Myers Squibb, Johnson & Johnson, Lilly Merck, Pfizer, Sanofi and Takeda are all participating in the project. It is focused on Alzheimer's diseases, type 2 diabetes and autoimmune disorders rheumatoid arthritis and systemic lupus erythematosus with the generated data to be made publicly available to biomedical researchers.

GSK continues to strive to collect patient insights within clinical development and throughout the lifecycle of medicines on such issues as diseases severity, a holistic vision of the patient journey including an understanding of the effects of disease on entire families and caregivers. Patients are asked, for example, to review patient education materials, evaluate the processes for the management of side effects and look at preferences for delivery mechanisms, looking at the clinical trial questionnaires to incorporate feedback for future studies and the efficient us of exit interviews (Figure 5).

These collaborations in the precompetitive space centre on disease area research and hopefully inform the regulatory process. The goal for industry should be to treat whole patients by developing medicines that address real-world factors such as co-morbidities, use of multiple medications and other specific concerns that revolve around daily life,

Moving forward

GSK has made a commitment to work toward developing a better understanding of disease processes and a holistic view of patients through the measurement and characterisation of their actual experience in disease management, their views on benefit-risk tradeoffs and their goals for treatment. The organisation seeks to expand participation in collaborative groups that include patients and their representatives along with researchers, developers, regulators, healthcare professionals and others. They plan a focus on diseases and disease endpoints, improving measures of efficacy and safety and learning how to collect more information on effectiveness. Progress has been made in the incorporation of the patient perspective and additional learning is both anticipated and welcomed.

IMI PROTECT WP5: What has been our experience in the collection of patient views and their use in benefit-risk analysis?

Kimberly Hockley

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Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (PROTECT), led by the European Medicines Agency and consisting of 31 public and private partners, aims at strengthening the monitoring of the benefits and risks of medicines. Within PROTECT, Work Package 5 seeks to find methods for continuous benefit-risk monitoring by integrating data on benefits and risks from multiple, different data sources.

The task of regulators is to make good and defensible decisions on the best available evidence regarding which medicines are safe and effective for which indications and for which patient populations. However, it has become increasingly important to be able to justify and explain these decisions to stakeholders, including patients. This led to two important questions that were posed as part of WP5: can more formal approaches of decision making and especially more modern methods of graphical display help regulators do these better? and can formal approaches of decision making be used to elicit preferences from patients and the public in a regulatory setting?

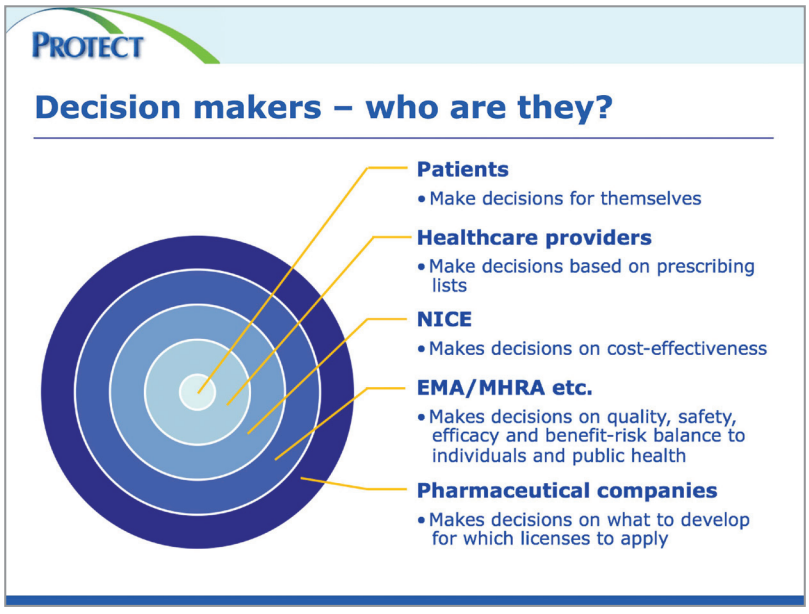

Figure 6. Many interdependent decisions are made in the development, regulation and reimbursement of medicines.

Many interdependent decisions are made in the development, regulation and reimbursement of medicines (Figure 6). In the traditional model, pharmaceutical companies decide which medicines to develop and for which licenses to apply, regulatory agencies such as the European Medicines Agency make decisions on the quality, safety and efficacy of those medicines and determine their benefit-risk balance to individuals, public health. Health Technology Assessors must then make cost-effectiveness decisions regarding the medicines, healthcare providers decide whether to prescribe and patients whether to use the medicines. WP5 sought to bring patient and public involvement forward earlier in this decision-making continuum, particularly at the level of regulatory decision making, making the "black box" process that produces the summary benefit-risk statements in regulatory public assessment reports more transparent and more defensible.

Patient and public are defined by the NHS as clinical trial participants, patients and potential patients, disabled people, parents and guardians, people who use health and/or social care services, carers, members of the public and the organisations who represent the interests of these consumers. Involvement is described as an active partnership between stakeholders in the research process, rather than the use of people as 'subjects' of research. Public involvement in research is often defined as doing research 'with' or 'by' the public, rather than 'to', 'about' or 'for' them.

Patient or public involvement (PPI) can be an explicit or implicit component of decision-making frameworks used to evaluate the benefits and risks of medicines. For example, PPI can be found in two descriptive decision-making methods that were among the multiple formal frameworks for benefit-risk decision making evaluated in WP5: the BRAT (CIRS-Benefit-Risk Action Team) and PrOACT-URL (Problems, Objectives, Alternatives, Consequences, Tradeoffs, Uncertainty, Risk tolerance, Linked Decisions). The CIRS-BRAT user guide specifies "Patient advocates may be included as optional stakeholders in the BRAT framework development team and provide external input at two key stages: the identification of outcomes and the assessment of outcome importance." PrOACT-URL briefly mentions the role of patients in a few steps of the decision-making process, although it does not detail their explicit involvement.

[Patient or public involvement] can be applied at specific stages by systematically investigating where it would be most meaningful and beneficial to involve patients at each step of the benefit-risk pathway . . .

Traditionally, PPI has taken place at two levels: in consultation, in which patient and public perspectives are used to inform regulatory decision making; and collaboration, in which regulators work together with patients and the public to form an active partnership and jointly participate in the decision-making process for a specific decision-making stage. Experience, however, has shown the potential for differences between the individual and population perspectives; that is, patients ask, "Would I take this treatment?" Regulators, on the other hand, ask, "Should a patient population with this indication take this treatment?"

Although PPI should be applied throughout the decision-making continuum, there are currently few methodological guidelines or resources to accomplish this goal. Alternatively, PPI can be applied at specific stages by systematically investigating where it would be most meaningful and beneficial to involve patients at each step of the benefit-risk pathway. WP5 team member determined that it would be meaningful and beneficial to incorporate PPI into the ranking and weighting of relevant outcome measures, which had been selected for assessment in a quantitative benefit-risk framework using the integration of clinical trial, post-marketing surveillance and preference data.

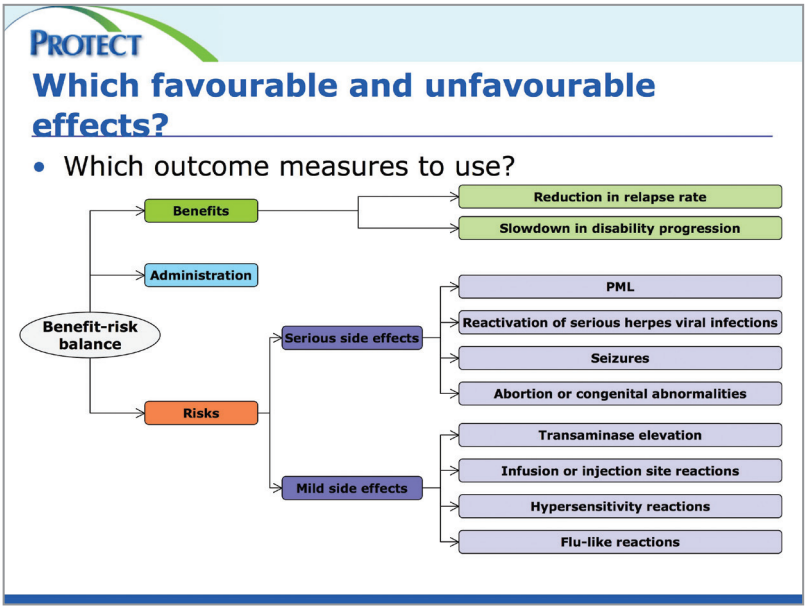

Figure 7. Benefit-risk decision makers must determine which of a medicine's attributes to evaluate.

Having determined when PPI should be applied, additional challenges were to decide whose preferences would be elicited, which methodology or methodologies for assessment would be used, which favourable and unfavourable effects would be assessed and how the results of the evaluation would best be communicated (Figure 7). It was decided that the preferences of organisations that represent patients and consumers would be elicited in two case studies. Methodologies were selected for their common use. For evaluation of the anti-obesity drug rimonabant, discrete choice experiment methodology was used and for natalizumab, the treatment for relapsing and remitting multiple sclerosis, discrete choice experiment, analytic hierarchy process, swing-weighting and MACBETH were employed. WP5 team members recognised the challenges in the selection of favourable and unfavourable effects including the need to limit the number of outcomes, the use of aggregate scores such as the Expanded Disability Status Scale, the range of severities that are possible such as in transaminase elevation and the use of surrogate measures such as 10% weight loss.

Finally, when communicating benefits and risks to patients, it was important to ensure that messages were worded so that patients could understand them and to use graphic representation when possible. Elements of benefit-risk communication that patients have indicated that are important to them include frequency, severity, duration and reversibility of treatment effects; personal vignettes and impacts on quality of life.

Conclusions

Eliciting patient preferences in regulatory assessments can add value and lead to more clinically relevant decisions. This can confer legitimacy, transparency, trust and communicability to ultimate decisions but this is still a work in progress. Many different formal methods of benefit-risk assessment can be used to elicit patient preferences, each with its own unique features, strengths and weaknesses but further exploration is needed to more fully assess these methods. Benefit-risk assessment methodologies support decision making but they are not meant to replace medical or regulatory expertise. There is no single, one-size-fits-all method for benefit-risk assessments that incorporate patient or public views.

Providing patient preferences into the regulatory discussions: What are the pathways being explored?

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Patients and regulatory agencies

Regulatory agencies in the United States and Europe are actively working to provide patient perspectives for benefit-risk assessment in drug development. In the US, the Food and Drug Administration (FDA) has a Patient Representative programme, in which patients are involved as members of public advisory committees acting as consultants providing scientific advice to the FDA Review Division during drug development. The FDA is also implementing a patient-focused drug development programme, which was mandated under the fifth iteration of the Prescription Drug User Fee Act (PDUFA-V), in which patient and caregiver perspectives are being solicited in a series of twenty public meetings over five years on specific disease areas.

The European Medicines Agency (EMA) has a standing working party with patients and consumers and there are permanent patient representatives on some EMA committees and advisory groups. However, patients are not represented on the Committee for Medicinal Products for Human Use (CHMP) and are effectively excluded from key decisions on licensing and direct involvement of patients with the disease under discussion is extremely rare.

Despite the fact that people with specific disease conditions know which outcomes and symptoms matter most to them, patients have been an underutilised resource. In particular, the values and preferences of clinical trial participants, who are the ideal target treatment group for a medicine after licensing, are generally not explored in a systematic way. Decision analysis, however, may provide a pathway for eliciting the patient perspective regarding the benefits and risks of medicines.

The VALUE study

Work Package (WP) 5 of the Innovative Medicine Initiative Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium (IMI-PROTECT) explored a variety of methodologies for eliciting patient benefit-risk preferences. As part of efforts in PROTECT WP 6 to validate these methodologies, the VALue and Utilities among European Patients (VALUE) study was conducted.

Decision analysis, however, may provide a new pathway for eliciting the patient perspective regarding the benefits and risks of medicines.

This pilot study evaluated the use of the Measuring Attractiveness through a Categorical Based Evaluation (MACBETH) software for eliciting patient preferences. This study, which was supported by the UK MS Society, employed a questionnaire with simple pair-wise comparisons between treatment options written in plain language. Using a decision model, 62 patients with multiple sclerosis evaluated several MS treatment outcomes that included the number of relapses over five years, the time to disease progression, disability due to disease progression, the number of deaths by liver failure in ten years, the number of deaths or severe debility from progressive multifocal leukoencephalopathy (PML) and the number of deaths from leukaemia. The patients rated the difference in attractiveness between two different outcomes, such as having no relapses in the next five years compared with one relapse in the next five years, with ratings ranging from extreme to very weak.

The patient interface collected qualitative data and MACBETH converted these data to quantitative scores to build a treatment decision model. The quantitative scores could then be used to determine for example, that Treatment A outperforms Treatment B on the number of relapses. The patients also weighted the outcomes in terms of importance to them by identifying which outcome, for example, mild disability, was most important in comparing treatments. Swing weighting was used to capture how big the swing was from worst case to best case. Results of the study in the form of value function curves indicated differing attitudes among the patients. The majority of patients assigned the highest weight to the treatment outcome reduction of disability due to disease progression and the ability to walk was a strong predictor of values or risk attitudes toward treatment side effects.

The methods used in this study complied with decision-making theoretical principles and data were easily collected via a web-based user interface that allowed participants to complete the questionnaire in their own homes and that could be used in other research to collect patient preferences in a remote setting, such as a clinical trial.

Future research

Further research is needed to assess the reproducibility and validity of responses and to determine the best methods for aggregating data and to evaluate regional differences in patient values and judgement. Therefore, the WP 6 study Visualizing Uncertainty Among Laypersons and Experts (VISUALize) will be launched in a larger number of patients (5600) across different disease areas (atrial fibrillation, breast cancer and diabetes). The study will use two different types of preference elicitation: discrete choice tests and MACBETH in eighteen questionnaires across the United Kingdom, the Netherlands and France and involve patients, healthcare professionals and regulators.

How do other decision makers collect information from patients and how does this influence decision making? Viewpoint from an HTA agency

Lizzie Amis

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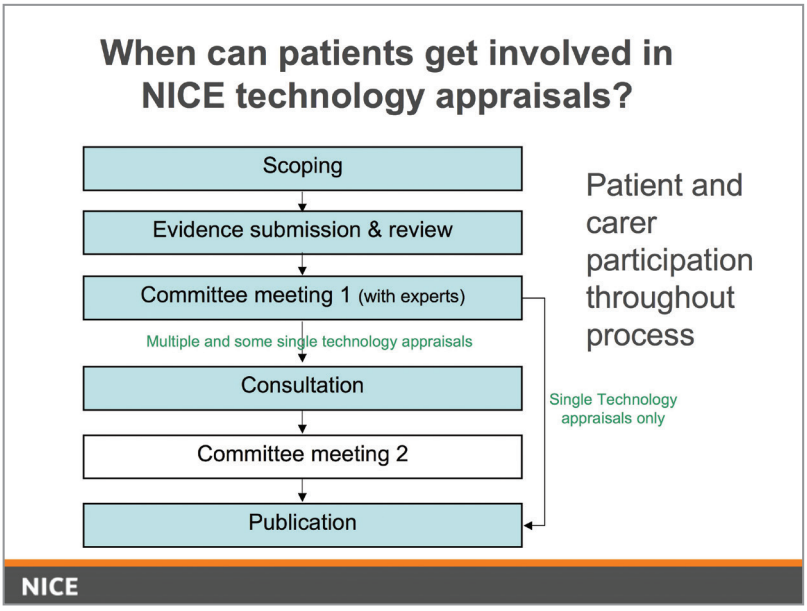
The National Institute for Health and Care Excellence (NICE) issues guidance, advice and quality standards to improve health and social care. NICE provides guidance on health technologies including pharmaceutical technology, interventional procedures, medical devices, diagnostics and ultra-orphan drugs. NICE guidelines include clinical guidelines for both full and short pathways of care, quality standards, guidance and standards for public health and social care.

Figure 8. Patient and carer participation during NICE technology appraisals



Patient and public involvement (PPI) is a fundamental, integral part of the business of NICE. It is overseen by a centralised, dedicated team that operates under a formal board-level policy and has the support of senior management. Through NICE PPI, patients and their carers participate throughout the process of appraisals, from scoping through publication (Figure 8). As part of the process, four drug health technology assessment (HTA) committees, meet in parallel once weekly at NICE to consider a monthly topic, most of which are single technology appraisals (STAs); that is, one drug for one indication. Each HTA committee has three full-time paid lay members with full voting rights, who are openly recruited through the NICE website. Additionally, national patient groups concerned with specific diseases can attend scoping workshops, comment on draft documents, provide written submission of evidence, nominate patient experts and appeal recommendations. Also, individual patients and caregivers can attend as patient experts and any member of the public can comment on draft recommendations. However, it should be recognised that the documents under consideration during appraisal are technical documents and only the final document is written in plain English.

NICE recognises that there is a need to obtain relevant evidence from real life and views and experience from patient and caregiver

stakeholders, especially evidence that might not otherwise be available, to help the committee understand the topic and issues. Therefore, formal evidence, including individual views and experiences from stakeholders, is presented. National patient organisations can submit this evidence using a formal template for STAs or free-text prose for multiple technology appraisals (a standard template is under development), both of which can be supplemented or endorsed by expert statements. Available on the NICE website, the STA template was updated in 2014 to increase clarity and to reflect changes to the NICE Methods Guide and congruence with the Health Technology Assessment international (HTAi) template.

Does patient and public information influence decision making?

Because patient input and evidence is integrated into the NICE appraisal process, it is challenging to evaluate its importance or impact. Individually, however, this evidence has helped increased committee awareness of patient issues and assisted in efforts, for example, in identifying sub-groups for seasonal asthma and gout, recognising the importance of kidney dialysis treatment location and determining relevant outcomes for patients with psoriasis. Additionally, NICE has increased the role of the committee lay members to ensure that patient evidence is proactively analysed.

Committee members have indicated that the impact of patient involvement is primarily in the decision-making process rather than in the decision-making outcome. Results of interviews show that 66% of committee members considered that having a lay member on the committee increased their awareness of patient issues, while 62% said that the lay members' input did not change the ultimate decision. Nevertheless, the majority of committee members said that the lay members' participation improves NICE address of patient issues (74%) and public relations (88%), is important in the conduct of public meetings (77%) and benefits NICE's international reputation (59%).

NICE recognises that there is a need to obtain relevant evidence from real life and views and experience from patient and caregiver stakeholders . . . to help the committee understand the topic and issues.

For more information

The following links are available for further information on NICE activities:

- Public homepage: www.nice.org.uk/getinvolved/patientsandpublic
- PPI policy: www.nice.org.uk/getinvolved/patientandpublicinvolvement/patientandpublicinvolvementpolicy/patient_and_public_involvement_policy.jsp
- PIP's leaflet: www.nice.org.uk/media/D92/88/PPIPLeaflet.pdf
- Search for NICE Guidance for the Public: www.nice.org.uk/patientsandpublic/index.jsp

What simple methods could be used to elicit patients' views on benefits, harms and relative importance? An academic viewpoint

Dr Lawrence Phillips

Emeritus Professor of Decision Sciences, London School of Economics and Political Science, UK

Defining importance

In the progressions from the analysis of efficacy and safety data to the assessment of the risks and benefits of new medicines, the intermediate steps are the consideration of the favourable and unfavourable effects and the clinical relevance of these effects. These steps require judgements by regulators and medical experts and by physicians and their patients (Figure 9) all of whom may differ in their conclusions.

A definition of the importance of a medicine's favourable and unfavourable effects is illustrated by considering the evaluation of the use of a triptan in the treatment of migraine headaches. In the evaluation of migraine treatments, a key question for patients is *which aspect of treatment is more important: reduction of functional disability (mild or no disability 2 hours after dosing) or the risk of myocardial infarction (MI) within 48 hours after dosing?* At a CIRS Workshop in June 2011, a Syndicate group assigned twice as much weight to the reduction of functional disability as to MI risk. Examining the process by which this conclusion was reached demonstrates a method for eliciting patients' views on benefits and risks of treatment.[1]

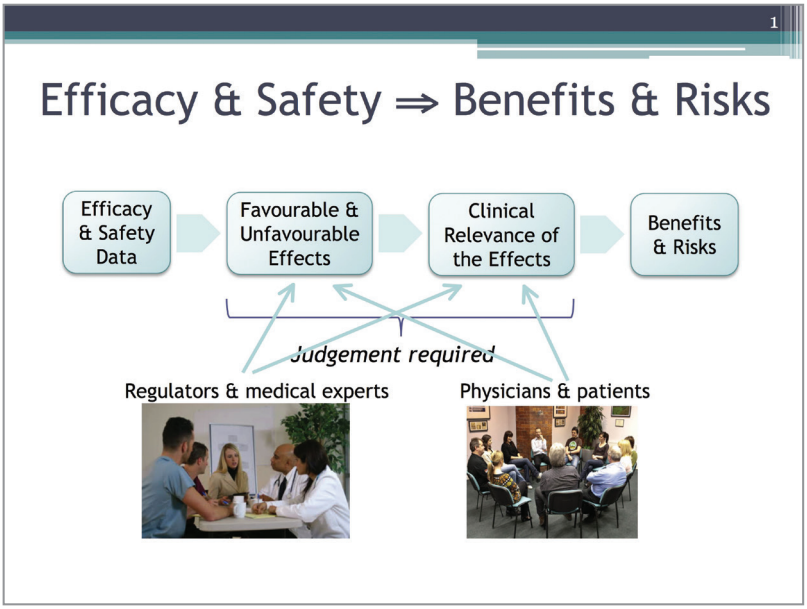


Figure 9. Efficacy and safety data are analysed to determine benefits and risks from differing perspectives.

Importance depends on context. In the triptan example, context includes the impact from the occurrence of a migraine on the patient's work and family, the patient's current state of health, especially of the heart and the level of risk for MI that is acceptable. Second, real-world differences must be confronted. For example, what is the difference between suffering the level of functional disability brought on by a full-blown migraine on the one hand and on the other hand reducing or eliminating the functional disability within two hours? Another difference is between the chance of experiencing an MI within 48 hours of using the medicine compared to that chance if the triptan is not taken. The correct question to ask a patient therefore, is not how important is this effect? but rather *how big is the effect difference and how much do you care about it?* Deciding how much those differences matter, however, requires that a judgement be made and as Professor Ralph Keeney stated in "Common mistakes in making value trade-offs," that judgement cannot be independent of the ranges of comparisons[2]

The process of swing-weighting

Swing-weighting offers a simple method to quantify the importance of an effect difference to an individual. First, criteria are defined so that they are comprehensible to people without a medical or scientific background. It should be recognised that it may be especially challenging to operationalise some complex therapeutic area scoring systems, such as those for arthritis or psoriasis. Next, scales with plausible ranges for the data are created and participants rank the effect criteria on the basis of the swings in added therapeutic value on those ranges. Finally, swings are weighted against one another to determine relative added value.

Five steps were used to apply swing weighting in the triptan migraine model:

Step 1 defined the effects to be measured: For example, *Functional disability* was defined as the proportion of patients who experience moderate or severe baseline disability with mild or no disability measured at 2 hours after receiving a 30-mg triptan dose. The *MI effect* was defined as the number of patients per 1000 patient-years who would have an MI within 48 hours of triptan dosing. These definitions were constructed to

make them comprehensible to non-medical people and operationalised as much as possible by the use of terms such as moderate or severe and measured.

In Step 2, a functional disability scale was created for each effect criterion with plausible ranges for the data. For example, for Functional disability, the range extended from 0% of patients who did not respond to the triptan to 70.0% of patients experiencing mild or no disability 2 hours after dosing. The MI scale ranged from 8.0 for patients receiving a placebo to 16.0 for patients receiving the 30-mg triptan dose.

In Step 3, the favourable effects criteria were placed in rank order based on their perceived added therapeutic value over the ranges and this was repeated for the unfavourable effects criteria.

In Step 4, swings for the favourable effects were weighted against one another for added value using the technique of paired comparisons. The largest swing was assigned a value of 100 and other swings were scored as ratios to those 100 points of added value. This process was repeated for the unfavourable effects. Then, the largest favourable effect swing was compared to the largest unfavourable effect swing. At the 2011 CIRS Workshop, this weighting showed a 2-to-1 preference for a swing from 0% to 70% for functional disability over a swing from 16 to 8 in MI risk.

In Step 5, the consistency of weights was checked using 'balance beam' comparisons and adjusting the weights that didn't seem correct. In this example, after weights were adjusted for favourable effects, headache relief plus pain-free response was judged to give 30% more added therapeutic value than sustained relief (Figure 10). After adjusting the swing-weights for favourable effects, the process was repeated for unfavourable effects until participants agreed that all assessed weights felt realistic and consistent.

The correct question to ask a patient therefore, is not how important is this effect? but rather how big is the effect difference and how much do you care about it?

Although patients can find swing-weighting puzzling at first, once they have experienced it and the concept of comparing added values becomes obvious, the weighting process proceeds smoothly.

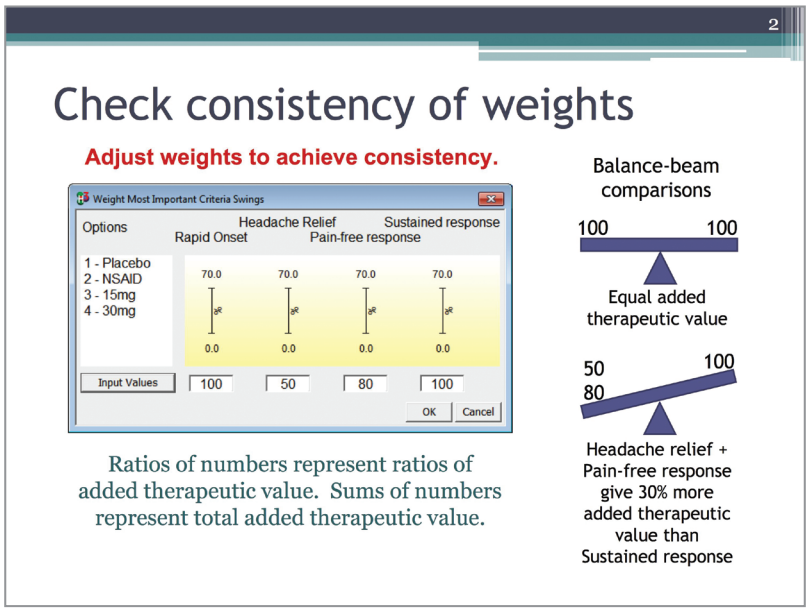


Figure 10. Checking the consistency of weights through paired comparisons.

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What simple methods could be used to elicit patients' views on benefits, harms and relative importance?

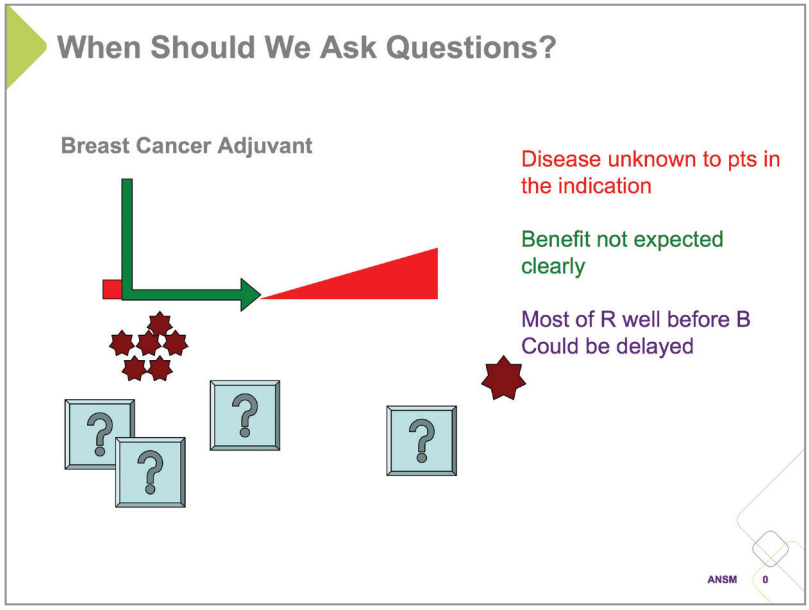
A regulatory viewpoint

Dr Pierre Démolis

Vice Chairman, CHMP, ANSM, France

It is not possible to identify the "average patient". Rather, patients with specific conditions can give insights into those conditions and range of effects can be characterised for a given target population. The appropriate time for eliciting patients' views on the benefits and risks of medicines depends on the disease under study. It also relates to the phases at which the patients have a clear understanding of the benefits they expect, the relative importance of any risks and the outcomes they are expecting or have experienced. For migraine, patient insights might be most valuable after the migraine crisis has ended. In MS patient insights might be most useful once the disease has reached a plateau. For end-stage renal disease, patient insights might be most important once disease progression is evident. In breast cancer, patient insights could be most informative throughout the interval between diagnosis and long-term follow-up and patients who have survived over the long term could have special insight into the benefits and risks of treatment (Figure 11).

Figure 11. The appropriate time point for eliciting patients' views depends on the disease..



The appropriate time for eliciting patients' views . . . relates to the phases at which the patients have a clear understanding of the benefits they expect, the relative importance of any risks and the outcomes they are expecting or have experienced.

Patients are experts on the diseases they have and as such their views are always important and they may be helpful in decision making. Furthermore, patients are often knowledgeable regarding the benefits of treatment, they sometimes are the best people to assess those benefits, they sometimes understand the risks of treatment and they may be able to assess the benefit-risk balance.

Whilst regulators should be prepared to be disappointed in the results of patient involvement at times, they should take every opportunity to ask patients their views on the benefits of treatment. However, it should be recognised that from a regulatory perspective, there is currently no single, simple method for eliciting patients' views on the benefits, harms and relative importance of treatment.

What simple methods could be used to elicit patients' views on benefits, harms and relative importance?

An industry viewpoint

Dr Jamie Cross

Regulatory Program Director, Genentech Inc, USA

Current methods

The many current methods of assessing patients' views on the benefit-risk balance of treatments include patient-reported outcomes, in which patients describe how they feel; conjoint analysis/discrete choice tests, in which patients choose from among a set of tradeoffs and multi-criteria decision analysis, in which patients deconstruct the tradeoffs. These methods involve soliciting information from patients; that is, they are patient-focused and they are flexible because they can be used at any time during drug development but they may not be simple to use or interpret.

Properties of a simple method

Properties required for a simple method to collect patient benefit-risk input are: understandability to the patient, interpretability to all, encompassment of all relevant outcomes and flexibility for different decisions (Figure 12). Each of these properties can be assessed with a series of questions that can be applied to methods in current use, as well as to new methods.

- **Understandability:** Can patients understand what is being asked of them? Does the format ensure reliable input? Is there potential for bias?
- **Interpretability:** Are the results from the method interpretable? Are the results quantitative or qualitative? If quantitative, do the units of measure make sense? Is there potential for incorrect application of the findings or conclusions from patients?
- **Encompassment:** Are there limitations to including all relevant benefits or risks? If there are too many outcomes, is there potential for cognitive burden? Is there potential for bias from arbitrary selection of outcomes to exclude? Does simplification distort the real-life trade-off?
- **Flexibility:** Can the method be used in both the pre-licensing and post-licensing stages? Can it involve subjects as part of a clinical trial and can product teams readily apply it? Is the method scalable to patients or the public in the post-licensing stage? Is it simple enough to apply during a short regulatory review cycle? Is the format conducive or cumbersome for patient participation?

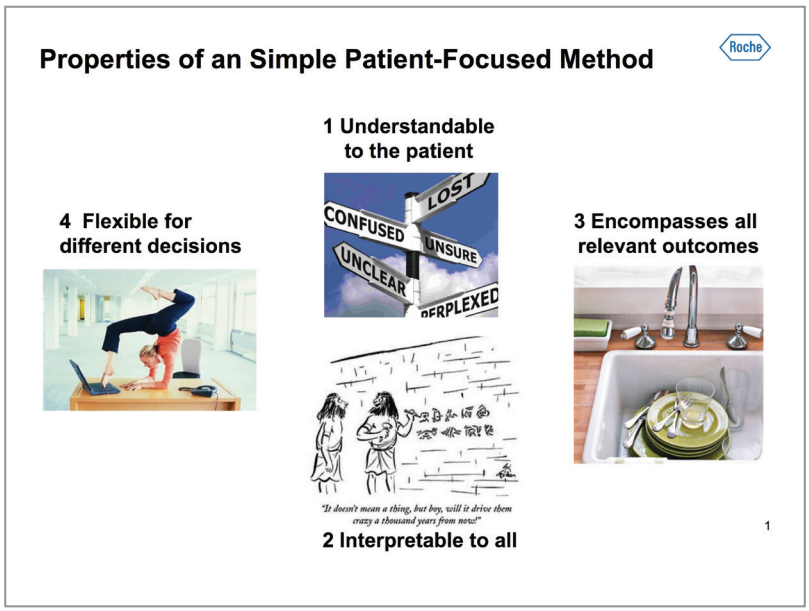


Figure 12. Each of the properties of a simple method for acquiring patient input can be assessed through a series of questions.

Possible methods

A discussion of potential simple methods to elicit patient viewpoints on benefit-risk is based on the assumption that it is possible for a method to be simple. Potential complications to simplicity, however, include the fact that collection of information from patients in most instances requires some form of Institutional Review Board or Ethics Committee approval. Moreover, the potential for bias in determining which patients are selected and how they are involved may be problematic. Nevertheless, there are potential "simple" methods for the acquisition of patient input which include qualitative survey research conducted by industry and medical and patient organisations and the use of online media and "big data" analysis (Figure 12).

Qualitative survey research collected by industry: Patient-oriented research currently used by drug sponsors is often cumbersome. An alternative to this type of data collection would be to solicit patient benefit-risk feedback as part of clinical trials or registries. This should be simple qualitative research, conducted at patient screening (with a potential comparison

between enrolled patients and screen failures). An assessment could be conducted prior to key development milestones such as the end of phase 2 and post-licensing registries could collect patient benefit-risk feedback. A follow-up survey could also be conducted for enrolled patients at the end of trial or discontinuation.

Qualitative survey research collected by medical organisations: The collection of patient data by medical organisations is currently underused. Vast amounts of data are shared at medical conferences but patients are largely absent from the discussion. Medical organisations could potentially partner with patient organisations in order to understand patient perspectives on the data being collected and shared before marketing authorisation has been achieved.

Qualitative survey research collected by patient organisations: Patient advocacy groups could also play a significant role using "simple" methods. Widely used websites for patients already present vast amounts of information and involved patient groups could coordinate the generation of data on benefit-risk assessment from the patient perspective, without a perceived conflict of interest.

Additionally "big data" methods could make sense of online patient experiences, which would be particularly helpful in the post-licensing stage to show real-world benefit-risk. Published articles have already demonstrated that such methods are feasible in the collection of data regarding influenza and dengue fever. epidemics[1,2]

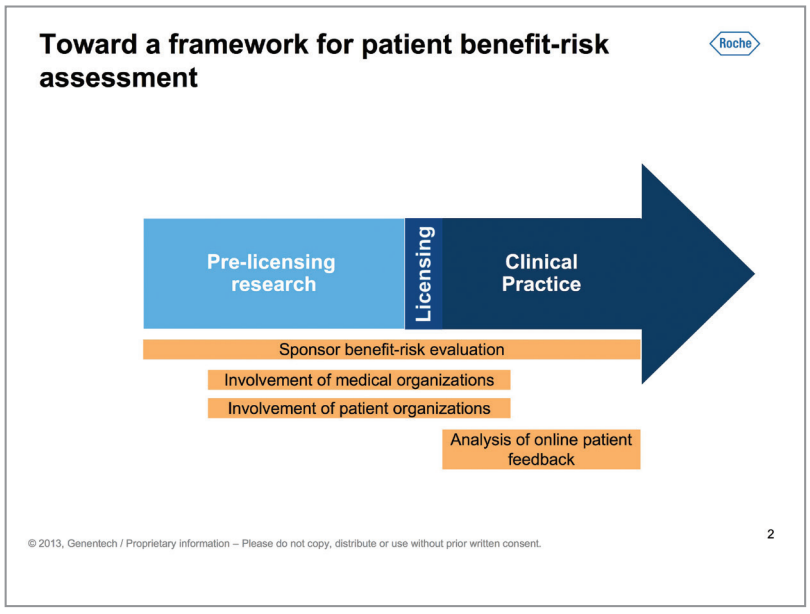


Figure 13. Potential simple methods for collecting patient benefit-risk input can occur throughout the product life cycle.

. . . it remains to be determined if the incorporation of patients' views on benefit-risk would decrease the number of type 1 or type 2 errors in regulatory decision making.

Conclusions

The current situation presents significant opportunities: Medical and patient organisations are largely untapped sources of patient-viewpoint benefit-risk research. Much of the online information is also unused and the full potential of rapidly advancing mobile technology has not yet been realised.

Challenges exist to the realisation of simple methods to assess patients' views of benefit-risk, however, including a lack of resources to systematically engage medical and patient organisations and questions about the applicability of big-data methods to benefit-risk decision making. Additionally, whether any of the methods are actually simple and whether they have the needed properties of understandability, flexibility and encompassment must be determined. In addition, the value added by these methods is currently unknown and it remains to be determined if the incorporation of patients' views on benefit-risk would decrease the number of type 1 or type 2 errors in regulatory decision making.

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The communication of benefits and harms to patients: How well are we doing and what needs to be improved? An industry viewpoint

Dr Yatin Shivkar

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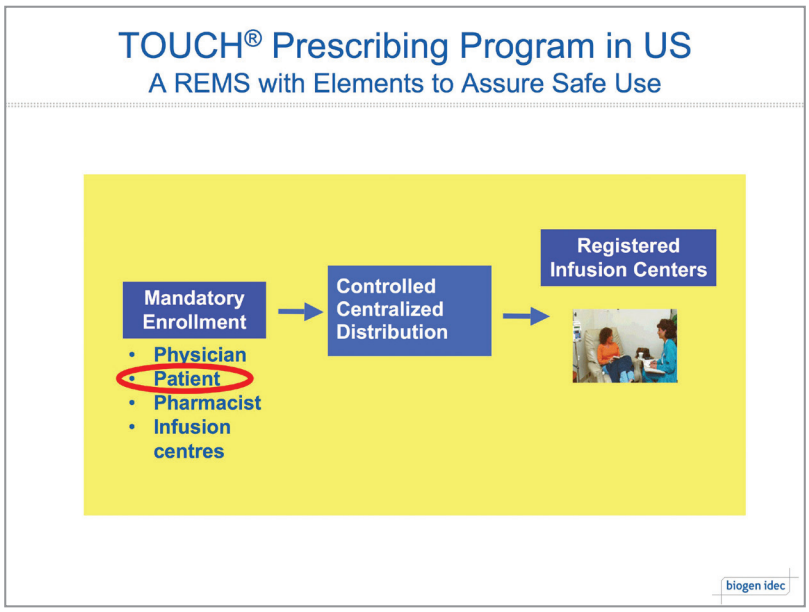
Communication of benefits and harms to patients

Risk communication is a fundamentally important tool in risk management but patients are no longer satisfied with receiving only information on risks and have become increasingly desirous of receiving more information on the benefits of the products that they use. Biogen Idec recently evaluated the effectiveness of its benefit-risk communication to patients in the context of the TYSABRI® Outreach: Universal Commitment to Health (TOUCH®) programme, a US risk management system for Tysabri (natalizumab), which is indicated for relapsing multiple sclerosis. The evaluation was part of the risk evaluation and mitigation strategies (REMS) Stakeholder Project that was initiated in 2010 to gain better understanding of various aspects of TOUCH, including patient feedback on benefit-risk communications.

Figure 14. The elements of the TOUCH programme.



In general, the majority of respondents (66%) preferred to receive an equal balance of benefit and risk information

TOUCH communication tools and stakeholders

TYSABRI, a monoclonal antibody, has been approved for use in 70 countries. Its approval was based on the significant efficacy (68% reduction in annualised relapse rates and 42% reduction in disability progression) observed in clinical trials. Observation of an increased risk of progressive multifocal leukoencephalopathy (PML) caused the voluntary withdrawal of TYSABRI from the US market in 2005. However, TYSABRI was re-introduced into the US market in 2006 under the condition of mandatory adherence to the TOUCH prescribing programme, which includes physicians, patients, pharmacists and infusion centres.

In the TOUCH programme, an enrolment form is completed by the patient and provided to the prescriber, the infusion site and the pharmacy; the medication guide is offered to the patient, the prescriber and the infusion nurse and a pre-infusion patient checklist is provided to the patient, the prescriber and the infusion nurse. Reauthorisation and discontinuation questionnaires are completed by the prescriber. All participants must certify that they have read and understand the risks of TYSABRI, the most serious of which is PML. In the US, distribution of the drug is centrally controlled and only registered infusions centres that have agreed to follow the requirements of TOUCH are authorised to administer TYSABRI. (Figure 14.)

REMS Stakeholder Project

To assess the effectiveness of TOUCH communications and to enhance understanding of the level of burden associated with participation, 700 participants were enrolled into the Stakeholder Project, of which 323 were patients using TYSABRI. Phase 1, a qualitative phase involving a small number of participants, was conducted to identify the questions about which quantitative data could be collected online in phase 2 and phase 3 was a qualitative focus on specific points. Qualitative data were collected through in-person and telephone interviews and focus groups and quantitative data were obtained through a web-based survey.

At the time of initial infusion, 66% of respondents

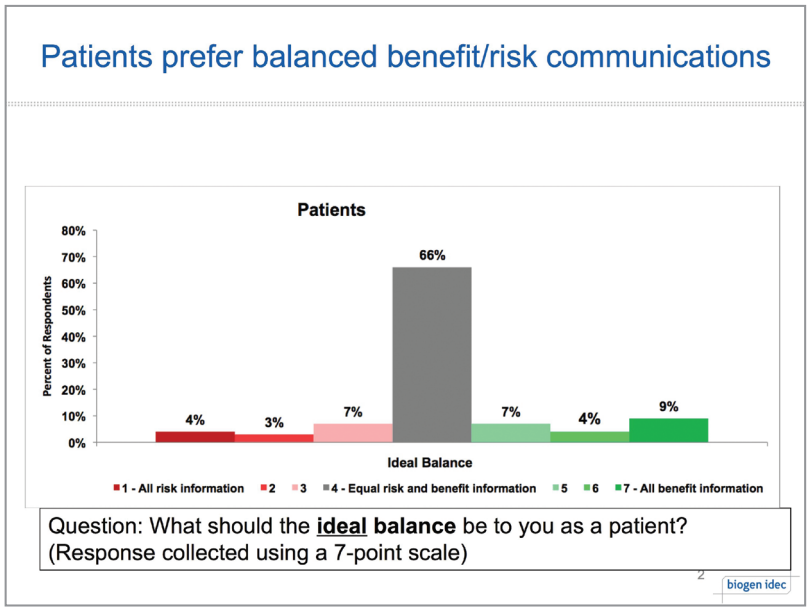


Figure 15. The majority of respondents in the TOUCH programme wanted to receive an equal mix of benefit and risk information.

thought that reading the medication guide was beneficial and valuable, although the perceived value of the guide decreased over time and respondents indicated that its utility could be improved through the highlighting of newly added information.

In general, the majority of respondents (66%) preferred to receive an equal balance of benefit and risk information (Figure 15). Specifically, 93% indicated that receiving information regarding risk factors for PML was important and 88% specified that information regarding both risk factors for serious infection and the prevalence of PML were key.

A preference for receiving communications directly from a healthcare provider was expressed by 37% of respondents, followed by email notification (30%). Significantly fewer participants expressed an interest in printed letters, the internet, telephone calls, patient conferences and webinars or podcasts.

Benefit-risk communication to patients: How well are we doing?

The patient is critical and should be taken into account in benefit-risk communications from both sponsors and regulators. Most patients are interested in receiving information about risks that is balanced by information on benefits. To this end, medication guides are a useful source that can be improved by highlighting new information and including information on the benefits of treatment. The front line of benefit-risk communication, however, is the healthcare provider, who must be educated and supported if benefit-risk communication to patients is to be successful.

The communication of benefits and harms to patients: How well are we doing and what needs to be improved? An agency viewpoint

Barbara Sabourin

Director General, Therapeutic Products Directorate, Health Canada

. . . two-way interaction would provide guidance for risk communications, leading to better health and safety outcomes and raise awareness and understanding of regulatory process.

Background supporting Canada's plain language labelling initiative

Communicating benefits and harms to patients is a responsibility for regulators, industry, healthcare professionals and patients that extends throughout a product's life cycle. While progress has been made in this area, there will always be room for improvement. Medication incidents are the most common single preventable cause of patient injury[1] and can be a symptom of this poor communication. Although a patient's most tangible source of information about a drug is its label, researchers have found that 46% of patients across all literacy levels misunderstand one or more dosage instructions and 54% misunderstand one or more auxiliary warnings that accompany those medications.[2] Over-crowded labels, unclear instructions or warnings and confusing names and packages are factors that have contributed to medication incidents, including serious patient harm or even death.

Resistance to change in current communication

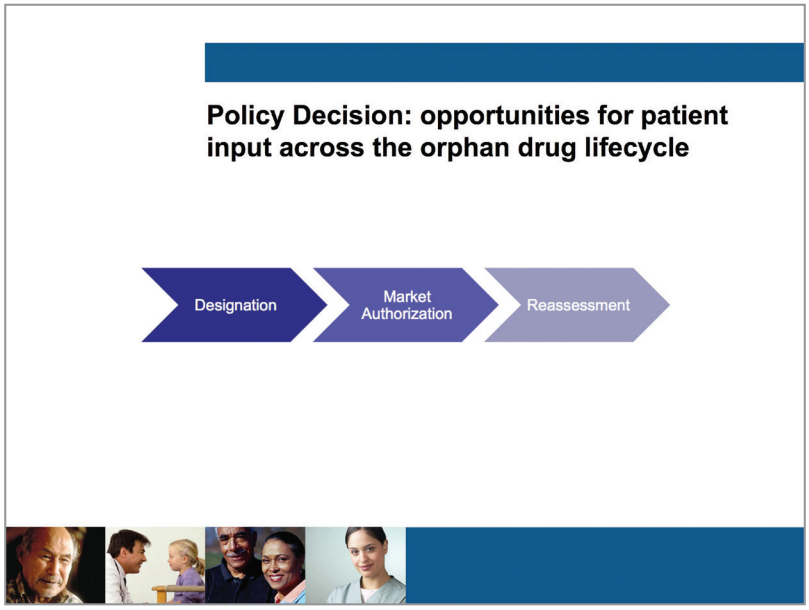
practices derives from concern that changes might result in the omission of important points, together with uncertainty that a change will be better for patients, caregivers and healthcare professionals. It is necessary to describe more carefully the problems with the current system and the vision for the future before significant approach changes are instituted.

Current initiatives

Information currently available from regulatory agencies after authorisation is variable. The US FDA provides lists of approved products with label information on its website drugs@fda. The last section of each product monograph on that site contains information for patients that is written in an approximation of plain language. In the EU, the rationale for the approvals of medicines in provided in the European Public Assessment Reports (EPARs). These, however, are written in technical language and because privacy laws vary among EU jurisdictions, some documents are redacted for confidentiality.

During the continued life cycle of the product, adverse events reports are captured and assessed, medical literature and reports from regulatory agencies are monitored and risk mitigation programmes are completed. Much of this activity takes place within agencies and sponsors and is not routinely made public. Furthermore, although these undertakings can result in changes to benefit-risk information on labels, communicating these changes is often left to sponsor.

Figure16. Patient input for orphan drugs will be solicited at three points of Health Canada decision making.



Health Canada initiatives

Health Canada has implemented, developed and planned several initiatives to improve the communication of benefit-risk to patients. The Plain Language Initiative does not merely reduce complex information to be comprehensible to a lay audience but provides a sensible organisational and presentational structure that is easy for the target audience to read and understand. This involves the use of appropriate language, layout and design techniques; short, simple sentences; the active voice; common words and simple expressions; white space and a question-and-answer format.

Lead by the Marketed Health Products Directorate, Health Canada, with the support of the Institute for Safe Medication Practices Canada and an Expert Panel, has developed a draft version of Best practices guide for the design of safe health product labels and packages, for internal and external review. The guide was designed to increase the clarity and readability of information presented on inner and outer labels and packages. Medication incidents with manufacturer labels and packages identified as a contributing factor were analysed, a review of literature and references covering regulators and patient safety organisations and a survey of expert advisory panel members and manufacturers was conducted to identify potential guide topics and create a proposal for information to be given most prominence on the main drug panel. Revised Look Alike/ Sound Alike Guidance provides industry with more detailed information on the assessment process and the submission requirements to demonstrate that a proposed name for a new medicine is not likely to be confused with another name authorised for use in Canada.

Consumer Medication Information enhancements include revised guidance for industry on the format and content of consumer information in part III of the product monograph and including part III on the Drug Product database as well as making other database improvements. Additionally, Health Canada will engage stakeholders to discuss options for providing Health Canada-approved patient information with dispensed products. Health Canada is also developing revised guidance for the format and content of Health Professional Information in the product monograph and is considering how to make health professional information easier to read and critical safety information easier to find in the product

monograph.

Patient input

Although agency-patient communication should flow in both directions, current practice at Health Canada consists of limited two-way dialogue. There are patient representatives on some advisory committees and patient reporting of adverse drug reactions is now encouraged. It is recognised, however, that patient input across the product lifecycle would identify real-life experience concerning the severity of disease, the unmet medical need and quality of life and views on benefits, harms and uncertainties. Hopefully, this two-way interaction would provide guidance for risk communications, leading to better health and safety outcomes and raise awareness and understanding of regulatory process.

Therefore the paradigm for patient communication is currently being changed on a trial basis through the use of the orphan drug regulatory framework. In this pilot, it is envisioned that there will be opportunities for patient input at these three phases of regulatory decision making for orphan drugs (Figure 16). At the designation and market authorisation phases, patient input will be sought through web-based surveys. At the market reassessment stage, input will be more focussed and targeted to patients who have been affected by the drug under review. When patient input is sought, a summary will be provided to the sponsor and when a decision is made, a summary of the input will be posted, together with an explanation of how it was used in decision making.

The pilot for the trial will simulate patient input at the market authorisation stage for one pharmaceutical and one biologic product from two different sponsors. Two sponsors/ drugs (one pharmaceutical and one biologic). patients, caregivers, healthcare professionals and patient groups will be recruited through the Canadian Organization for Rare Disorders (CORD) and other disease-specific patient groups, as appropriate and surveys will be posted on Health Canada's consultation website with access limited to pilot participants. It is hoped that the pilot will systematically gather patients' perspectives on unmet medical need, anticipated benefits and risk tolerance; will determine methods and test internal Health Canada processes for incorporating patient input into real-time submission reviews and will identify areas where patient education and/or reviewer training are required.

Proposed position statement

Ms Sabourin concluded her presentation by reiterating that the communication of benefits and harms to patients is a multi-stakeholder responsibility that continues throughout the lifecycle of a product with regulatory agencies, industry, health professionals and patients each with roles to play. While progress has been made in communicating benefits and harms, there will always be room for improvement. All parties should continue to assess their current systems and initiatives to provide information that is relevant, timely and useful to patients and caregivers.

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The communication of benefits and harms to patients:

How well are we doing and what needs to be improved? A patient viewpoint

Prof Marcus Longley

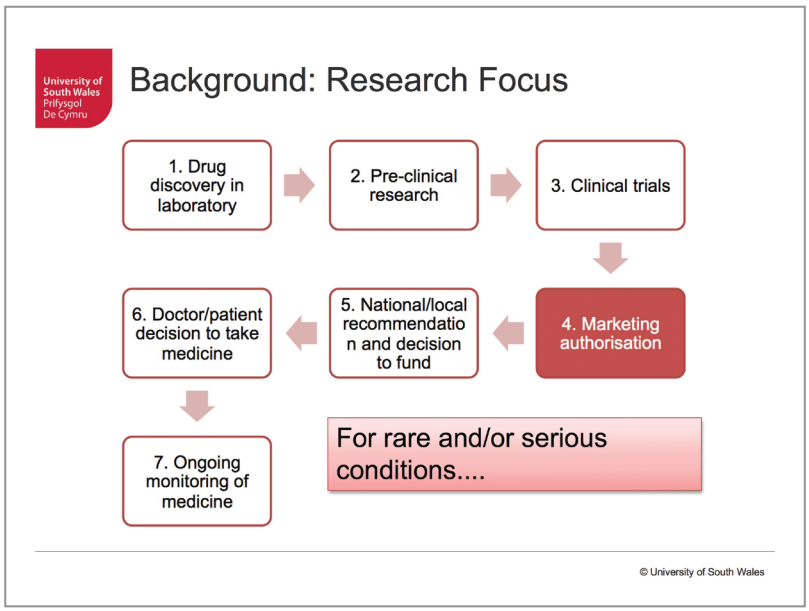
Director, Welsh Institute for Health and Social Care, University of South Wales, UK

. . . two-way interaction would provide guidance for risk communications, leading to better health and safety outcomes and raise awareness and understanding of regulatory process.

Research aims, focus and methods

The Welsh Institute for Health and Social Care in collaboration with the Genetic Alliance recently conducted research into patient involvement in benefit-risk decision making in a two-phase project. In phase 1, a risks and benefits citizens jury was convened in 2011 to examine how patients and families affected by rare and serious conditions perceive the risks and benefits of new medicines. In 2013, the European perspective on this topic was examined in phase 2 through the conduct of workshops in the Netherlands and Ireland and a survey in eight languages across Europe. In addition to validating the original project findings in other countries the project entailed work with patient groups and decision-making bodies across Europe in using the recommendations to influence how decisions about new medicines are made. (Figure 17.)

Figure 17.A two-phase programme examined rare disease initiatives in the UK and Europe.



What is a citizens' jury?

A citizens' jury is based on the premise that average people, given enough time, support and resources, are eminently capable of arriving at decisions about complex policy matters. Key elements of a classic citizens' jury include 12-16 jurors, questions, witnesses, a moderator, issuance of a report, a steering group and transparency. The jury is held over 3-4 days with paid participants who hear testimony from expert witnesses who are scrutinised through direct questioning. The independence of such a jury has been expressed as "disinterested common sense."

The actual 2011 citizens' jury in this research programme met for 5 days, consisted of 12 people (10 patients with a serious and rare condition and 2 parents of children with similar conditions) and heard 16 witnesses. The jury addressed three questions: (1) How do patients with rare and/or serious conditions perceive the risks and benefits of new medicines? (2) To what extent should regulators be more permissive in their marketing authorisation decisions? (3) How should patients be involved in the assessment of risks and benefits and regulatory decision making?

Key findings: citizens' jury, European workshops and European survey

Findings were combined from both phases of the project. Jurors, participants in the workshops and respondents to the European survey made four key recommendations:

1. Regulators should include psychosocial factors in their decision making (Figure 18).

   Scoring highly in both the survey and face-to-face deliberations were autonomy/control, fatigue, employment status and anxiety.

2. Jurors and workshop participants agreed that regulators should be more permissive in their assessment of those treatments for people with rare and/or serious conditions.

   This is reflected in the fact that more than 80% of jurors reported being willing to take greater risks than the system currently

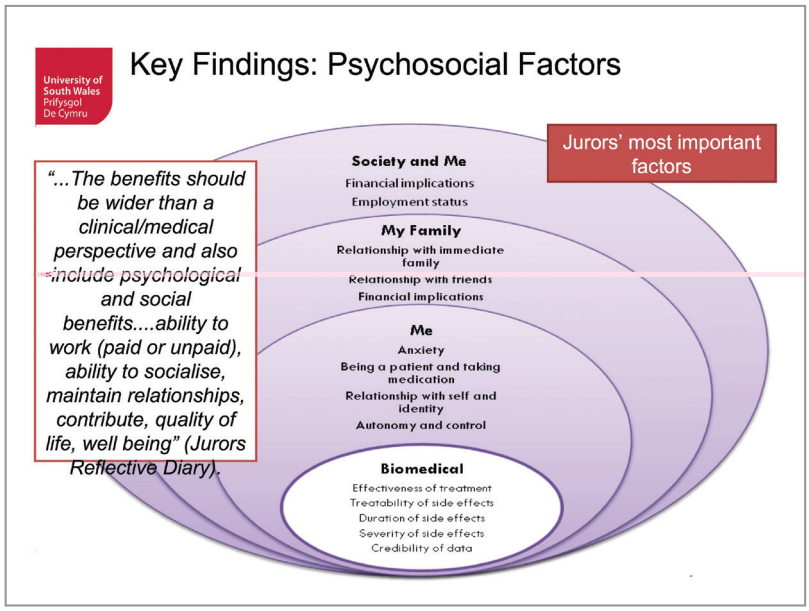


Figure 18.The citizen's jury recommended that regulators consider psychosocial factors in their decision making.

allows. Survey respondents felt that patients with serious conditions should be allowed access to medicines if they choose where it is uncertain how the medicine will work, where the medicine has been tested on fewer people than normal, or only to an earlier clinical phase than a standard product evaluation.

3. Patients should be more involved in all stages of the process, from setting the research agenda to post-marketing authorisation decisions.

   Participants considered these choices: A) allowing patients to decide, B) joint decision making (patients having equal votes with regulators and others), C) active involvement of patients in discussions with regulators but not having a vote and D) consultation before deciding (views of patients collected but the decision made by regulators and others). Participants favoured B) joint decision making.

4. Patients should be better supported to make their own decisions.

Key reflections

This research programme resulted in several key reflections. Participants agreed that regulators and pharmaceutical companies should work more closely to encourage the measurement and assessment of a broader framework of benefits. It was further understood that regulatory decisions should be more transparent and decision processes should be clearly articulated to reduce misunderstandings and to improve patients' confidence in the system and that further work should be undertaken to explore differences in decision making between regulators and patients. Additionally, there was consensus that changes should be made to improve the way in which patients are involved in regulatory processes and that the process should be more flexible for rare and serious conditions, involving patients and clinicians in an additional decision-making step if it looks as though a new medicine is going to be denied. Finally, it was agreed that better evidence on psychosocial factors can help inform the decision-making processes at the health technology assessment and prescribing level.

Future perspectives — looking forward to 2020: What will be the role of the patient?

Moira Daniels

Vice President, Head Global Patient Safety Services, PAREXEL International, UK

The patient's role today

To minimise the risks and maximise the benefits of medicine use, the FDA recommends that patients follow the directions printed on the label, read the label every time they fill a prescription and use it, take the recommended dose exactly as prescribed, finish all the medicine as directed and pay attention to how they feel and notify their healthcare team of any problems. Despite these recommendations, however, research indicates that 30% of patients decide not to take their prescribed medication at all, often on the basis of messages on social media.

Because improving the health of patients is a priority for industry, the European Federation for Pharmaceutical Industries and Associations (EFPIA) now publishes health information by disease on its website and there is active pharmaceutical company participation in the activities of the Innovative Medicines Initiative

(IMI). However, the European Commission-funded Ascertaining Barriers to Compliance (ABC) project team estimated that as many as 50% of patients fail to take their medication correctly.[1] This failure often results from limited disease knowledge, skewed perception of the value of the medicine, forgetfulness, or avoidance of side effects with resulting poor health outcomes and economic and personal waste.

Patient perspective

Perspective is key in assessing the benefit-risk balance of medicines. Whereas regulators evaluate benefits and risks for the population and healthcare providers evaluate them for individual patients, the patient evaluates them in terms of personal values (Figure 19). The physician-patient relationship is critical to good benefit-risk decision making and informed patients improve the dialogue between these two stakeholders. An informed patient, however, requires access to reliable information.

Understanding the disease condition from the patient point of view is based on the answers to key questions: What are the clinical manifestations of the disease that have the greatest impact? Are there other aspects of the disease that have a significant impact on daily life such as impaired mobility or sleep problems? How do the clinical manifestations change with disease progression? How do the other aspects of the disease change with disease progression?

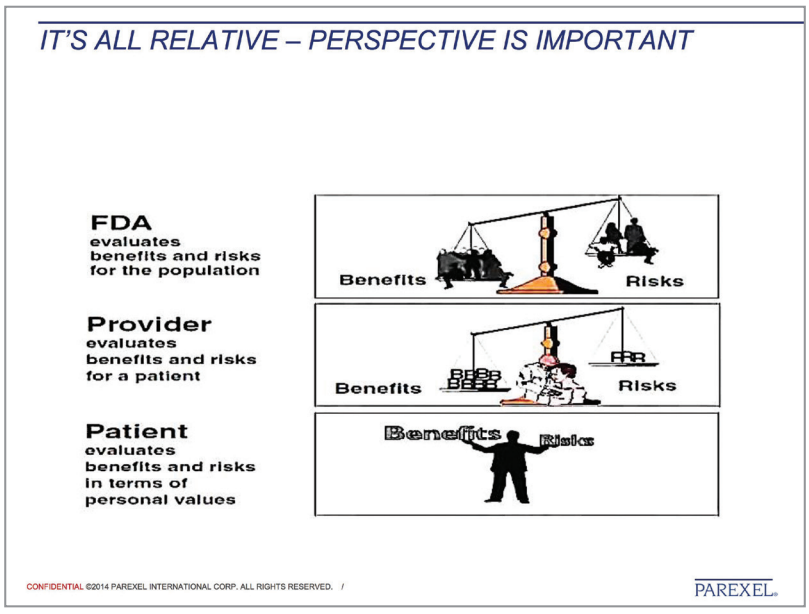


Figure 19.Benefit-risk decisions depend on the perspective of the decision maker.

Industry supports the creation of a "health citizen" responsible for making their own healthcare decisions.

Industry can benefit from patient input in determining disease areas for research as they look to develop treatments for conditions that are chronic and symptomatic and that affect functioning and activities of daily living. Also of interest are areas for which important aspects of the disease are not formally captured in clinical trials; those for which there are currently no therapies or very few therapies, or for which the available therapies do not directly affect how a patient feels, functions, or survives; areas that reflect a range of severity; areas that have a severe impact on identifiable sub-populations such as children or the elderly and areas that represent a broad range of the affected population.

Industry's assessment of treatment options, which also comprises patient perspectives, includes determining effectiveness in treatment of the clinical manifestations of the disease, mitigation of other aspects of the disease, alteration of disease progression and assessment of how effectiveness varies by patient sub-population.

Regulatory efforts to involve patients

The FDA has been aggressively seeking patient perspectives through a series of workshops scheduled to be held over the next few years. Disease-specific seminars held or scheduled thus far have included myalgic encephalomyelitis/ chronic fatigue, HIV, lung cancer, narcolepsy, sickle cell disease, fibromyalgia and pulmonary arterial hypertension. Whilst these meetings represent an excellent opportunity to acquire patient input into the development of treatment guidelines, the challenges may be how to implement these findings and how best to communicate this information worldwide to avoid further global divergence in disease management.

EMA is also working to increase patient involvement with increases evident in core regulatory activity areas: Scientific advisory group/ad hoc expert meeting, safety communications, Committee for Medicinal Products for Human Use (CHMP) consultations, scientific advice meetings and workshops (Figure 20). In their advisory role to regulators, patients ideally seek answers to specific questions such as

- What are the claimed benefits?
- How durable is the benefit?
- What are the risks?
- Are the patients in these studies representative of the typical patient?
- Do the data prove what the company claims it does or are they just interesting data that indicate the need for further research?

Industry patient engagement

A number of companies in the European region are hosting patient seminars in disease-specific areas. These companies believe that patients who have been involved in clinical programmes or who have used specific medicines may provide useful insights, contribute to discussions and connect clinical outcomes with research programmes. This kind of engagement demystifies living with a disease burden for both carers and patients.

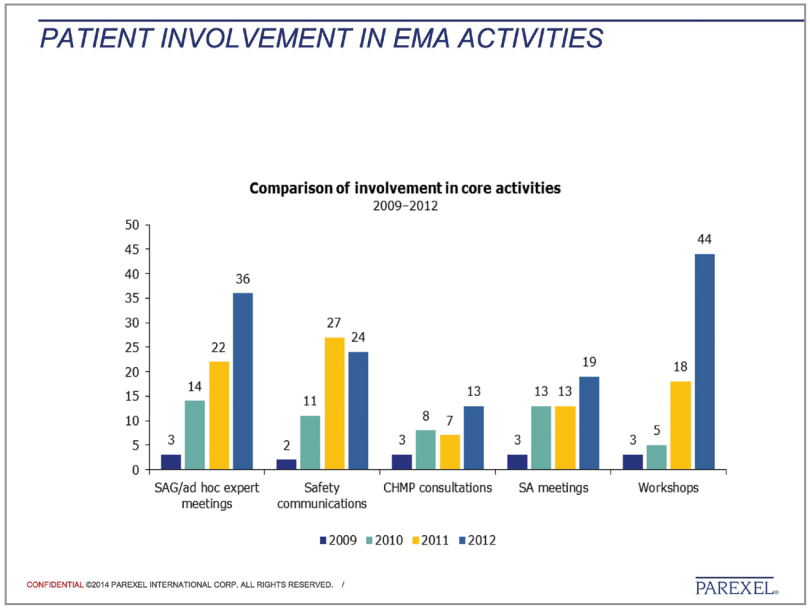
Despite these efforts, however, it must be recognised that any treatment that requires patient decision making requires patient education and information comprehension. Furthermore, any risk management plan that requires patient cooperation requires both patient cooperation with and patient comprehension of technical issues (e.g., testing for liver function, haematology and pregnancy and contraception use).

The way forward

Patients should be involved in the medicine development continuum, from the targeting of research areas through the development of medicines to the marketing and post-authorisation assessment of a product. Currently, patient involvement is occurring much earlier in the medicine development process and has revealed insights and helped to shape clinical research activities. Patient insight activities are being conducted within project teams in research and development and patient views have shaped patient-reported outcome tools and influenced the type and frequency of clinical activities such as invasive test procedures. Patient involvement has been especially important in geriatric and paediatric clinical research.

Industry supports the creation of a "health citizen", responsible for making their own healthcare decisions. To that end, it is providing structures and resources that empower the people of the European Region to make use of their own assets, be active participants in shaping health policy, respond to health challenges by improving health literacy, ensure that their voices are heard in patient-centred health systems and participate in community and family life.

Figure 20. Patient involvement has increased in EMA activities.



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Future perspectives – looking forward to 2020: What will be the role of the patient?

A regulatory viewpoint

Dr Pierre Démolis

Vice Chairman, CHMP, ANSM, France

. . . if regulators build patient confidence in regulators and the regulatory process, patients will trust in regulatory decisions and in the ability of regulators to include their perspectives in their decision making.

The CHMP opinion process and patient input

In the development of a European Medicines Agency (EMA) opinion on a new medication, the Committee for Medicinal Products for Human Use (CHMP) considers patients' perspectives before writing the opinion. Currently, CHMP is working to develop a table format for presenting information on a new drug in a way that patients can readily understand. This process as it exists today provides a basis for predicting what the situation will be in 2020.

Before forming an opinion, the CHMP attempts to understand patients' views on benefits and risks and sometimes, on benefit-risk assessments, using various tools including patient-reported outcomes (PROs) and quality of life (QoL) instruments. The CHMP is currently discussing the use of such tools and their role in assessing new medicines, the values of which may vary, depending on the indication. For example, the Oncology Working Party (OWP) recently examined health-related questionnaires in cancer treatment and concluded that the use of such tools may be challenging because of their subjective nature. Furthermore, very few examples of cancer treatment have been found to have favourably influenced QoL, since treatment benefits often involves a trade-off in terms of QoL. Patient assessment tools could be useful in the framework of a marketing application. However, as this would change the scope of the application, an advance agreement between regulators and sponsors as to the particular use of the tools would be necessary.

Patients are often the best assessors of the benefits of treatment. The value of patient views (and of some physicians) is less certain, however, in an effective assessment of the risks of a treatment, as they may have no experience regarding this risk and therefore may not recognise the harm as a true event. In addition, as patients typically advocate for earlier regulatory decisions, positive decisions and an extended acceptability of risks it should be recognised that these factors can effectively change the balance in the decision-making process.

Patients' participation with EMA today

Patient involvement is very important in the regulatory process and is currently evolving. Patients can be involved as permanent attendees in committees including the Committee for Orphan Medicinal Products (COMP), the Pharmacovigilance Risk Assessment Committee (PRAC), the CHMP and the Committee for Advanced Therapies (CAT). Patients have voting rights in the PRAC, whereas patients attend CHMP meetings but have no vote. In the CAT, patients are considered global representatives, rather than representatives for specific diseases.

Patients may also be involved in on-demand EMA functions for specific diseases. These include work in scientific advisory groups (SAGs), the CHMP, the Scientific Advice Working Party (SAWP) and possibly the CAT, PRAC and COMP. In these on-demand functions, patients can be informative regarding the disease and meaningfully contribute to the discussions; for example, patients may offer oral presentations in CHMP meetings, especially in cases in which the CHMP is moving toward a negative decision. However, in SAGs, patients must be prepared and fully participate in deliberations to achieve the full value of patient involvement. Issues that must be determined in patient involvement include whether they should be in attendance during company presentations or in a separate room where an interpreter could translate questions and answers into non-technical language.

The role of patients in the future

The role of patients will evolve between now and 2020 and it is likely that patients will have an established role in the CHMP by the end of this decade. This evolution will encompass individual patients with specific diseases and disease-specific patient associations such as those for breast cancer and multiple sclerosis. Patient involvement in pharmacovigilance will

also be very important and will include access to agency website portals for specific diseases and symptoms. The evolution of the role of patients should be based on the principle that if regulators build patient confidence in the regulatory process, patients will trust in regulatory decisions and in the ability of regulators to include their perspectives in their decision making.

Future perspectives — looking forward to 2020: What will be the role of the patient?

The patients' viewpoint

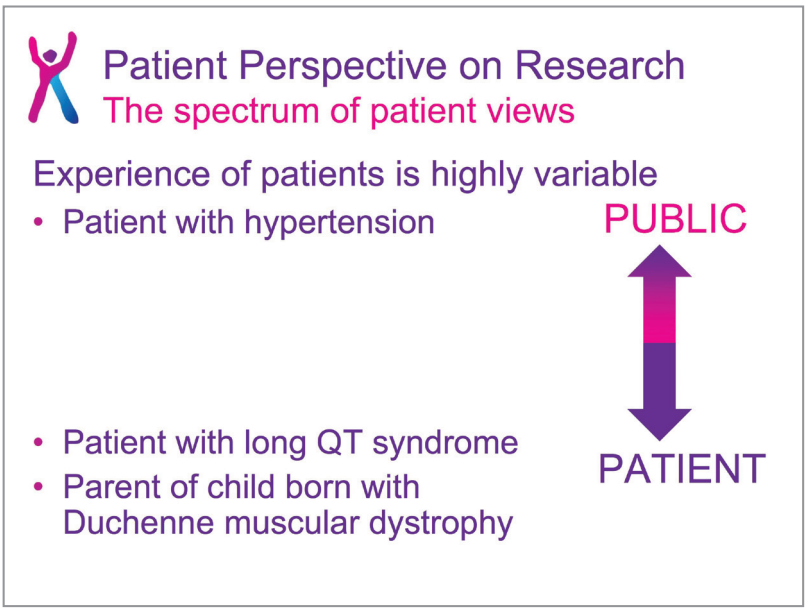
Christopher Friend

Trustee, Genetic Alliance, UK & Medical Advisory Service

Genetic Alliance UK

The Genetic Alliance UK is a national charity of 160 patient organisations supporting people who are affected by genetic issues that range from rare, single-gene disorders to common, multi-factorial conditions. The alliance is involved in both policy and projects on behalf of its members, the largest of which is the British Heart Association.

Figure 21. Patient experience with research is highly variable.



A current key initiative is Rare Disease UK (RDUK), which involved industry, clinicians and patients. Part of a larger initiative by other European governments, RDUK is an effort by the four home countries of the UK to develop a strategy for addressing rare diseases.

Changing attitudes 1960s – 2020

Societal attitudes about issues such as interethnic and gay marriage have been changing since the 1960s and are likely to continue to change through 2020. Societal changes have also been reflected in changing patient attitudes and recent decades have seen the rise of patient support groups and patient advocacy. Unfortunately, some of the advances in patient advocacy have been criticised as tokenism, with patients being included in processes in ways that limit their influence,

It is envisioned, however, that by 2020, patients will be routinely and formally involved in a variety of functions:

- Pre- and post-marketing medicines research
- Membership in strategic national and regional alliances, plus disease-specific organisations
- Policy and research projects
- Concordance (an educated dialog between physicians and patients)
- Self-care plans
- Regulatory involvement
- Formal consultation

The role of patients in 2020 will be influenced by new technologies, activities promoting the patient viewpoint, legislation and other government actions and the Internet. In the UK government sphere, significant recent developments include the development by the National Health Service (NHS) of the Expert Patient concept in 2002, the Social Care Act of

2012 and the Rare Disease Strategy of 2014. Sources of healthcare information on the Internet will continue to be a mixture of good and bad material. However, patient support groups are becoming increasingly proficient at sorting the good from the bad.

Barriers

Barriers to patient involvement persist. Patients in different parts of the UK experience inequality in access to medicines and healthcare services. Some physicians continue to resist patient involvement in decision making and the typical general practitioner is severely restricted in the amount of time that can be devoted to an individual patient, making it difficult to conduct a meaningful conversation about risks and benefits of treatment. In addition, the assessment of risks and benefits requires a clearer definition of whose risks and benefits are being discussed. Similarly, assessment of outcomes requires an understanding that the outcome in a particular case may differ significantly in the viewpoints of clinicians, pharmaceutical companies and patients.

The spectrum of patient views

When considering the patient perspective, it should be recognised that the experience of patients is highly variable (Figure 21).

This range is illustrated by the examples of patients with hypertension at one end of the spectrum and patients with long-QT syndrome and parents of children born with Duchenne muscular dystrophy at the other. For patients with hypertension, beta-blockers are less expensive than ACE inhibitors but many patients taking beta-blockers are functionally impaired. Although ACE inhibitors overcome this problem to a degree, they are more expensive. The critical question for the patient in this instance is a trade-off between expense and quality of life. Despite the availability of treatment options for many such illnesses, the majority of the public in the UK believe that research continues to be important, with 97% of one survey's respondents indicating that it is important for the NHS to support research into new treatments. Furthermore, in another poll, 82% of the public think it is important for the NHS to offer opportunities to take part in clinical studies and fewer than 7% indicated that they would never take part in research.

The way forward

The patient is important at every stage of medicine development, including post-marketing research and the role of patients should be equal with other stakeholders with their perspective on benefit-risk assessment actively elicited (Figure 22). A recent collaboration between the Genetic Alliance UK and the University of South Wales in the assessment of medicines for serious conditions provides an example of the value of this active elicitation Regulators should include psychosocial factors in their decision making and consider being more permissive in their evaluation of treatments for people with rare or serious conditions.

Mr Friend concluded his presentation by remarking that during a time of personalised/ stratified medicine and economic pressures, formal collaboration with academia, regulators and industry will be the hallmark of patient involvement in medicine development in 2020, including involvement in pharmacovigilance and the provision of formalised HTA input. This involvement will hopefully be accompanies by a greater understanding by all parties of serious, rare and long-term conditions.

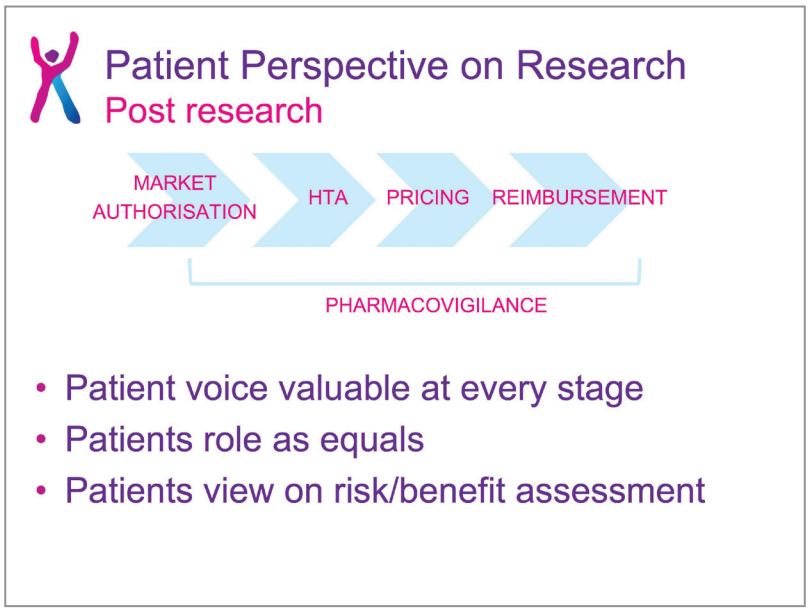


Figure 22. Patient viewpoints are important at all stages of research including post-approval.

Appendix: Workshop Attendees

Academic institutsions and patient organisations		
Andrea Beyer	Senior Researcher	University of Groningen, The Netherlands
Kimberley Hockley	Research Assistant, Imperial Clinical Trials Unit	Imperial College London
Prof Marcus Longley	Director, Welsh Institute for Health and Social Care	University of South Wales, UK
Dr Lawrence Phillips	Emeritus Professor of Decision Sciences	London School of Economics & Political Science, UK
Nancy Pire-Smerkanich	Educational Liaison / Doctoral Candidate	International Center for Regulatory Science, School of Pharmacy, University of South California, USA
Prof Sam Salek	Director, Centre for Socioeconomic Research	Cardiff University, UK
Dr Mary Baker	Immediate Past President	European Brain Council
Christopher Friend	Trustee	Genetic Alliance UK
Jean Mossman	Policy Lead	European Brain Council
Margaret Walker	Chief Executive Officer	ELPA European Liver Patients Association, Belgium
Health technology assessment and regulatory agencies		
Lizzie Amis	Senior Public Involvement Adviser	National Institute for Health and Care Excellence, UK
Prof Sir Alasdair Breckenridge	Former Chairman	Medicines and Healthcare Products Regulatory Agency, UK
Dr Pierre Démolis	Vice Chair, CHMP	ANSM, France
Dr Ea Dige	Senior Medical Office	Danish Health and Medicines Authority
Dr Petra Dörr	Head of Communication and Networking	Swissmedic
James Leong	Senior Regulatory Specialist	Health Sciences Authority, Singapore
Associate Prof John Lim	Chief Executive Officer	Health Sciences Authority, Singapore
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