THE PATIENT'S ROLE IN THE BENEFIT-RISK ASSESSMENT FOR THE SUBMISSION AND REVIEW OF NEW MEDICINES

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WORKSHOP REPORT

CIRS Centre for Innovation in Regulatory Science

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THE PATIENT'S ROLE IN THE BENEFIT-RISK ASSESSMENT FOR THE SUBMISSION AND REVIEW OF NEW MEDICINES

Section 1: Executive Summary

Background to the Workshop

As the framework for the benefit-risk evaluation of new medicines is developed, it has become apparent that the role that patients should play in informing regulatory and reimbursement decisions is increasing in importance. Indeed, at the annual Centre for Innovation in Regulatory Science (CIRS) Benefit-Risk Workshop held in June 2011, all of the Syndicate discussion groups made a recommendation to include patients' perspectives early in the development of a new medicine as well as considering these views as part of the weighting process when evaluating conditions involving subjective benefits and harms. It is believed by agencies and companies that patient input could be invaluable in informing the thinking of decision makers such as regulators and researchers.

Advancing the patient's role is complex, however, both in terms of eliciting the perspective of benefits and harms based on evidence generation from patients being studied during clinical development as well as in determining how these perspectives should be used in regulatory decision making.

Over the last five years, a number of organisations such as the European Medicines Agency (EMA), US Food and Drug Administration (FDA), the CIRS Four-Agency Consortium (the COBRA Initiative), individual companies and across companies such as the Benefit-Risk Action Team (BRAT) initiative have developed qualitative, semi-quantitative and quantitative benefit-risk methodologies, all of which have a number of common elements. Therefore, CIRS are now endeavouring to see how these different approaches can be brought together, which they have called Unified Methodologies for Benefit-Risk Assessment (UMBRA). Several of these groups are now undertaking pilot projects to apply the models/methodologies to real-world cases. The question that is being asked is how and when patients should be involved in informing the benefit-risk decision.

This Workshop explored these issues by gaining a perspective from various stakeholders in the development and review of new medicines, with a particular emphasis on the opportunities and barriers to including patients' perspectives in the submission and review of new medicines. The findings of this current Workshop will inform the discussion at the CIRS annual Benefit-Risk Workshop in June 2012 (*Building the Benefit-Risk Toolbox*), where the questions being posed are when and how should patients be involved and what would facilitate their involvement with regard to the benefit-risk assessment of new medicines?

Workshop Objectives

- **Identify the issues and opportunities** for patients, companies and regulators in including patients' views in the benefit-risk assessment of medicines
- **Clarify how as well as when** patients' views should be incorporated into the benefit-risk assessment of medicines
- **Develop a proposal for discussion at the CIRS June Workshop** to identify the methodologies to achieve a consensus on a scientifically acceptable approach for including patients' perspectives in benefit-risk decisions

Key points from presentations

Throughout history, great medical thinkers from Hippocrates to Avicenna to Miomedes have advocated for strong patient participation in medical decision making. More recently Professor Hans-Georg Eichler and colleagues wrote that ". . . the time has come to bring patients fully into the decision process as equal partners."[1] Saying that combining patients' value judgements with the technical expertise of regulatory scientists is expected to enhance the legitimacy of and public trust in the licensing process, CIRS Executive Director, Lawrence Liberti welcomed participants to this Workshop on the role of patients in the benefit-risk assessment of medicine.

SESSION: TRANSPARENCY IN EVALUATING NEW MEDICINES FOR COVERAGE DECISIONS SHOULD BE A COMMON GOAL

Day one Chair, Professor Sir Alasdair Breckenridge, *Chairman, Medicines and Healthcare products Regulatory Agency, UK*, began the session by stating that although there has been much progress in the work on the benefit-risk assessment of medicines in the past several

decades, relatively little attention has been paid to the patient, who should be considered as the primary stakeholder. The fact that the views of patients and especially their caregivers on the risks and benefits of medicine may differ quite widely from those of the sponsor, regulator and healthcare technology assessor is just beginning to be appreciated and will hopefully be advanced by this Workshop.

SESSION: DEVELOPING THE CASE FOR THE INCLUSION OF PATIENTS' PERSPECTIVES IN A FRAMEWORK FOR BENEFIT-RISK ASSESSMENT

In order to fully participate in healthcare decision making, patients and their advocates must establish credibility, collect evidence and contribute to discussions. **Dr Mary Baker**, *President, European Brain Council,* discussed one method to improve the level of patient involvement – the successful ongoing collaboration between the European Federation of Neurological Associations and the London School of Economics to provide educational courses for patient advocates, including patient-centred research, patient-reported outcomes and patient-centred training to understand benefit-risk and improve health literacy.

The European Patients' Academy on Therapeutic Innovation (EUPATI) is also providing an educational programme to prepare patients for different levels of participation in HTA decision making. **Prof Bruno Flamion**, *Professor of Pharmacology, University of Namur, Belgium* explained that through these and other efforts HTA bodies and payers' organisations are moving cautiously towards increased patient involvement. He cautioned that although HTA and payer agencies should engage with patients at several levels to create a fair deliberative process, robust evidence should be gathered through social science research for the best methods to elicit patients' perspectives.

Moira Daniels, *Vice President, Regulatory, Policy, Intelligence and Labelling, AstraZeneca, UK* detailed the inroads in patient involvement in the development of medicines already made by the pharmaceutical industry including participation in patient education efforts such as those cited by Dr Baker and Professor Flamion, organising formal patient input surrounding specific disease targets and collecting patient-centric views for development programmes. Much work remains, however, as new tools and methodologies must be developed to more effectively communicate non-promotional information about the safest and most effective use of medicines to achieve the highest benefit, while finding a way to effectively communicate to patients that no medicine comes without risk of harm.

Because regulators of new medicines are service providers who should be responsive to the preferences and priorities of patients as their primary "customer," **Professor Hans-Georg Eichler**, *Senior Medical Officer, European Medicines Agency* proposed a two-prong approach to fulfilment of this mandate: bringing patients and their preferences and values into the regulatory system. Patients can be brought into the regulation of medicine in Europe through public hearing and representation on committees, while one way to incorporate patient values into the regulatory system is through the systematic exploration of the input of patients enrolled in clinical trials.

The United States Food and Drug Administration has a history of support for programmes designed to help ensure that the patient voice is reflected in the regulatory decision-making process. **Dr Janice Soreth**, *Deputy Director, US Food and Drug Administration Europe Office* provided details of planned FDA initiatives to obtain the patient perspective on disease severity and the unmet medical need in specific disease areas, including commitments proposed as part of the Prescription Drug User Fee Act (PDUFA) V.

Developers of new medicines are challenged in determining which clinical trial outcomes are of clinical value to patients and clinicians and which effect sizes are clinically meaningful. James Cross, Regulatory Program Director, Genentech Inc., USA outlined the conjoint analysis recently undertaken by researchers at Genentech to determine the relative importance that individuals placed on a defined set of disease or treatment outcomes. In addition to gathering clear information regarding which endpoints and effect sizes would be clinically meaningful in a trial of the medication under development, the researchers were able to obtain subgroup data based on patient demographics that may be helpful when designing studies and analysing the resulting data.

Patient and carer involvement forms one of the core principles of the National Institute for Health and Clinical Excellence (NICE). **Victoria Thomas**, *Associate Director: Patient and Public Involvement Programme, National Institute for Health and Clinical Excellence, UK* explained that patients

and the general public participate throughout the development and implementation of NICE guidances at a variety of levels and through this participation, NICE is able to obtain data regarding patient preferences and learn about subgroups who might benefit more or less from a technology. Additionally, the information challenges professional or researcher views and elucidates areas needing further research.

Reference

1. Eichler HG, Abadie E, Baker M, Rasi G. Fifty years after thalidomide; what role for drug regulators? *Br J Clin Pharmacol.* 2012; Feb:1365-2125.

Recommendations from across the Syndicates

- CIRS should survey the heads of research and development for perspectives on and ideas for patient involvement in drug development
- CIRS should carry out a survey of regulatory authorities, pharmaceutical companies and health technology assessment agencies to identify when, where and how patient groups can and should be involved in the decision-making process
- Develop a guideline for the involvement of patients throughout the life cycle of medicines and consider a pilot for its implementation among selected companies
- Continue and build on the work of the Innovative Medicines Initiative (IMI) Pharmacoepidemiological Research on Outcomes of Therapeutics (PROTECT) with patient involvement
- Using the Scottish Medicines Consortium model of participation by patient representatives, include patient representatives in deliberations by the Committee for Medicinal products for Human Use (CHMP)
- Build on ongoing efforts in patient education and training regarding the regulatory and HTA/Payer procedures
- Inform patients about which treatment they received and the study outcomes at the end of each clinical trial
- Establish government funding for patient organisations
- Form an industry consortium in the precompetitive space to uncover patient priorities, engaging regulators through the use of patient-reported outcomes and utilities
- Publish white papers on cutting-edge methodologies in patient involvement such as data mining
- Develop learnings about patient input from other sectors such as over-the-counter medications or gather patient perspectives on drugs that failed during development
- Develop regulatory guidelines around patient engagement
- Engage legislative bodies to eliminate potential legal barriers to patient involvement in benefit-risk decisions
- Organise a Workshop including different stakeholders, for example, regulators, industry and patient groups to use a structured framework to develop an appropriate methodology for regulatory benefit-risk assessment that engages patients' perspectives and patient-reported or patient-relevant outcomes. Include an evaluation of various visualising tools and incorporate different milestones throughout the product lifecycle

Workshop Programme

DAY 1: 25 APRIL 2012	
Session 1: Developing the case for the inclusion of patients' perspectives in a framework for benefit-risk assessment	
Welcome	**Lawrence Liberti**, *Executive Director, Centre for Innovation in Regulatory Science*
Chairman's introduction	**Prof Sir Alasdair Breckenridge**, *Chairman, Medicines and Healthcare products Regulatory Agency, UK*
What are the opportunities and issues to including patients' perspectives on benefits and risks of new medicines for utilisation in the decision to submit and decision to approve/reject	
Patient viewpoint	**Dr Mary Baker**, *President, European Brain Council*
Payer viewpoint	**Prof Bruno Flamion**, *Professor of Pharmacology, University of Namur, Belgium*
Industry viewpoint	**Moira Daniels**, *Vice President, Regulatory, Policy, Intelligence and Labelling, AstraZeneca, UK*
What are the current Initiatives/models being used for new medicines and how and when are patients' perspectives being included in the decision making process?	
EMA approach	**Prof Hans-Georg Eichler**, *Senior Medical Officer, European Medicines Agency*
US FDA approach	**Dr Janice Soreth**, *Deputy Director, US Food and Drug Administration Europe Office*
Company case study	**Dr James Cross**, *Regulatory Program Director, Genentech Inc., USA*
NICE model for inclusion of patients	**Victoria Thomas**, *Associate Director: Patient and Public Involvement Programme, National Institute for Health and Clinical Excellence, UK*
Session 2: Syndicate Sessions	
Syndicate A: How should patients be involved in the benefit-risk decision and why?	
Chair	**Dr Mary Baker**, *President, European Brain Council*
Rapporteur	**Dr Nicola Course**, *VP Global Regulatory Affairs, Europe, GlaxoSmithKline*
Syndicate B: When should patients be involved and what are the possible methodologies for the decision to submit	
Chair	**Dr Diana Hughes**, *VP, Worldwide Safety Strategy Primary Care, Pfizer*
Rapporteur	**Dr Susan Welsh**, *VP, Global Pharmacovigilance & Epidemiology, Medical Safety Assessment Therapeutic Area Head - Oncology & Immunology, Bristol-Myers Squibb, USA*

Syndicate C: When should patients be involved and what are the possible methodologies for the decision to approve?	
Chairperson	**Prof Robert Peterson**, *Executive Director, Drug Safety and Effectiveness Network, Canadian Institutes of Health Research*
Rapporteur	**Dr Sinan B Sirac**, *Senior Medical Office, Danish Health and Medicines Authority, Denmark*

Day 2: 26 APRIL 2012	
Session 2: Syndicate sessions continue	
Session 3: Inclusion of patients in benefit-risk decision-making for submission and review: how and when?	
Chairman's introduction	**Prof Robert Peterson**, *Executive Director, Drug Safety and Effectiveness Network, Canadian Institutes of Health Research*
Feedback from Syndicate sessions	
Panel discussion This session is to have a reaction from different stakeholders to the ideas suggested by the syndicates as well as to facilitate discussion.	
Payer viewpoint	**Prof Angela Timoney**, *Chair, Scottish Medicines Consortium*
Views from patient groups	**Jean Mossman**, *Policy Lead, European Federation of Neurological Associations, UK*
Industry perspective	**Moira Daniels**, *Vice President, Regulatory, Policy, Intelligence and Labelling, AstraZeneca, UK*
Regulatory perspective	**Barbara Sabourin**, *Director General, Therapeutic Products Directorate, Health Canada*
Chairman's summary and next steps	

Section 2: Syndicate Discussions

Three Syndicate groups were asked to discuss three different aspects of involving patients in the assessment of the benefits and risks of medicines.

Background

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

Syndicate 1	
Chair	**Dr Mary Baker**, *President, European Brain Council*
Rapporteur	**Dr Nicola Course**, *Vice President, Global Regulatory Affairs, Europe, GlaxoSmithKline*
Syndicate 2	
Chair	**Dr Diana Hughes**, *Vice President, Worldwide Safety Strategy Primary Care, Pfizer Inc. USA*
Rapporteur	**Dr Susan Welsh**, *Vice President, Global Pharmacovigilance & Epidemiology, Medical Safety Assessment Therapeutic Area Head - Oncology & Immunology, Bristol-Myers Squibb, USA*
Syndicate 3	
Chair	**Prof Robert Peterson**, *Executive Director, Drug Safety and Effectiveness Network, Canadian Institutes of Health Research*
Rapporteur	**Dr Sinan B Sirac**, *Senior Medical Office, Danish Health and Medicines Authority, Denmark*

Syndicate 1: How should patients be involved in the benefit-risk decision and why?

This Syndicate group was asked to discuss why patients should provide their perspectives on the benefits and harms that should be considered by both companies and agencies as a new medicine is being developed and evaluated as well as to identify how patient involvement should take place.

Questions for consideration

- Why should patients be involved in the benefit-risk decisions for new medicines and what are the main issues that need to be resolved?
- At what stages in the development and approval of a new medicine should patients be involved in providing a perspective on benefits and risks/harms: prior to the initiation of development, during early development, late development, the regulatory review process and payer coverage decision?
- How and in what way should patients become involved in providing their perspective on benefits and risks of medicines, considering the different levels of involvement from advocacy within a disease area to individual patient involvement in clinical trials?
- What are the mechanisms that can

be established to enable more direct involvement of patients in the benefit-risk decision?

Critical issues

To members of this Syndicate, there was no question as to whether there should be patient involvement in the benefit-risk evaluations in the development and regulation of medicines. It was agreed that there have been many examples in which the quality of pharmaceutical development, regulation and health technology assessment has been improved through patient involvement, such as those cited by Ms Thomas (page 28) and economic research has established that an informed patient is cost effective for both industry and society. In fact, what the group did call into question is the legitimacy of decision making that does not involve its primary stakeholder and customer. Questions do have to be resolved, however, surrounding the methodology and timing of that involvement.

Although industry and agencies must be clear regarding the high value that they place on patient input, industry may be constrained in the extent of its outreach, because there is a potential for industry funding of patient groups to result in public criticism of real or perceived bias. A parallel case was posed regarding whether sponsorship of patient groups by regulators could influence their decision-making. There is also the question as to whether a single patient can provide a representative opinion and some concern that the needs of individual patients may unduly influence their decisions. Finally, patient input to decision making needs to be credible and the lack of technical knowledge of the average lay person represents a significant obstacle to that credibility.

Strategies

All stakeholders in the development of medicines must be part of the solution to these critical issues and all must be bold in their actions and willing to risk criticism. Important work is already ongoing in patient involvement, which should be continued and built upon. Patients – particularly those in clinical trials – must be involved in all aspects of the development of medicines. However, regulators should seek the input of patients in a more systematic and structured way and government funding for training and education for patient groups would provide the necessary credibility for patient input.

Recommendations

- CIRS should survey the heads of research and development for perspectives on and ideas for patient involvement in drug development
- Develop a guideline for the involvement of patients throughout the life cycle of medicines and consider a pilot for its implementation among selected companies
- Continue and build on the work of the Innovative Medicines Initiative (IMI) Pharmacoepidemiological Research on Outcomes of Therapeutics (PROTECT) with patient involvement
- Using the Scottish Medicines Consortium model of participation in decision making by three patient representatives, include patient representatives in deliberations by the Committee for Medicinal products for Human Use (CHMP)
- Build on ongoing efforts in patient education and training regarding the regulatory and HTA/Payer procedures
- Inform patients about which treatment they received and the study outcomes at the end of each clinical trial
- Establish methods for government funding for patient organisations

Syndicate 2: When should patients be involved and what are the possible methodologies for the decision to submit: An industry perspective

Using an industry perspective, this Syndicate group was asked to discuss the involvement that patients should have in the development of a new medicine with respect to its benefits and harms. They were also asked to identify the methodologies that companies use or could use to obtain the patient's input into the development of new medicines so that at the time of submission they are certain that the drug's benefit-risk profile is aligned with the needs of patients in the disease area.

Questions for consideration

- From a company's perspective, when should patients be involved in providing

input into the benefit-risk evaluation and what are perceived as the main issues in that involvement? Consider ways in which patient involvement could aid decision making at critical development milestones such as proof of concept, go/no go decisions and submissions.

- How do companies currently involve patients and patient groups at the various developmental stages, what value do companies get from these interactions and how might this change in the future?
- What methodologies are or could be of value in eliciting patients' perspectives and why?
- What are the critical issues that are faced in using different methodologies for decision making?
- From the companies' perspective what are the mechanisms to improve patient involvement in the benefit-risk decision and what needs to be done in the short and long term, to enable these mechanisms to occur?

Critical issues

Syndicate two agreed that patients can provide insights into the development of medicines that may have not been considered by research and development teams, including uncovering incentives for patients to participate in clinical trials. Patients should be involved throughout the life cycle of medicines (Figure 1), but it is particularly crucial to discover the basic unmet needs of these primary stakeholders as early as possible in development and the precompetitive time point represents the most significant gap in patient input.

In considering the methodology for patient involvement, the group emphasised the importance of identifying the most appropriate group of participants within the patient community, the identity of whom may change throughout the stages of product development. One method for this identification is a survey of patient organisations. For surveys and other points of patient-industry contact, non-commercial patient liaisons within pharmaceutical companies should be named, but the use of third-party groups and social media may be the ideal methods for patient-industry contact to avoid the perception of promotional activity.

Barriers to enhanced patient participation exist, however; for example, companies typically focus primarily on clinicians in the development of new pharmaceuticals or may feel that existing programmes for patient engagement at their company are sufficient. Furthermore, although the enhancement of patient input into benefit-risk assessments seems ideal, the reality of time and resource constraints require that a business case be developed for its promulgation.

Strategies

Using conjoint analyses before phase 1 may be the ideal strategy to obtain patient input, providing enough information exists regarding the relevant disease state. Although all stakeholders should be involved in providing input into these analyses, this Syndicate indicated that the appropriateness of obtaining input from payers at this stage is debatable.

Before phase 2, patients can provide input on the external validity and real-world relevance of trial protocols and the development of value propositions for research. The use of "professional" patients or those who understand regulatory and HTA processes may be of particular value here, but for other clinical trial patients, clear and careful communication of expected benefits and harms of a new medicine is essential to avoid an unwarranted perception of expected benefit.

During phase 3, patient-reported outcomes (PROS) should be more widely employed, but social scientists may be needed to help design and validate questionnaires and clinical investigators recruited to provide anonymous simple forms to trial participants to gather patient information in addition to PROS.

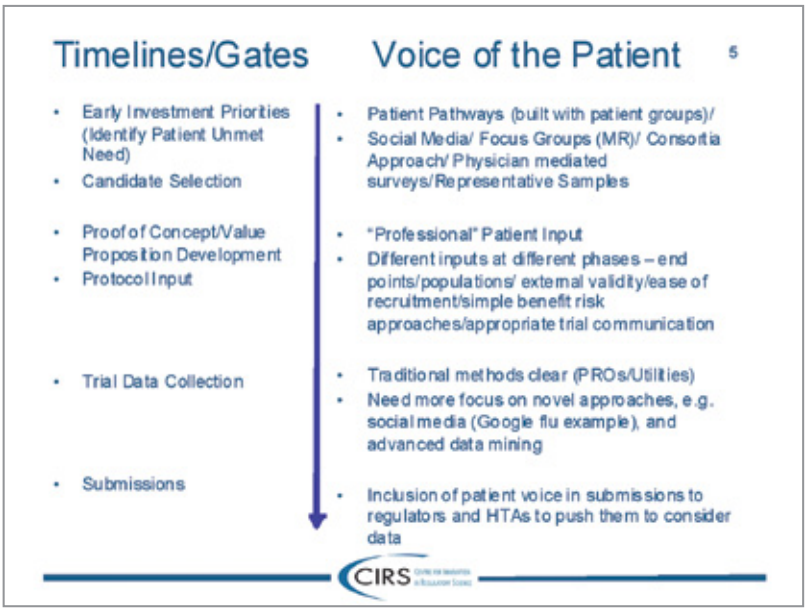


Figure 1. Potential points of patient engagement throughout the lifecycle of a medicine.

Finally, the group encouraged the open collection of information through market research and through novel approaches such as social media. "Google Flu" was cited as an example in which an Internet technology was used to identify influenza outbreaks through an assessment of the number of patient searches for information about flu-like symptoms two weeks in advance of alerts issued by the US Center for Disease Control.

Recommendations

- Form an industry consortium in the precompetitive space to uncover patient priorities, engaging regulators through the use of patient-reported outcomes and utilities
- Publish white papers on cutting-edge methodologies in patient involvement such as data mining
- Develop learnings about patient input from other sectors such as the over-the-counter medications or gather patient perspectives on drugs that failed
- Develop regulatory guidelines around patient engagement
- Engage legislative bodies to eliminate potential legal barriers to patient involvement in benefit-risk decisions

Syndicate 3: When should patients be involved and what are the possible methodologies for the decision to approve/reject? An agency perspective

Using the perspective of a regulatory agency, this Syndicate was asked to discuss the involvement patients should have in the review of a new medicine with respect to benefits and harms. It was also asked to identify the methodologies that agencies and companies use or could use to elicit patient input into the development of new medicines that would enable the drug benefit-risk profile to be aligned with the needs of patients in the disease area.

Questions for consideration

- From an agency's perspective, when should patients be involved in providing input into the benefit-risk framework and what are perceived as the main issues in that involvement?
- How do agencies currently involve or seek information from patients and patient groups, what value do agencies obtain from these interactions and how might this change in the future?
- What methodologies are or could be of value in eliciting patient perspectives and why?
- What are the critical issues that are faced in using different methodologies for regulatory decision making?
- From an agency's perspective, what are the mechanisms to improve patient involvement in the benefit- risk decision and what needs to be done in the short and long term, to enable these to occur?

Critical issues

As with Syndicates 1 and 2 it was the consensus of members of Syndicate 3 that patient input should be considered throughout a product's life cycle, specifically shortly after proof of concept, early in phase 2 development, prior to submission and at the time of post-marketing through a survey.

Currently, the US FDA involves patients and patient representatives in the late phase of decision making, for example at advisory committee meetings and at re-launch. Swissmedic conducts yearly strategic meetings with patient organisations, but these groups are not directly involved in the decision-making process. As mentioned by Professor Eichler (page 21) patient groups are involved in various committees at the EMA except for decision making at the CHMP. Because most patient groups are nationally based, the international scope of the EMA adds additional complication for patient involvement.

Conjoint analysis, patient preference studies and structured frameworks, such as value trees or multi-criteria decision analysis (MCDA) are methodologies that are or could be of value in eliciting patient perspectives. However, complex methods such as MCDA may require professional expertise. The transparent and simple communication of results from randomised clinical trials, a common understanding of terminology and the involvement of the appropriate patient at the right time are among the mechanisms to improve patient involvement in the benefit-risk decision. Unfortunately, clinicians often have difficulties in interpreting trial results that involve statistical analysis, using for example, number needed to treat or p-values.

Strategies

Patients should be involved earlier in decision making at the US FDA, for example, in the definition of disease area endpoints. Timing for patient-agency meetings must be clearly identified and issues regarding payment, ethics and conflict of interest in the relationships between industry and patient groups must be resolved. Patient input and its majority standing must be validated and confidentiality issues resolved. Terms such as weighting, valuing, benefits, risks and scoring need to be understood clearly by all stakeholders and the role of patient-reported outcomes versus patient-important or patient-relevant outcomes elucidated.

Industry and agencies should consider whether the goal of patient involvement is informed or empowered patient groups and remember that answers from patients will only be as valuable as the questions that are posed. The development of methods to clearly communicate the uncertainty surrounding clinical trials is vital. In fact, the ultimate question to be answered in patient involvement in the benefit-risk decision is how best to inform patients and patient groups, so that they can make better informed decisions.

Recommendations

- Organise a Workshop including different stakeholders, for example, regulators, industry and patient groups to use a structured framework to develop an appropriate methodology for regulatory benefit-risk assessment that engages patients' perspectives and patient-reported or patient-relevant outcomes. Include an evaluation of various visualising tools and incorporate different milestones throughout the product lifecycle
- CIRS should carry out a survey of regulatory authorities, pharmaceutical companies and health technology assessment agencies to identify when, where and how patient groups can and should be involved in the decision-making process

PANEL DISCUSSION: REGULATORS' REACTIONS TO SYNDICATE RECOMMENDATIONS

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

Ms Sabourin strongly agreed with the all three Syndicate groups regarding patient input along the continuum of medicines development, through a variety of mechanisms and with different extents of engagement along that continuum. She cautioned, however, that the development of methods is required to ensure that patients and patient groups can appropriately participate in ways that are not only free from bias but free from the perception of bias.

It is also important to regulators that patient input into relevant clinical trial outcome measurements be obtained at the time of trial design rather than being retroactively solicited to justify unexpected results. Patient-reported outcomes are not yet a part of labelling decisions in most jurisdictions and much work remains to design their standardised incorporation in trials and regulatory decision making.

Regulators are accustomed to the use of logical, rational, systematic processes validated through scientific research and publications in their evaluations. A deeper understanding of other mechanisms for input such as social media is required before they can be used in the processes for drug development and for the approval system in general. Ms Sabourin cited a formula for overcoming resistance to change that specifies three necessary components, two of which were implemented through this Workshop. One component is dissatisfaction with the current system, in this case, dissatisfaction was expressed for a system for the development and review of medicines that does not adequately incorporate patient participation. The second factor is a vision of the future, such as that proposed in all of the Syndicate discussions, in which that patient participation has been successfully accomplished. The third component needed to overcome resistance to change consists of taking the first steps. She encouraged industry and patients to "push" regulators for change and encourage them to take the series of small necessary steps toward the goal of patient participation. She further suggested that agencies' support for the Syndicate recommendation for a survey of

current practices and their participation in the annual CIRS benefit-risk Workshop in Washington DC would be among the appropriate activities.

Prof Angela Timoney, *Chair, Scottish Medicines Consortium*

Saying that payers have employed a paternalistic approach to healthcare, Professor Timoney explained that reimbursement agencies have primarily focussed on the viewpoints of healthcare professionals who have advocated for patients without necessarily obtaining or listening to their input. In addition, the use of highly technical terminology such as health technology assessment further excludes patient participation in the assessment of medicines. To find a methodology to overcome this cultural tradition of longstanding, however, is challenging.

Three patient representatives currently bring patient and public viewpoints to the assessments of the Scottish Medicines Consortium and those viewpoints have been at least partially informed by submissions from patient interest groups. Professor Timoney described this as a less than perfect process and said that more weight would be attached to evidence formed with regulatory input, with this evidence more likely to drive the outcome of HTA assessments.

If regulators are less willing to accept risk than patients, HTA assessors may be less willing to accept risk than regulators because of their mandate to look for benefits for whole populations as well as individual patients. Professor Timoney concluded by remarking that if the expressions of robust evidence though the patient voice can lead to the convergence of the perspectives of regulators, patients and health technology assessors, it is a worthwhile goal.

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

Ms Mossman also agreed with the necessity for patient participation in assessment throughout a medicine's life cycle. She suggested the collection of examples in which the quality of decision making was improved through patient input to demonstrate its value to stakeholders who remain unconvinced of its significance. She further agreed with Professor Timoney that technical terminology such as "conjoint analysis" can act as a barrier to patient inclusion and should be avoided.

Although enacted to avoid the perception of promotion, regulations that surround industry-patient interaction may act as another barrier to patient engagement in healthcare decision making. When the disclosure of even small contributions to a patient advocacy group could impede inviting patients to public meetings, the regulations stand in the way of the common interest of all stakeholders: the improved health of patients.

Ms Mossman disagreed, however, with the idea that one patient cannot provide representative views. Although it is true that a single person cannot speak for an entire population, she said that a methodology should be developed that follows the model of clinical trials in which industry and regulators accept the generalisability of the results of testing new medicines in limited populations.

Whilst the involvement of patients in the development of medicines is complex, multiple programmes and mechanisms are already being developed or are in place. INVOLVE, for example, is "a national advisory group that supports greater public involvement in NHS, public health and social care research."[1] and similar activities are promoted by other organisations. An inventory should be made of these existing programmes, activities and available learnings, but new and bold thinking and actions are also required to ensure that the voice of patients is represented in healthcare decision making.

Moira Daniels, *Vice President, Regulatory, Policy, Intelligence and Labelling, AstraZeneca, UK*

Bold action was also suggested by Ms Daniels to expedite patient involvement, but she advised that care be exercised to ensure that patient involvement is recruited at the appropriate level where the most value can be added. Patient participation in a discussion about preclinical genetic toxicology testing, for example, may be of limited usefulness.

The inclusion of patients in benefit-risk evaluations would be greatly facilitated through the development of visualisation tools to clearly articulate the potential benefits and harms to a lay person. Inclusion must also be facilitated through simple logistics, however, and issues such as transportation, funding and handicap accessibility for patients and their advocates cannot be ignored.

Although appreciative of the hopeful optimism and consistency among the strong recommendations from the representatives from various healthcare sectors at the Workshop, Ms Daniels suggested that future discussions include representation by treating clinicians to obtain their perspective on the application of labelling information to individual patients.

She concluded by echoing the recommendation of other participants that a survey be conducted on the current state of patient inclusion, but also added that the survey should be repeated to determine if the involvement of patients throughout the entire life cycle of medicines ultimately results in an improvement in the quality of decision making.

Reference

1. Involve. Available at http://www.invo.org.uk/ accessed May 2012.

Section 3: Presentations

What are the opportunities and issues to including patients' perspectives on benefits and risks of new medicines for utilisation in the decision to submit and approve or reject

The patient viewpoint

Dr Mary Baker

President, European Brain Council

The challenges of disease management

Using the expenses associated with the treatment of brain disease as an example of the precipitous rise in healthcare costs, Dr Baker explained that in 2010, Europeans spent nearly 800 billion Euros across thirty countries in the management of nineteen groups of neurologic disorders. In addition to this financial burden, brain diseases, like all serious illness, also exert an enormous strain on society, health systems and families.

The ever-increasing age of society has further exacerbated the toll of disease. For example, a baby girl born today in Japan has a 50/50 chance of living to be 100 years of age. Whilst this longevity is an incredible achievement for society, it unfortunately will also result in a dramatic increase of people suffering from chronic disabling illnesses and requiring multiple medications. Adding to this challenge, the falling birth rate and changing role of women in society have resulted in drastically fewer familial caregivers and fewer employed people supporting the cost of public healthcare.

At the same time, the treatment of many illnesses has grown in complexity and the provision of culturally relevant treatment to an increasingly migratory population has added to that complexity. Despite these barriers, the time allotted to the provision of healthcare during a routine doctor visit has decreased to an average of 12 minutes per patient. Furthermore, access to medication across Europe is extremely uneven in terms of both availability and the system's and patient's ability to pay. Finally, it has been estimated that worldwide, approximately 2000 people die every day because of adverse events or lack of efficacy associated with the use of counterfeit medicines.

. . . patients are frequently willing to accept a high risk of harm associated with a medication that may effectively treat or at least palliate their disease and that this tolerance of risk may change with the severity of their disease . . .

Partnership and communication among all healthcare stakeholders is essential to meet these challenges. Effort and education regarding the prevention of disease must become a priority, with government, society and individual patients assuming responsibility.

The way forward: Industry and regulator responsibilities

Although understandably, ensuring the safety of new medications is of prime importance to regulators, patients may perceive that this concern unnecessarily impedes their access to innovative therapies, especially for patients with rare or critical disorders. In fact, medical decision makers should be aware that patients are frequently more willing to accept a high risk of harm associated with a medication that may effectively treat or at least palliate their disease and that this tolerance of risk may change with the severity of their disease or for other reasons that health care professionals may regard as "unscientific". It should also be remembered, however, that full comprehension of the benefits and risks of medicines among patients is highly individual and variable.

The clinical development process for new medicines must be improved. In a rapidly ageing world, the relevance of clinical trials that often exclude patients over 65 years of age should be reconsidered and there should be a stronger focus on patient-reported outcomes. For example, clinical evaluation of the progression of Parkinson's disease, currently primarily relies on the measurement of the length of stride and arm swing of patients. To patients, however, it may be more important to capture information regarding the effects of the disease that are more crucial to their every-day lives such as associated anxiety, depression, sleep pattern disturbances and gastrointestinal, urinary and sexual dysfunction. Finally, despite legitimate concerns regarding the need for long-term

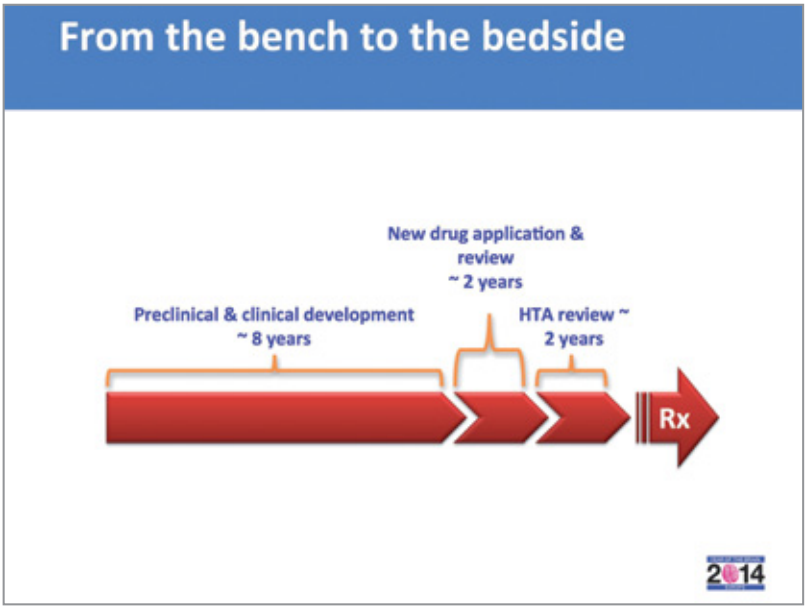


Figure 2. The time to access new medicines must be shortened.

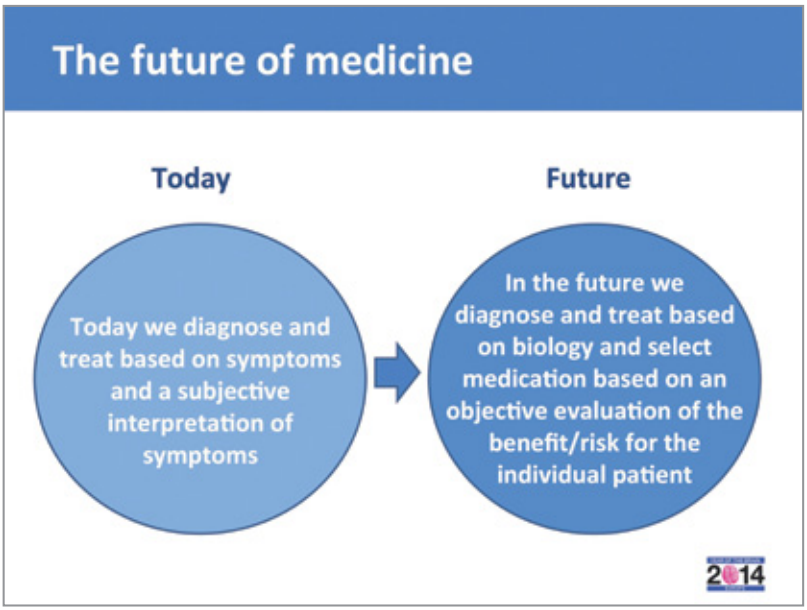
safety and real-world effectiveness data, it can currently take as much as twelve years for patients to access new medicines and this time must therefore, be shortened (Figure 2).

Patient responsibilities

Although health technology assessment may seem to represent another roadblock to access to medicines, patients must develop an understanding and appreciation of the complexities associated with the evaluation and payment for new medicines within the constraints of limited budgets. In the United Kingdom, for example, 60% of the National Health Service budget is allocated to manage so-called "life-style" conditions such as sexual dysfunction, infertility, smoking, obesity and drug and alcohol addiction. In addition to this understanding, effective patient advocates must establish credibility, collect evidence and substantively contribute to healthcare discussions.

In pursuit of these necessary attributes, the European Federation of Neurological Associations initiated a collaboration with the London School of Economics in 2009 to provide educational courses for patient advocates, which have met with great success. Efforts there concentrate on patient-centred research, patient-reported outcomes and patient-centred training to understand benefit-risk and improve health literacy.

Figure 3. Medicine will continue to become more individualised.



Societal responsibilities

Today, clinicians diagnose and treat illness based on symptoms and a subjective interpretation of symptoms, but in the future, diagnosis and treatment may be more heavily based on biology and medication selection will be based on an objective evaluation of the benefit-risk for the individual patient (Figure 3). However, this will require superb communication and true partnership between patients and clinicians. The management of long-term chronic illnesses will involve the patient's ability to adapt and self manage and to be able to participate in social activity despite disease-related limitations, but patients must have a voice and be included in a partnership of healthcare decision making.

To regain some control over their lives after the watershed moment of diagnosis, patients require information from clinicians, from industry and from fellow patients. Much information has become available to patients as regulators and industry follow legislated mandates to provide more detailed information about the development and regulation of new medications. Effective communication and true transparency, however, require that this information be translated into language accessible and understandable to the lay person.

Societal involvement in ensuring the flow of information is critical and the realisation of the cost-effectiveness of an informed patient may be key to that involvement. Industry, healthcare professionals and patient organisations must overcome natural competiveness for intellectual property, prestige, financing and services and work together to share resources and advance

science. This challenge to society requires co-operation and partnership from a range of stakeholders. Creating high performing networks is essential and the European Brain Council and the Year of the Brain are examples of this in practice.

Patients' perspectives on benefit-risk of new medicines:

HTA/payers' viewpoint

Prof Bruno Flamion

Professor of Pharmacology, University of Namur, Belgium

Are reimbursement systems too complex for the inclusion of patients' perspectives?

Health technology assessment (HTA) agencies and payer organisations are moving cautiously toward increased patient involvement in decision making for new drugs. Understanding the complexities surrounding the development, regulation and reimbursement of medicines, however, represents a significant hurdle for patient participation.

Requirements and standards for evidence of efficacy, real-world effectiveness and value for medicines vary greatly among decision makers and among world economies, with groups variously employing clinical trials, clinical guidelines, observational trials and pharmacoeconomic and budget impact studies in their decision making. Regulators have made some progress toward harmonisation of assessment requirements, language and concepts among jurisdictions, but efforts in this regard among health technology assessors are only in the initial stages and have been further complicated by the sheer number of HTA organisations. For example, the International Network of Agencies for Health Technology Assessment (INAHTA) comprises 59 members from 23 countries.

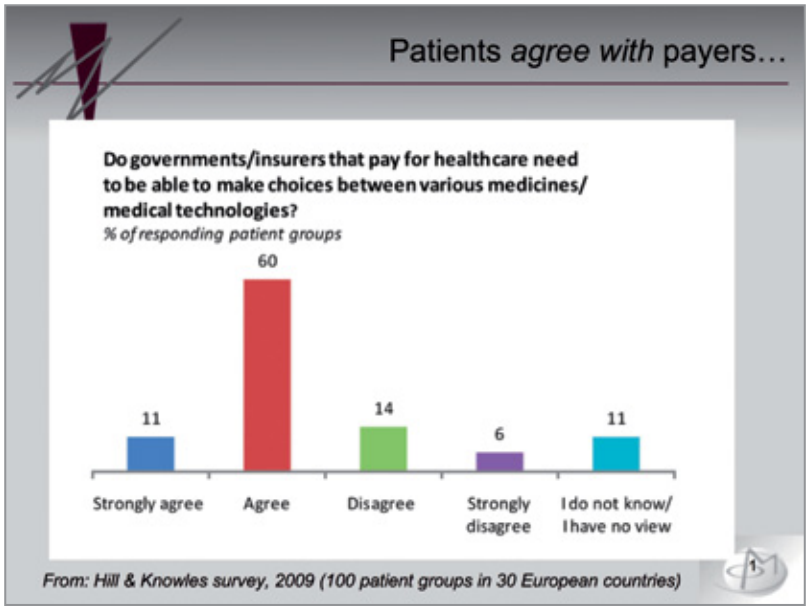


Figure 4. The majority of patients surveyed agreed that health technology assessors and payers must be able to choose among the most appropriate therapeutic options.

In health technology assessments, medical assessors, health economists and clinical experts often must make reimbursement decisions with scarce real-world data, using multiple comparisons in ill-defined patient groups. Assessors render complex judgements in the face of two opposing forces: a necessary impartiality versus a natural empathy for patients and in the end, some products must be rejected for reimbursement. Payers are also faced with multiple challenges. Cost-effectiveness and budgets must be balanced and resources allocated between inpatients and outpatients and purchasing power organised for different regions and levels of government. Other payer challenges include the need to accommodate or manage agreements to reimburse with prior approval, the need to address generic or biosimilar substitutions, the use of treatment combinations and an incomplete characterisation of pathways of disease care.

Some HTA organisations do indicate that they include patient-centred values in decision making. For example, the new technology assessment model used by the National Institute for Health and Clinical Excellence (NICE) includes social value judgements. However, although many HTA bodies claim patient involvement as a standard and worthwhile goal, evidence for the actual role of patients in HTA decisions is limited.

The patient viewpoint

It might be assumed that health department officials, HTA agencies and payers are primarily concerned with budgets and cost management and value, whilst patients consider healthcare a basic right for everyone that should be widely available. However, results of a survey conducted among one hundred patient groups across 30 European countries revealed that 71% of respondents agreed that governments or insurers that pay for healthcare need to be able to make choices among various medicines and medical technologies, even though such decisions would limit the availability of some medicines (Figure 4). Thirty-two percent of respondents also thought that health technology assessment was the only way to make those choices, even though 59% of those surveyed said they have little or no knowledge about HTA and 54% thought that HTA is the province of clinicians and academics who exclude patients from decision-making processes. Most tellingly, 83% thought that patients should participate in the European HTA process.[1]

Professor Flamion quoted several statements from the survey agreed to by the majority of respondents as proof of the rational thinking of the average patient concerning the assessment of new health technologies:

- The value of a medicine or medical device can never be properly evaluated until it has been widely used by patients (58% respondent agreement)
- If a medical technology is approved by a regulatory agency and deemed cost-effective by an HTA agency, it should be automatically reimbursed (58% respondent agreement)
- Some public money should be saved to reimburse non-medical interventions besides medicines, such as surgery, medical devices and public health measures (48% respondent agreement)
- All EU citizens should have access to the same choices of prescription medicines and medical technologies (82% respondent agreement)

Survey participants were additionally able to indicate additional factors that HTA should take into account: quality of life, the ability to live an independent life, the ability to return to work, the impact on caregivers and choices available for the other medical interventions.

Patients could play an important role in post-marketing and HTA studies and managed entry schemes, for example, by using patient satisfaction as an outcome measure in a pay-for-performance agreement.

Patient inclusion in practice

The new vision for personalised healthcare, according to the Nuffield Council on Bioethics involves "individualised management customised to a person's specific genetic, physiological or psychological characteristics . . . providing healthcare in response to consumer demand."[2] However, consumer presence and involvement in the decision making surrounding medicines is an absolute requirement for an understanding of consumer demand.

This involvement can be realised at different stages in the lifecycle of medicines. Patients can provide input into clinical development by indicating health outcomes of personal importance such as quality of life, by their acceptance or refusal of certain levels of risk of harm associated with medicines and by providing patient-reported outcome data. Patients could play an important role in post-approval and HTA studies and managed entry schemes, for example, by using patient satisfaction as an outcome measure in a pay-for-performance agreement. Methods to improve patient interaction in clinical and post-approval development, such as online data collection and registry development should be more rigorously explored and patient input should inform the resolution of privacy issues that surround data collection.

There are limitations to patient involvement. Patients' organisations are not available for all diseases and patients typically have limited knowledge of and experience with the healthcare reimbursement and payer system. In addition, it is debatable whether links between patient associations and the pharmaceutical industry should be encouraged or prohibited. Once initiated, however, patient participation in healthcare reimbursement decision making must be periodically and scientifically assessed. Danner and associates recently published such an assessment in the International Journal of Assessment of Health Technology that proposes methods to assess patient participation in payment decisions.[3]

Some efforts to involve patients in HTA and payer decision making have occurred or are ongoing. Tapestry Networks reported on three pilots of

"multi-country, multi-stakeholder consultation in drug development promoting clarity on sources of medicinal value" including patient advocates. Patient participants in these pilots reported that despite extensive effort, a lack of understanding of technical issues and reimbursement processes presented significant challenges and they concluded that the investment in time required for their participation in the studies was not in balance with their final contribution. They advised that sponsors of new medicines should prepare briefing documents that highlight issues that are important to patients, including side effects and quality-of-life metrics and that they should pose relevant questions directly to patients.[4]

Other programmes have been initiated by patients themselves. PatientsLikeMe.com is a social networking healthcare site in which more than 150,000 patients suffering from more than 1,200 diseases input their medical history and treatment data and detail the progression of their disease. This significant collection of data allows patients to compare their disease and treatment course against the experience of others and to find ongoing clinical trials for which they may be appropriate participants. It has also allowed patients to participate in clinical research. After results of a small study published in 2008 showed that lithium might have a positive effect on amyotrophic lateral sclerosis (ALS)[5] hundreds of site members with ALS began taking lithium. Wicks and colleagues published the self-reported data from 348 of those patients over a period of 9 months and using other patient data from the site as controls, showing that unfortunately, lithium had no effect on ALS progression.[6]

Education initiatives that would prepare patients for this type of participation are underway however, such as the European Patients' Academy on Therapeutic Innovation (EUPATI), launched in March 2012 in Copenhagen. The goals of this project include a certificate training programme that would prepare 100 individuals to become patient advocates invited to decision-making meetings; an educational tool box, for 12,000 patient advocates that would include printed material, slide presentations and webinars and an Internet library on specific aspects of drug development expected to be appropriate for approximately 100,000 patients with lower medical literacy levels (Figure 5).

Professor Flamion expressed the belief that patient participation will continue to progress in a stepwise fashion and that within the next five years, there will hopefully be many more instances of full stakeholder inclusion in healthcare reimbursement decisions.

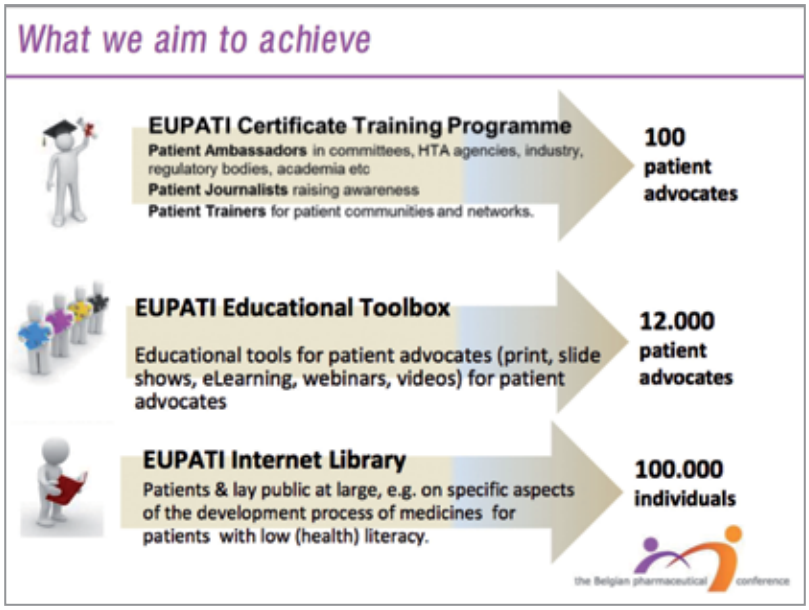


Figure 5. The European Patients' Academy on Therapeutic Innovation aims to prepare patients for various levels of participation in healthcare reimbursement decision making.

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The patient's role in the benefit-risk assessment for the development, submission and review of new medicines: An industry view

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The informed patient

All people become patients within their lifetime, each with the common shared objective of access to high-quality effective medicines used within an effective healthcare system. Fulfilment of this objective requires our confidence as patients in the regulatory framework for pharmaceuticals and our confidence in the reliability of the data supporting that framework. We must believe that the decision-making processes used within the system are robust, transparent and reproducible and be given the assurance that we will understand how to use a medicine effectively. But patients also have individual roles to play in the development of medicines and as such, we may be biased and even understandably selfish, wanting a medicine that will be effective for us personally and be personally driven in the risks we are willing to take to achieve that effectiveness.

A patient-centred approach to the evaluation of healthcare, while essential, requires informed, health-literate patients. Informed patients, who are taking more control of their own healthcare, are a growing segment of society. In fact, 66% of healthcare consumers research information on illnesses and conditions to ensure that they or their family obtain the best available treatment, even though 43% find the information available today as confusing as it is helpful. Over a third of patients have approached their doctor with a branded medicine in mind (Figure 6).

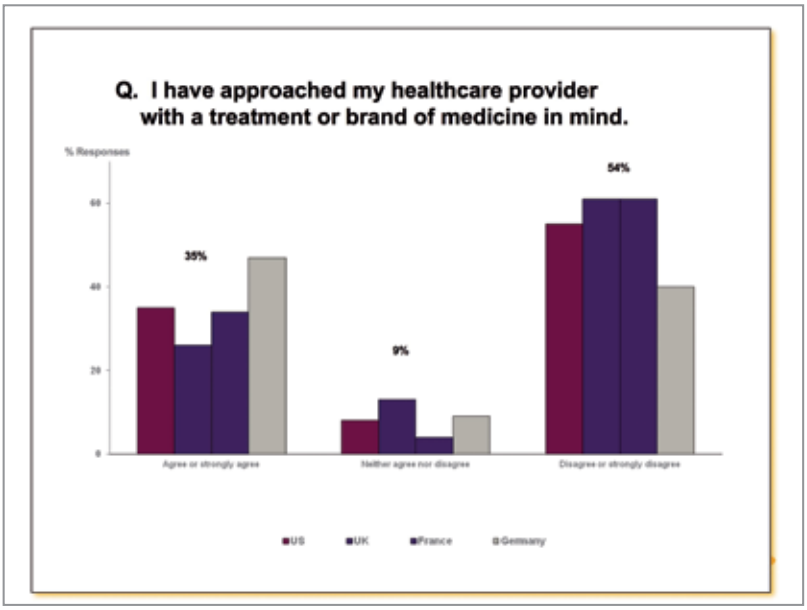

Figure 6. More than one third of patients have gone to their health care provider to ask for a particular medicine.

The involved patient

Patient advocacy groups should be present for early developmental discussions with industry. Patients are critical in determining unmet medical need and by sharing their personal experience, patients and caregivers contribute essential individual perspective on disease severity and benefits and risks. It must be remembered, however that regulatory and HTA decisions are complex and population based and regulators and assessors are mandated to avoid basing decisions on a single individual voice.

The ability of patients and caregivers to accept risk is often underestimated by developers of new medicines and regulators and a well-developed benefit-risk framework assists educated structured and transparent communication around this topic. Constructive well-informed input assists the communication of the outcome of decision-making, articulating the basis of the decision and framing it at the patient level.

The patient's role in helping to inform the outcome of a regulatory decision is crucial. They can identify potential topics that would benefit from additional patient consultation and actively contribute to patient information and communication related to medicines, ensuring that patients and patient organisations can access useful and understandable information. They may also be called on to disseminate committee outcomes when they become public, passing on information to other patients and patients' organisations. Patients can bring specific expertise from a patient-communication perspective, for example, putting safety issues into context and they can contribute to the decision on when to communicate such findings. They can also ensure that information in any document for patients and the general public such as package leaflets or question-and-answer documents is clear and understandable by the target audience and advise and support regulators on the feasibility of planned research, such as paediatric investigation plans.

New tools and methodologies must be developed to more effectively communicate non-promotional information about the safest and most effective use of medicines to achieve the highest benefit

The importance of communication

The pharmaceutical industry has made inroads into patient involvement in the development of medicines, participating in patient education efforts such as those cited by Dr Baker and Professor Flamion, organising formal patient input surrounding specific disease targets and collecting patient-centric views for development programmes, focusing diseases and the impact of symptoms to determine the intrinsic value of a medicine. They have anticipated, especially in post-approval regulatory decision-making, the potential for extreme polarisation on the issues, with some patients who may have experienced adverse events versus those who may have experienced benefits. But much remains to be accomplished. Patient compliance and informed decision making can be enhanced by improved patient-level communications. New tools and methodologies must be developed to more effectively communicate non-promotional information about the safest and most effective use of medicines to achieve the highest benefit, while finding a way to effectively communicate to patients that no medicine comes without risk of harm.

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

The EMA approach

Prof Hans-Georg Eichler

Senior Medical Officer, European Medicines Agency

François Houÿez represents EURORDIS, the non-governmental patient alliance at the Patients' and Consumers' Working Party at the European Medicines Agency (EMA), where he is topic leader on risk communication and an external expert for the evaluation of marketing authorisation applications. In the recent public hearings on patient interests in medicines in Europe, Mr Houÿez stated that medical regulation could be enhanced in Europe by "greater involvement of the public, a better understanding of regulatory decisions and by participation in decision making by providing different insight."[1]

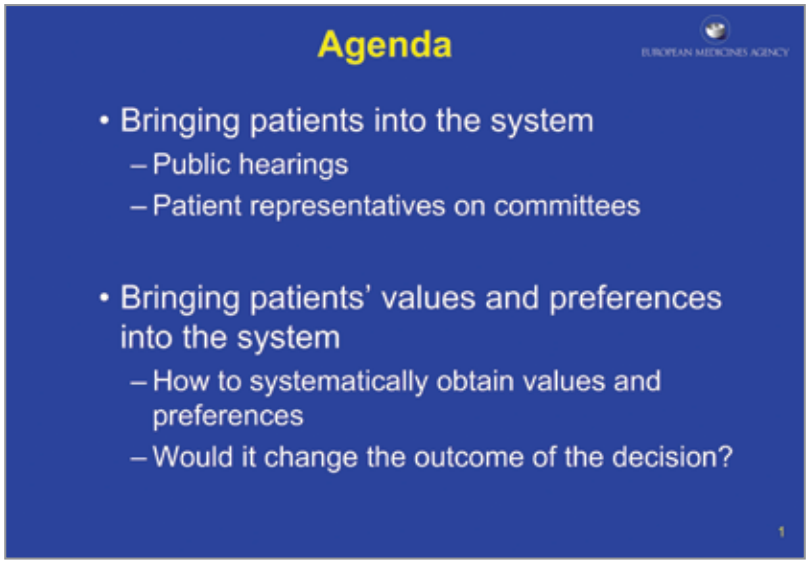

Figure 7. Two methods for achieving patient input into the regulation of new medicines

In agreement with this advice, Senior EMA Medical Officer, Professor Hans-Georg Eichler described regulators of new medicines as "service providers" who should be responsive to the preferences and priorities of patients as their primary "customer." Professor Eichler proposed a two-prong approach to fulfilment of this mandate: bringing patients and their preferences and values into the regulatory system (Figure 7).

Bringing patients into the system

Patients can be brought into the regulation of European medicine through public hearings and indeed the legislature has already made provision for this:[2]

- "Where the urgency of the matter permits, the [Pharmacovigilance Risk Assessment Committee] PRAC may hold public hearings, ... The hearings shall be held in accordance with the modalities specified by the Agency and shall be announced by means of the European medicines web-portal. The announcement shall specify the modalities of participation.
- The Agency shall, in consultation with the parties concerned, draw up Rules of

Procedure on the organisation and conduct of public hearings..."

In the face of this legislation, questions remain, however, such as whether the ultimate purpose of public hearings is transparency or engagement. Additionally, other issues have not yet been clarified such as the optimal timing for the hearings, the identity of contributors, the location and language to be employed, the ground rules for participation and the time and other resources to be expended.

In addition to public hearings, patients can also be brought into the regulation of medicine in Europe through representation on committees and there is a standing EMA working party with consumer and patient representation. There are also permanent patient representatives on some EMA committees and Advisory groups, but the direct involvement of patients with diseases under discussion by regulators is extremely rare, although it has occurred in some exceptional instances such as when the use of thalidomide was being considered in patients with melanoma. This absence of patient representation on the Committee for Human products for Medicinal Use (CHMP) means that the key stakeholder group in medicines is effectively excluded from key decisions on licensing in Europe.

Bringing patient values into the system

Regulatory decisions are rendered through the evaluation of data that indicate the probability of the occurrence of an event as the result of a medication, multiplied by the positive or negative value associated with the event, that is, its "utility" or "disutility." In addition, all evaluations take place against a backdrop of uncertainty.

In a recent article in the *New England Journal of Medicine*, Beasley and colleagues discussed assigning values to two different treatment outcomes and weighting those outcomes relative to each other:

"If stroke or systemic embolism and major haemorrhage were considered equally undesirable. . . Most people would agree, however, that the irreversible effects of strokes and systemic emboli have greater clinical significance than non-fatal bleeding. Any benefit-risk assessment in which strokes and systemic emboli are given more weight than non-fatal bleeding . . ."[3]

In terms of listening to the patients' voice, patients enrolled in clinical trials are an underutilised resource.

Any documented discussion of the weighting of benefits and risks of treatments represents a positive step in the development of scientifically accepted models for medicines' evaluation. However, it must be understood whose values are being considered in these weightings. Although the evaluation of regulators of the scientific evidence for the efficacy and safety of medicines is undoubtedly critical in licensing decisions, it is the values of patients and their willingness to tolerate uncertainty and to trade the risk of harm or non-effectiveness for the benefit of disease cure or amelioration that should be taken into consideration in regulatory decision making.

There are methods for the quantification of patient value judgements that have been in use for some time[4] and that are currently being used by health technology assessors despite regulators concerns regarding their validation. "Patients" in this instance, however, does not necessarily mean "patient representative," but rather patients with the specific disease or condition to be treated, who know which outcomes and symptoms matter most to them. In terms of listening to the patients' voice, patients enrolled in clinical trials are an underutilised resource and despite the fact that they are the target group for a drug that has been licensed, their values and preferences are typically not investigated in a systematic way.

The impact of patient values on regulatory decision making

There are three types of potential regulatory error. In the Type I error a false-positive decision is made to license a drug, or to allow it to stay on the market, even though it produces more harm than good. The Type II or false-negative error occurs when the decision to deny a drug a license, or to withdraw it from the market is made when use of the drug would have produced more good than harm. A Type III error is the opportunity cost of risk-averse behaviour. For example, a request for additional data on one product may have the unintended consequence that the resources required to obtain the data are not available for research and development into another medicine that might yield more public health gain for the resources spent.

It is possible that concerns regarding public reaction to Type I error have created an incentive for the risk-averse behaviour in regulators that results in Type II or III errors. Professor Eichler

hypothesised that patient input, including information regarding the weighting of values and tolerance for risk and uncertainty, will have a positive impact on regulatory decisions, potentially reduce the occurrence of Type II and III errors and ultimately improve the disconnect between the regulatory "provider" and their "customers."

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FDA benefit-risk assessment and patient-focussed drug development

Dr Janice Soreth

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The FDA and benefit-risk assessment

In 2008, the United States Food and Drug Administration (US FDA) initiated an effort to explore more systematic approaches to the assessment and communication of benefits and risks as part of the drug review process. Emerging from this work, the qualitative Benefit-Risk Framework aids expert judgement and serves to capture a review team's careful evaluation of the evidence while facilitating their deliberations. It was developed through extensive review and analysis of prior regulatory decisions, working directly with the review staff who played a role in those decisions.

The framework supports but does not replace sound expert judgement and identifies and respects areas of expert disagreement. It is constructed through an intuitive design based on a "mental model" approach. Use of the framework allows the regulator to "tell the story" by answering relevant questions such as

- What is the problem?
- What other potential solutions exist?
- What is the benefit of the proposed solution?
- What am I worried about? and
- What can I do to mitigate/monitor those concerns?

The Framework is constructed as a table with rows outlining the five key review considerations or decision factors: *Analysis of Condition* and *Unmet Medical Need* provide the clinical context for weighing the benefits and risks of the drug under review. *Clinical Benefit* and *Risk* provide an assessment of the submitted evidence and the expected benefits and potential risks to the intended patient population in the post-market setting. *Risk Management* summarises the activities that could help to further understand or mitigate the potential risks.

Additionally, the Framework columns outline the two types of input needed for each consideration to inform the regulatory decision: **Evidence** and **Uncertainties** present the facts that have the most bearing on the reviewers' assessment of benefits and risks, as well as any important study quality issues or data gaps. **Conclusions** and **Reasons** capture the reviewers' interpretation of the quality and clinical relevance of that evidence, noting any disagreements in conclusions. The final row of the tabular Framework, *Benefit-Risk Summary and Assessment*, provides specific instruction, asking reviewers to integrate the individual components into an analysis of the factors and their tradeoffs and summarise the resulting regulatory recommendation.

A work in progress, the Framework is currently being beta-tested with several new molecular entity applications in FDA/CDER. The future plans for this work include more expansive implementation as specified in commitments for the Prescription Drug User Fee Act (PDUFA) V.

Patients who live with a disease have a direct stake in the drug review process and are in unique position to contribute to drug development.

Patient participation in benefit-risk decisions

Assessment of a drug's benefits and risks involves analysis of severity of condition and current state of treatment options. Patients who live with a disease have a direct stake in the drug review process and are in the unique position to contribute to drug development and the regulatory review process could benefit from a systematic approach to obtaining patients' perspectives on disease severity and unmet medical need.

The FDA has a history of support for programmes designed to help ensure that the patient voice is reflected in the regulatory decision-making process. For the past several decades, the agency has included at least one patient or consumer representative on its Advisory Boards for new drug evaluation. In addition, a portion of each public advisory meeting is dedicated to a so-called "open public hearing' at which time any member of the general public, including patients, may speak to the topic at hand, whether product specific or concerning draft guidance or policy. At one such meeting in 2006, patients and caregivers spoke compellingly about the life-changing benefits they experienced with the use of Tysabri (natalizumab). Safety concerns about progressive multifocal leukoencepholapathy had resulted in the withdrawal of this drug. FDA's reassessment of benefit-risk took into account the important voices of patients and caregivers who gave testimony at the public hearing, together with panel members' recommendations and FDA data analyses. FDA concluded that the benefits of Tysabri outweighed the risks and the product was reintroduced to the US market.

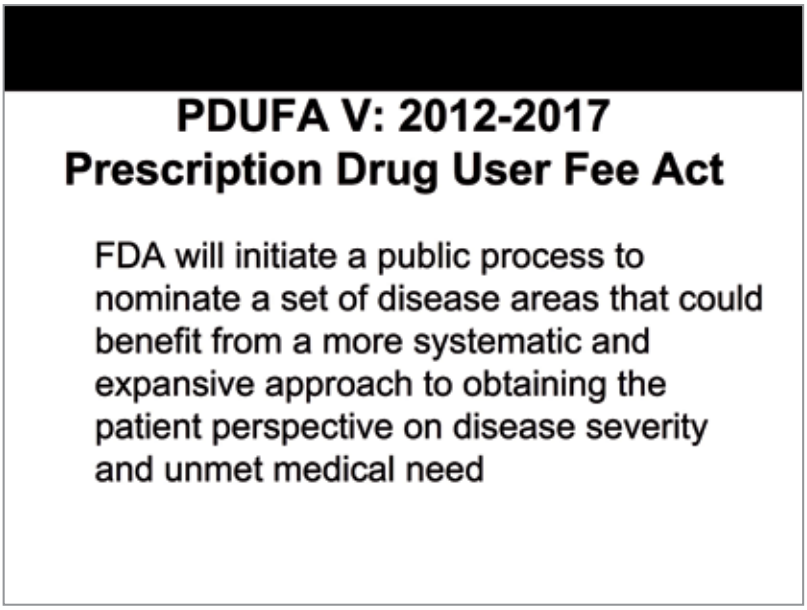

Figure 8. The Prescription Drug User Fee Act V proposed by the US FDA is currently under legislative review.

As a next step in this support of patient involvement and because the FDA is now seeking a greater understanding of how patients define and perceive benefits and risks related to medical products, the FDA held the inaugural Patient Network Annual Meeting in May 2012. The event was hosted by the FDA Office of Special Health Issues in collaboration with the Center for Drug Evaluation and Research (CDER), the Center for Biologics Research and Evaluation (CBER) and the Center for Devices and Radiological Health (CDRH) at the FDA White Oak Campus in Silver Spring, MD. The objectives of the meeting were to review the drug and medical device regulatory processes; discuss where patient input is practical and most valuable; and to explore practical approaches to collecting meaningful patient input. The meeting included a series of presentations, exercises and panel discussions to facilitate a conversation with the patient community about these important topics. The event was attended by patients, caregivers and patient advocates and members of the general public, healthcare professionals, academia and industry representatives were also invited to participate in person or through a webinar.

The FDA has instituted several other initiatives to facilitate patient participation and communication. At the FDA consumer website (http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/default.htm) patients can utilise resources related to the medical products they use, including safety updates and new approvals and patients and patient advocates can access information about proposed policy initiatives and public meetings where public comment is encouraged, as well as discover opportunities for patients and patient advocates to actively participate in the FDA Patient Representative Program.

Another patient resource, the *Patient Network News* is a twice-monthly newsletter containing FDA-related information on a variety of topics, including new product approvals, significant labelling changes, safety warnings, notices of

upcoming public meetings, proposed regulatory guidances and opportunity to comment and other information of interest to patients and patient advocates.

PDUFA V: 2012-2017

PDUFA V, the fifth legislation to be proposed to help fund FDA drug review activities since 1992, was under consideration for approval by the US Congress at the time of this Workshop. As with previously approved Acts, this funding will be conditionally granted relative to the FDA completion of specified performance commitments. In addition to expanded implementation of the benefit-risk framework, PDUFA V commitments also include a more expansive approach to obtaining the patient perspective on disease severity and the unmet medical need in specific disease areas (Figure 8). To accomplish this goal, the FDA will convene four meetings per year, each meeting focused on a different disease area and including participation by the patient advocacy community, FDA review divisions and other stakeholders. The FDA will also publish a summary analysis of input received by FDA relevant to the consideration of disease severity and unmet medical need and use this knowledge to more fully develop an understanding of disease severity and an assessment of the current state of therapies, both critical components of the benefit-risk framework in regulatory decision-making and communication. After the first two meetings, the FDA will also develop a proposal for how the agency will incorporate these perspectives into FDA's decision-making.

Additionally, the FDA will increase utilisation of Patient Representatives as Special Government Employee consultants to CDER and CBER to provide patients' views early in the medical product development process and to ensure those perspectives are considered in regulatory discussions.

Some challenges to planned patient involvement still must be addressed such as outlining the criteria for participation, developing FDA training for this process and assigning responsibilities for action. An appropriate format(s) for patient input must be decided that faithfully captures patient views and that will result in usable input to future FDA reviewer assessments of severity of condition and unmet need. Finally, accessible and reliable approaches must be developed for all types of public meetings and for providing both paper and electronic patient input to FDA documents.

New models for including patient perspectives in product development: A company case study using conjoint analysis

Dr James Cross

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Rationale

The goal of pharmaceutical development is to demonstrate evidence for a favourable benefit-risk profile for a new medicine, associated with a meaningful improvement in patient well-being. Developers are challenged, however, in determining which outcomes are of clinical value (importance) to patients and clinicians and the magnitude of effect that is considered clinically meaningful. A possible solution to this challenge is to approach patients early in the drug development process to learn what is of clinical value to them, what effect sizes might be relevant and to build their feedback into the design of the development programme.

Conjoint analysis is a survey-based method for determining the relative importance that individuals place on a defined set of disease or treatment outcomes. As such, it is a potential tool for determining the preferences of patients. It is important to understand that conjoint analysis is not the same as patient-reported outcomes; that is, stating one's preferences (i.e., making choices) is not the same as providing a self-rating of health status. The goal of conjoint analysis is to obtain weights for different outcomes such as disease effects or positive or adverse events associated with treatment in order to understand their importance. Although numeric evaluations of subject preferences are subjective and variable, as noted by Dr F Reed Johnson in a 2009 presentation, subjects "can provide ordinal rankings for outcome profiles [and the] hypothetical trade-off data reveal their implicit relative importance weights."[1] Dr Cross provided an example of conjoint analysis conducted by Johnson and associates in which

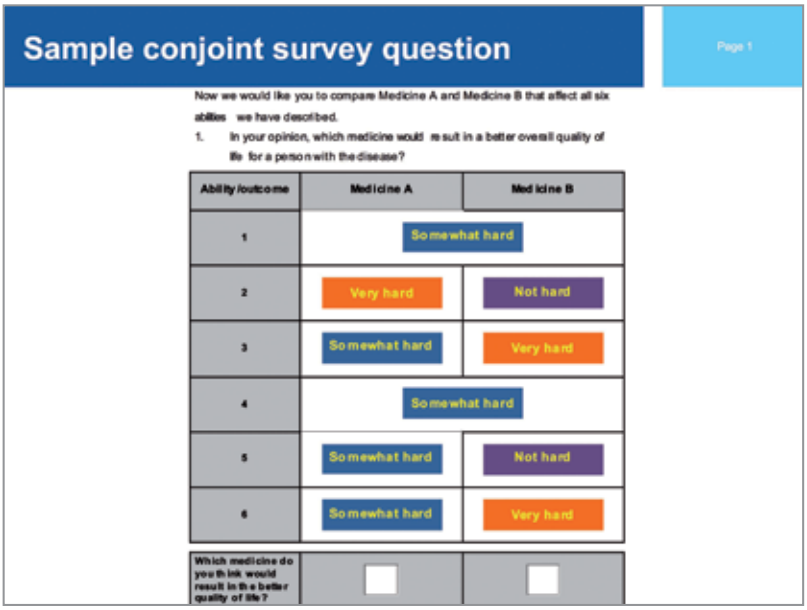
patients were asked to select among potential treatments for vasomotor symptoms based on their associated positive and negative effects.[2]

Case study

Genentech is currently in the early stage of development for a therapy with great unmet medical need. Most patients with this disorder require caregiver assistance for daily function. As there are currently no approved therapies for the disease, there are no clinical development comparators, established regulatory endpoints, nor agreement on relevant effect sizes for endpoints.

The research objective for the conjoint analysis was to better understand the outcomes and relative effect sizes that were of greatest importance to caregivers, who served as proxies for patients. The method involved quantifying preferences for potential improvements in outcomes associated with the disease in terms of both the relative value of an outcome and the value of size of improvement required. To devise the survey, a team was assembled at Roche/Genentech with clinical development knowledge together with a vendor with conjoint analysis expertise and extensive expertise in the disease in question. A survey was then created that included disease attributes of interest and the comprehension level was evaluated and adapted as necessary. Next a pre-test survey was conducted through face-to-face interviews to ensure internal validity of the survey instrument. Finally, the survey was fielded to caregivers.

Figure 9. Caregivers were asked to compare the effects associated with two hypothetical treatments on quality of life.



Survey results also showed that a small improvement in one outcome might matter more to caregivers than a full improvement in another . . .

After appropriate screening and demographic questions, "ramp-up" questions obtained information about the participants' perspectives of the disease and each outcome of interest. Finally, the "trade-off questions" asked respondents to compare two hypothetical treatments that affect the various features of the disease and then asked their opinion as to which medicine would improve the quality of life of the person with the disease (Figure 9).

Although Dr Cross cautioned that the results were still under review, they appear to have given researchers additional insights into the relative value that caregivers of patients with this disease place on disease features or outcomes. The value is scaled relative to the disease outcome showing the greatest change importance to respondents, in this case outcome three (Figure10). Survey results also showed that a small improvement in one outcome might matter more to caregivers than a full improvement in another (e.g., outcomes 2, 3 or 5 versus outcomes 4 or 6). In addition to gathering clear information regarding which endpoints and effect sizes would be clinically meaningful in a trial of the medication under development, the researchers were able to obtain subgroup data based on patient demographics that may be helpful when designing a study and analysing the resulting data.

The research does have limitations consistent with all survey-based research: the reliability of the results are a function of the survey design and the generalisability is a function of the sample of respondents. There is a potential for a correlation or crossover in some of the treatment or clinical attributes in the survey and they are not an exhaustive list of those associated with the disease. Significant strengths add weight to the data, however. There were more than 600 responses from a highly educated population and the internal validity tests did not indicate evidence of confounding in correlation tests.

Dr Cross expressed optimism regarding the willingness of regulators to consider new approaches to incorporating the patient voice into clinical development and may consider the data as scientific evidence to support clinical development plans. He acknowledged that it

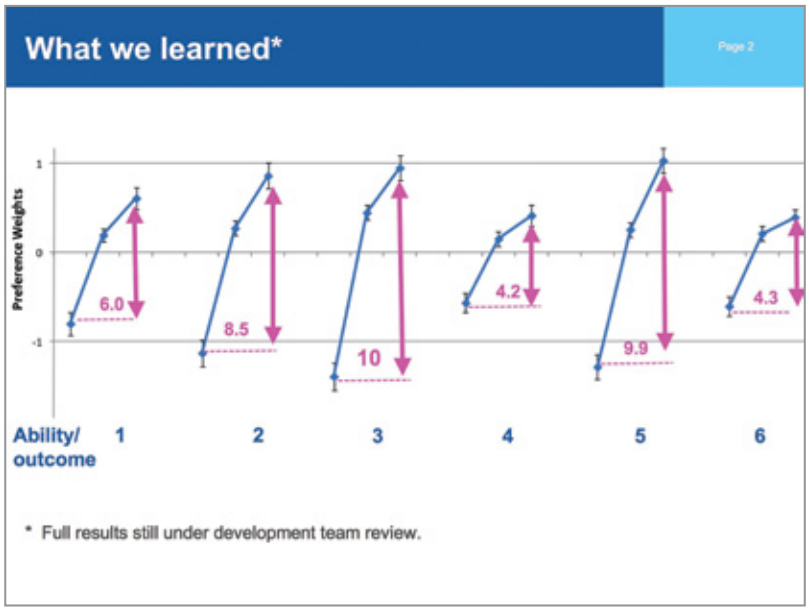


Figure 10. Survey results showed the relative importance of treatment outcomes to caregivers.

would be ideal to engage with health authorities in a dialogue over the meaning of such results in the context of the specific clinical development programme. Researchers at Roche/Genentech are continuing to review the data and consider next steps.

References

1. Johnson FR. *Stated benefit-risk tradeoff preferences from conjoint analysis.* Presented at DA/DIA Conference on Assessing Benefits and Risks of Medicinal Products in Regulatory Decisions, Bethesda, MD, 3-5 November 3-5, 2009. Available at http://www.rtihs.org/request/index.cfm?fuseaction=display&PID=14121 Accessed May 2012.
2. Johnson FR, Ozdemir S, Hauber B, Kauf TL. Women's willingness to accept perceived risks for vasomotor symptom relief. *J Wom Health*. 2007;16:1028-1040.

Including patients in decision-making: the NICE model

Victoria Thomas

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The National Institute for Health and Clinical Excellence (NICE) is an independent UK organisation responsible for the provision of recommendations to the National Health Service (NHS) regarding the cost effectiveness of new and existing medicines and devices. Amongst its other outputs, it also produces clinical guidelines for the appropriate treatment for specific diseases and conditions. To produce this guidance NICE relies on a comprehensive evidence base, expert input, independent advisory committees and patient and carer involvement.

Patient evidence has proved most useful to NICE committee decisions when it has been presented as a summary that balances positive and negative viewpoints.

This is an open and transparent process of genuine consultation with consideration of equalities and practice of regular review.

Patient and public involvement in NICE

Patients and the general public participate throughout the development and implementation of NICE guidance at a variety of levels (Figure 11). Each NICE committee includes at least two lay people (technology appraisal committees have three) who provide direct input to decision making. In addition, while not part of the decision-making process, individual patients and carers may be invited to provide personal testimony of their experience of the disease or the treatment under consideration at the public portion of committee meetings. In fact, all NICE guidance is subject to public consultation, particularly consultation with advocacy groups, who help shape the scope of appraisals at the start of the process as well as provide a review of draft guidance before publication. NICE's Citizens Council ensures that societal views are reflected in NICE's methods and processes. Patients Involved in NICE (PIN) is an independent group of patient and carer organisations providing mutual support for organisations who engage with NICE and

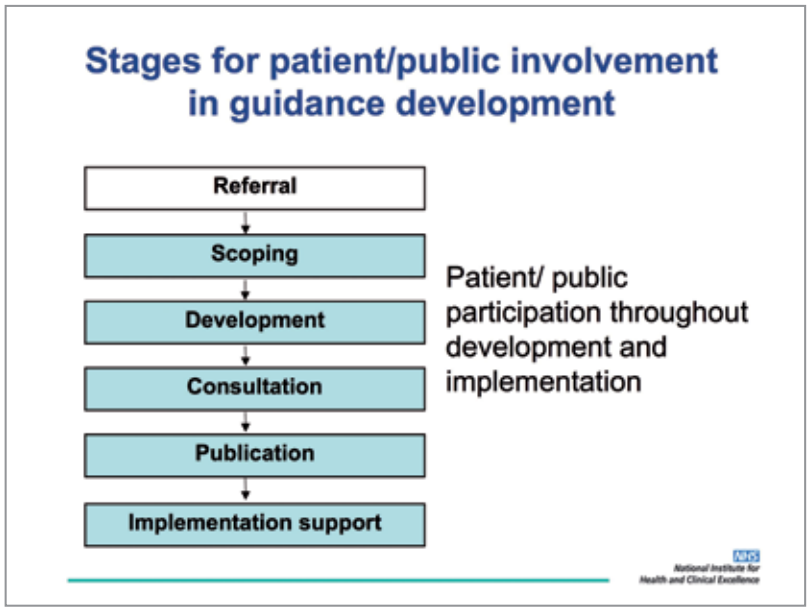

Figure 11. Patient input and involvement plays an ongoing important role in NICE activities.

comment collectively on NICE's strategic public consultations.

The effect of public involvement

Patient evidence has proved most useful to NICE committee decisions when it has been presented as a summary that balances positive and negative viewpoints. This input provides a variety of useful information to committees, including the impact of a patient's condition on physical and social functioning and quality of life as well as its impact on family, friends and employers. Patients also share information regarding the outcomes that they would like technology to influence and the actual effects a technology has had on the symptoms of their disease and its progression, as well as information on its ease of use, side effects and costs. Through this public participation, NICE is able to obtain data regarding patient preferences and learn about subgroups who might benefit more or less from a technology. Additionally, the information challenges professional or researcher views and elucidates areas needing further research.

Patient input can also influence NICE recommendations regarding the mode of administration for a new or existing technology, as it did when patients who underwent regular dialysis testified that, contrary to the appraisal committee's assumptions, outpatient dialysis was preferred by some patients to an in-home treatment that left patients feeling that their illness dominated their lives. Patient contributions have also exerted an influence on the validation of clinical research outcomes. For example, although clinical research in psoriasis had previously indicated that the amount of psoriasis was the factor of the disease that most affected patient quality of life, patients themselves reported that it was the location of the flare-up, for example, the face or joints that was more significant to their day-to-day lives.

Public concerns

All NICE recommendations and guidance are available for patients and the public in simple language, easily understood by the lay person. Although detailed information about a particular disease or condition is not included, contact details for support organisations that can provide additional information are provided. Despite these efforts, members of the public have expressed the concern that the technical language and economics of NICE evaluations are difficult for the lay person to comprehend. The public has identified other challenges associated with NICE processes, including a lack of research evidence on patient and carer views, experiences and preferences. It is also felt that despite the opportunity for patient testimony, the quality-of-life measures used in NICE evaluations often do not reflect the issues of most importance to patients and there is a lack of patient participation in the weighting of evidence. Finally, it has been expressed that existing NICE policies do not consider or address the wider societal costs of disease and therapies and that there is wide variability in patients' ability to access NICE-recommended technologies.

The Health and Social Care Act passed by the UK Parliament in 2012 means new and different roles are emerging for NICE. Quality standards in clinical and public health, will now form a significant part of future work for the organisation, with social care to become part of the NICE remit from April 2013. NICE will no longer be part of the NHS in 2013 and the implications for patient involvement are unknown. However, because healthcare decisions that impact patients should not be made without taking patient views into consideration, Ms Thomas expressed the hope that public and patient involvement will continue to play a vital role at NICE.

Appendix: Workshop Attendees

Patient organisations		
Dr Mary Baker	President	European Brain Council
Ingo van Thiel	Editor	Deutsche Leberhilfe e.V., Germany
Jean Mossman	Policy Lead	European Federation of Neurological Associations, UK
Jeremiah Mwangi	Policy and External Affairs Director	International Alliance of Patients' Organisations, UK
Sally Penrose	Chief Executive	Lymphoma Association, UK
Regulatory and government agencies and academic institutions		
Andrea Beyer	Researcher	University of Groningen, The Netherlands
Prof Sir Alasdair Breckenridge	Chairman	Medicines and Healthcare products Regulatory Agency, UK
Prof Hans-Georg Eichler	Senior Medical Officer	European Medicines Agency
Prof Bruno Flamion	Professor of Pharmacology	University of Namur, Belgium
Cordula Landgraf	Head of Networking	Swissmedic
Dr Huei-Xin Lou	Acting Division Director	Health Sciences Authority, Singapore
Prof Robert Peterson	Executive Director	Drug Safety and Effectiveness Network/Canadian Institutes of Health Research
Barbara Sabourin	Director General, Therapeutic Products Directorate	Health Canada
Dr Sinan Bardakci Sarac	Senior Medical Officer	Danish Health and Medicines Authority, Denmark
Dr Janice Soreth	Deputy Director	US Food and Drug Administration Europe Office
Victoria Thomas	Associate Director, Patient and Public Involvement Programme	National Institute for Health and Clinical Excellence, UK
Prof Angela Timoney	Chair	Scottish Medicines Consortium
Pharmaceutical companies and consultancies		
Conny Berlin	Global Head, Statistical Safety Sciences, DS&E Statistical Safety Science	Novartis Pharma AG, Switzerland
Robert Blakie	Head of EU Regulatory Affairs	Daiichi Sankyo Development, UK
Dr Graham Burton	Senior Vice President, Global Regulatory Affairs, Pharmacovigilance and Corporate QA Compliance	Celgene, USA
Dr Nicola Course	Vice President, Global Regulatory Affairs, Europe	GlaxoSmithKline, UK
Dr James Cross	Regulatory Program Director	Genentech Inc, USA
Moira Daniels	Vice President, Regulatory, Policy, Intelligence and Labelling	AstraZeneca, UK
Dr John Ferguson	Global Head Medical Safety and Pharmacovigilance	Novartis Vaccines, USA
Dr David Guez	R&D Special Projects Director	Institut de Recherches Internationales Servier, France
Dr Christine Hallgreen	Post-Doctoral Fellow	Novo Nordisk A/S, Denmark
Dr Diana Hughes	Senior Vice President, Global Regulatory Affairs, Pharmacovigilance and Corporate QA Compliance	Celgene, USA

Dr David Jefferys	Senior Vice President, Global Regulatory, Government Relations, Public Affairs and European Product Safety	Eisai Europe Ltd, UK
Dr Mariska Kooijmans	Vice President, Safety and Benefit-Risk Management and EU QPPV	Biogen Idec Limited, UK
Dr Thomas Lonngren	Strategy Advisor	Independent Consultant
Diane Mackleston	Senior Director, Regulatory BioMedicines	Eli Lilly and Company Limited, UK
Trevor Mill	Vice President, Regulatory Affairs – Europe, Global Emerging Markets	Biogen Idec Limited, UK
Dr Becky Noel	Senior Research Scientist	Eli Lilly and Company, USA
Dr Meredith Smith	Senior Scientific Director, Risk Management, Global R&D	Abbott Laboratories, USA
Dr Isabelle Stoeckert	Head, Global Regulatory Affairs Europe/ Canada	Bayer Pharma AG, Germany
Dr Ulrich Vogel	Head, Strategic Data Analysis	Boehringer-Ingelheim GmbH, Germany
Dr Mel Walker	Senior Director Value Expert Engagement and Collaborations	GlaxoSmithKline, UK
Dr Susan Welsh	Vice President, Global Pharmacovigilance & Epidemiology, MSA TA Head, Oncology & Immunology	Bristol-Myers Squibb Co, USA
Centre for Innovation in Regulatory Science		
Nicola Allen	PhD Student	
Patricia Connelly	Manager, Communications	
Lawrence Liberti	Executive Director	
Dr Iga Lipksa	Senior Research Fellow	
Dr Neil McAuslane	Director	
Prisha Patel	Portfolio Manager	
Dr Franz Pichler	Manager, HTA Programmes	
Professor Stuart Walker	Founder	
Tina Wang	Research Analyst	