HTAi Conference, Tokyo May 2016

Informing Health Care Decisions with Values and Evidence

Panel Session Report

Multi-stakeholder Approaches to Improve Evidence-Based Decisions in Rare Diseases: Engagement of Patients and Patient Organizations

Key points

- Patients with rare diseases have unique experiential knowledge about living with a condition, current treatments, preferred treatment modes and important outcomes, in a field where other clinical evidence may be sparse.
- There are good examples of patient engagement activities in medicines' development, regulation and HTA, many of which have related to rare diseases. However, patient engagement is not consistent or widespread and its impact is not measured.
- Rare disease patient organizations want to provide information and evidence to healthcare decision-makers that will make a difference, but they need support to do this.
- Rare disease patient organizations are keen to support research and some lead major collaborative research programmes that are seeking to inform regulatory and HTA decisions.
- Capacity building is needed to enable patients to participate in multi-stakeholder technical processes, and to train stakeholders on effective mechanisms of patient engagement.

- Patient engagement has many forms and is a continuous learning process that should be developed in a coordinated way among all stakeholders in partnership with patients to ensure it can support fair and transparent decision-making.

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About HTAi

Health Technology Assessment international (HTAi) is the global scientific and professional society for all those who produce, use, or encounter HTA. HTAi has members from over 65 countries and embraces all stakeholders, including researchers, agencies, policy makers, industry, academia, health service providers, and patients/consumers. HTAi is the neutral forum for collaboration and the sharing of leading information and expertise. This panel was selected for presentation by an independent review panel.

The HTAi 2016 conference was organized in Tokyo in May 2016, gathering around 900 international delegates. The theme of the meeting was "Informing Health Care Decisions with Values and Evidence**"**. The scientific programme can be accessed at:
http://meeting.htai.org/events/tokyo2016/agenda-4023afce0ec04ab387500e87f0a6a42d.aspx

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1. Introduction

Dr Alicia Granados, Head Global Health Technology Assessment Scientific Strategy, Sanofi Genzyme

Dr Alicia Granados introduced the panel session by reflecting on the changing role of patients, at an individual and organisational level. Individual patients are no longer simply passive recipients of care; they can work in partnership with their doctors to make shared decisions about their care. Likewise patient organizations have evolved and can have a major influence in multi-stakeholder discussions about the design, planning and delivery of health research, health care services and development and evaluation of new health technologies. Such multi-stakeholder discussions can be challenging, and trustworthy relationships need to be built. However, it is not yet entirely clear how, when, where and which patients should be engaged in these processes. This panel presents practical examples of patient engagement in medicine's development, regulation and HTA, reflecting on key success factors and challenges.

2. Multi-stakeholder Approaches to Improve Evidence-based Decisions in Rare Diseases: Engagement of Patients and Patient Organizations – Industry Perspective

Ruzan Avetisyan, MD PhD, Global Evidence and Value Development Lead, Sanofi Genzyme

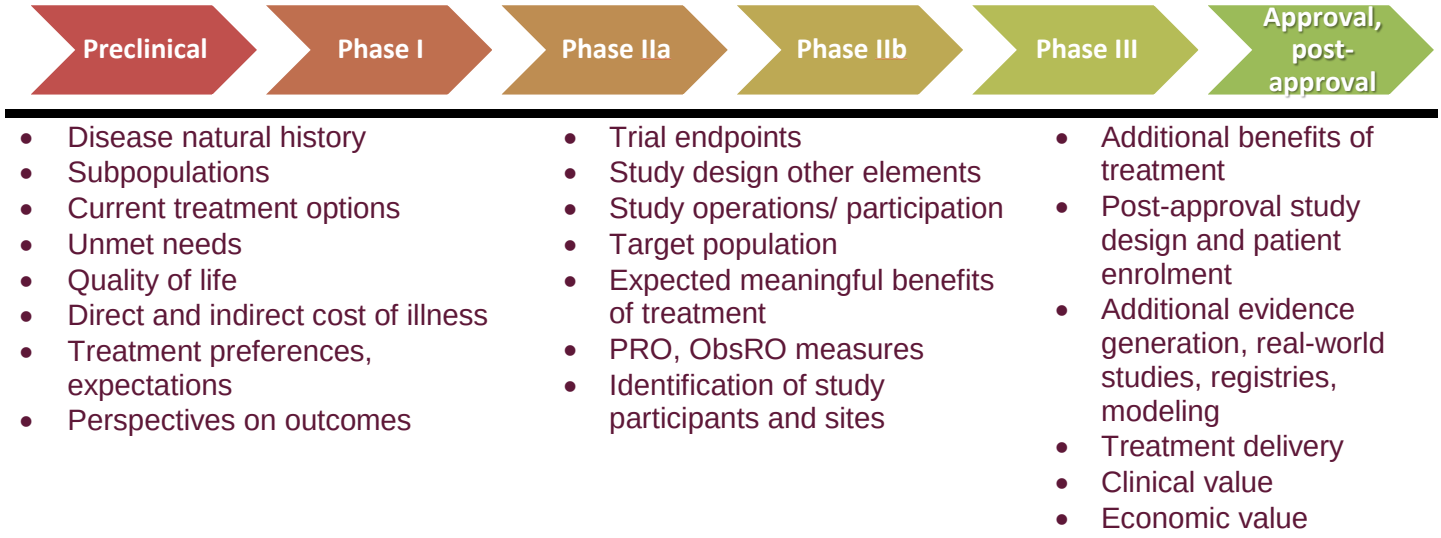
There are thousands of rare conditions, but only about 5% have approved treatments. Approximately 80% of rare conditions are of genetic origin. Many have onset in childhood and present as life-long multi-systemic disorders with heterogeneous manifestations and a variety of clinical phenotypes. There is often a lack of knowledge about the underlying pathogenesis of a rare disease and its natural history. This can lead to a delay in disease diagnosis and, in the context of research and development, causes difficulty in identification of biomarkers and agreement on appropriate clinical endpoints. Furthermore, clinical trials are challenging in rare diseases, not only due to the small numbers of patients available for study and their varied phenotypes, but because patients' homes are widely spread geographically.

There are myriad of challenges faced by various stakeholders, in health care research and decision-making for rare diseases. Engagement of patients and patient organizations has been reported to add significant value in developing and evaluating new technologies. However, these collaborations and the integration of patient input have not been consistent and widespread.

Patients with rare diseases (and their caregivers) are often experts in their own condition. They are now more informed than ever before, as a result of evolving science and technologies allowing better access to scientific knowledge. Furthermore rare disease communities have a unique interconnectedness, which arises from patient support and advocacy efforts, social media and other avenues offered by enhanced communication technologies. Many patients and patient groups are keen to move beyond simply participating in a study or lobbying politically for a treatment and want to contribute meaningfully to research and development. They want to help address the challenges of studying new treatments for rare diseases, and to do that processes need to be developed to support their engagement with industry and other stakeholders, throughout the research and development process. For these processes to be successful and sustainable, this cannot be done in isolation. Instead, multi-stakeholder alignment is needed; more specifically, efforts of patient engagement with the therapy developers, assessors and approvers of the new technology would need to be coordinated.

Sanofi Genzyme's ultimate goal is to help patients with rare diseases live a healthy and fulfilling life, by providing therapies and tools to manage their condition. This means that all its work is patient-driven and patient-focused. This is achieved by seeking patient input early in research and development, developing therapies that are most needed by patients and targeting development programs to generate evidence that is most relevant and meaningful to patients. This is described in Figure 1.

Figure 1: Value of Patient Input on Evidence and Design Concepts throughout R&D and Post-Approval



Although such patient engagement approaches should be encouraged for the development of any medicine, it is particularly important for rare diseases, where there are numerous unmet needs and limited disease related and clinical knowledge. Therefore, patients' insights starting as early as in the preclinical and phase I stages of therapy development is key. The value of patient engagement in medicine research and development can be highlighted by using the following studies in rare diseases.

Acid Sphingomyelinase Deficiency (ASMD), also called Niemann-Pick Disease Types A and B, is a rare, progressive life-threatening genetic autosomal recessive disease. It results from an inborn error of metabolism, specifically a genetic deficiency of an enzyme acid sphingomyelinase. It is a very rare condition, occurring in approximately 0.5 per 100,000 people. ASMD is a multi-systemic disorder with heterogeneous clinical manifestations and a range of phenotypes that have a major impact on the functioning and quality of life of patients and their caregivers. There are significant unmet needs associated with this condition, and currently disease management is limited to symptomatic/palliative care only. A study was undertaken by Sanofi Genzyme to understand patients' experiences of the condition in partnership with ASMD patient organizations and to develop a disease-specific patient reported/relevant outcome (PRO) measure(s) specific to ASMD reflecting concepts important and meaningful for patients.

Partnering with patient organizations, patients and families in various steps of the research was key factor. A few examples of the activities undertaken with the patient organizations include:

- reviewed aspects of the study design
- provided information (in newsletters, website, social media, meetings) about the study, to encourage patients to participate
- used their meetings as a venue to undertake the research

As a result of this collaboration, the initial qualitative research to start development of the PRO included interviews with 22 patients and/or their caregivers from around the world in just a few months. This was particularly impressive for such a very rare disease. These interviews identified health issues and concerns that were experienced by all patients and known in the medical literature (such as splenomegaly, respiratory symptoms and severe fatigue), but also others that have not been previously reported (such as some gastrointestinal and musculoskeletal problems). Collaboration with patient organizations, patients and families continues.

For another rare disease area, Fabry disease, a one-day multi-stakeholder meeting was held to discuss the medical value and clinical program plans for a new therapeutic approach as early as in Phase I of development. Patients were invited and provided valuable input on unmet needs, treatment expectations and their perspective on trial design. Although this was early in the product development life cycle, this sharing of perspectives developed a mutual understanding of needs and helped identify what outcomes were important to patients.

Sanofi Genzyme believes that there is a significant value in patient engagement throughout the medicine development process, in order to have a development program generating evidence that is most relevant and meaningful to patients, and thus continues to seek the most effective, impactful and sustainable processes. The factors that have found to have contributed to success, and barriers and challenges are shown in Table 1.

Table 1. Lessons learned from patient engagement in medicine development

Success factors	Barriers and challenges
• Openness and Transparency • Trust and Understanding • Mutual goals • Partnership • Complementary capabilities • Partner early • Culture • Internal alignment of organisation to patient-centered approach • Key point of contact with patient organisation	• Lack of definitions, methods, standards, best practices • Delays due to potential or unknown risks – Patient privacy, data confidentiality – Possible conflicts of interest – Misinterpretation as if ‘competitive advantage’ or ‘promotional’ • Lack of laws, policies or rules to govern and protect partnerships

Early and continuous patient engagement in the multi-stakeholder environment of medicines research and development can lead to more informed, targeted and effective therapy development. Additionally, coordinated efforts of patient engagement with therapy developers, assessors and approvers of the new technology would be most useful for all involved and particularly for patients and families.
There are still barriers and challenges that need to be addressed and it is important to ensure that rules and regulations are clear and supportive of this type of research effort that embodies collaboration between industry research and patients and patient organizations. Ultimately we all in the heath technology ecosystem, including health technology developers and reviewers must move from the concept of thinking that patient engagement is “nice to have” to realising that it is a “must have”.

3. Multi-stakeholder Approaches to Improve Evidence-based Decisions in Rare Diseases: Engagement of Patients and Patient Organizations - US FDA's Patient-Focused Drug Development Initiative

Theresa M Mullin PhD, Director, Office of Strategic Programs, Food and Drug Administration, Center for Drug Evaluation and Research

The Food and Drug Administration (FDA) evaluates benefit-risk taking account of five key areas outlined in Table 2.

Table 2. Benefit-Risk considerations

Unmet medical need (Clinical context)
Severity of condition (Clinical context)
Effectiveness/efficacy (Benefit)
Safety (Risk)
Risk management plans

Patients clearly have perspectives that could contribute to discussions of benefit-risk and in the past individual patients have primarily been involved via the Patient Representative Program and have participated in FDA Advisory Committees for some products, but a more systematic approach was called for by patients. So, in the fifth authorization of the Prescription Drug User Fee Act (PDUFA V) it was agreed that the FDA would establish a Patient-Focused Drug Development (PFDD) initiative. This aims to more systematically gather patients' perspectives about their condition and available therapies. These perspectives are intended to inform understanding of the context for medicine development, benefit-risk discussions and regulatory decisions about specific products.

For the PFDD, FDA is planning to complete 24 public meetings on different diseases over the course of the five-year PDUFA authorization period. Half of these meetings relate to rare diseases (chronic fatigue syndrome, narcolepsy, sickle cell disease, pulmonary arterial hypertension, inborn errors of metabolism, hemophilia, idiopathic pulmonary fibrosis (IPF), Chagas disease, Huntingdon's disease, Alpha-1 antitrypsin deficiency, non-tuberculosis mycobacterial lung infections, hereditary angioedema).

The meetings have similar formats but are tailored to address specific issues relevant to each disease. The meetings focus on questions about:

- burden of disease (such as symptoms that have most impact, changes in symptoms over time, what worries you most)
- burden of treatment (such as what is current treatment, how well does it work, what are the downsides, what would you look for in an ideal treatment).

The output from the meetings is "The Voice of the Patient" public report, which summarizes the input provided by patients and patient representatives[1].

One example is the discussion of IPF, which is a progressive fibrosis of the lung that has a median survival of 3-5 years after diagnosis. Forty IPF patients or patient representatives attended the meeting in person and 20 joined via webcast. They clearly described the major issues associated with uncontrollable, prolonged coughing attacks, difficulty in breathing, fatigue and various resulting impacts on work and home life. They also described psychological issues related to the stigma from other peoples' perceptions of their coughing

[1] http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm368342.htm

and the isolation this caused. The burdens associated with oxygen therapy and steroids were highlighted, as well as the major impact of lung surgery. In response to questions posed by the facilitator, IPF patients who participated in the meeting expressed the view that an ideal treatment would slow disease progression, improve symptoms and quality of life and oxygen therapy could be made more convenient to use. As a result it was recognised that the traditional physiological measures measured in clinical trials, such as pulmonary capacity, do not fully capture the potential benefits of a treatment. The Voice of the Patient report for IPF was published in March 2015[2] and two new treatments for IPF were approved by the FDA in October 2015.

These PFDD meetings have demonstrated that patients with rare diseases are experts on what it is like to live with their condition. Their "chief complaints" may not be factored into medicine development plans as outcomes and so they are keen to help develop and evaluate new treatments.

As a result of this PFDD initiative, FDA will produce guidance on how to conduct such meetings with patients. In addition, it will continue to engage with other stakeholders to discuss more methodologically sound, practical, approaches that systematically collect patients' input, in order to inform medicine development and benefit-risk assessment. The aim will be to produce guidance for patient communities, researchers and medicine developers on pragmatic and methodologically sound strategies to gather and use patient input.

4. Multi-stakeholder Approaches to Improve Evidence-based Decisions in Rare Diseases: Engagement of Patients and Patient Organizations - Regulators in the EU and the role of patients

Dr Jane Moseley, Scientific Officer, Scientific Advice, European Medicines Agency

The European Medicines Agency (EMA) has been evolving the ways in which it includes patients in its work at strategic and operational level[3].

At policy level, there is active commitment to patient engagement led by the EMA Chief Executive. Guido Rasi has said "patients are at the heart of what we do and we should be constantly looking for new routes to engage patients in our decision making activities and we should recognize the value of patient engagement." As a result, patient engagement is one of the eight principle activities of the organization.

This commitment is also demonstrated in the European Regulatory Network for Medicines Strategy, which states that "Patients are the ultimate beneficiaries of medicines and their voices must be heard. We should explore how the perspectives of patients and society can be brought into innovation and regulation at European and national levels."

EMA engages with patients to discuss product specific issues and with patient organizations to discuss processes and strategic issues. Processes for engagement are presented in the

[2] http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM440829.pdf

[3] http://www.ema.europa.eu/ema/index.jsp?curl=pages/partners_and_networks/general/general_content_000317.jsp&

revised Patient Engagement Framework[4]. This framework supports systematic patient engagement across all EMA activities (scientific advisory groups, working parties, committees, management board, communications). It describes the underpinning processes for engagement including selection criteria for different activities, declarations of interests and confidentiality agreements.

There is much experience from pilots and procedures. Amongst the range of activities in this area are:

Parallel scientific advice between regulators and HTAs – 11 cases where patients were engaged, 70% of which related to rare diseases. Examples of issues raised by patients in scientific advice include:

- Neuromyelitis optica (NMO) - debilitating nature of disease and feasibility of a randomized controlled trial (RCT)
- Systemic sclerosis – spectrum of symptoms
- Cystic fibrosis – practical issues associated with taking current medicines
- Metabolic disease – importance of proposed outcomes in confirmatory trials.

Preference elicitation – piloting quantitative approaches with patient panels, regulators and healthcare professionals. The elicitation processes were quite challenging and took time and so may not fit well into the regulatory timetable. However, it suggested that different stakeholder groups may have different preferences (e.g. regulators and healthcare professionals vs patients). Further work is being undertaken in this area by the EMA.

Patients involved in oral explanations - sharing their experiences of living with the condition. Three pilots concluded that for effective engagement, patients need good early contact, more focused questions and expectations need to be managed. One example that demonstrated the value of such engagement was for Scenesse, a treatment for intolerance to sunlight, which was licensed under exceptional circumstances because it was RCTs were difficult to undertake as patients were unwilling to expose themselves to sunlight.

Greater use of PROs in benefit-risk assessment – particularly for cancer treatments in order to recognise the importance of patients' perspectives.

Patients require practical support to engage effectively in these processes and so EMA offers group training and one-to-one support for individuals in advance of a meeting. Reimbursement is also provided for travel and subsistence.

Challenges to engaging patients include:

- identifying relevant patients especially in shorter regulatory timeframes
- managing patients' expectations
- supporting patients to overcome anxieties about their contribution and encouraging them to give their unique experience
- deciding whether to include individuals or undertake surveys or other research to get a range of views
- the technical language that is used in many meetings
- making best use of information technology and social media
- time and resources required
- measuring impact of patient engagement.

[4] http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500018013

Despite these challenges, experience at EMA shows the intrinsic value in engaging patients across all its activities. It supports good governance, transparency and education, and also creates a unique picture of living with a disease that cannot be captured via traditional evidence from controlled clinical trials. So for EMA, it is not a question of "if" patients should be engaged, but "how" best they can be engaged.

5. Multi-stakeholder Approaches to Improve Evidence-based Decisions in Rare Diseases: Engagement of Patients and Patient Organizations – HTA Perspective

Francois Meyer MD, Advisor to President of Haute Autorité de Santé, Shaping European Early Dialog, Project Lead

Haute Autorité de Santé is beginning to involve patients in its medicine appraisal process. There are challenges because it is a rapid 90-day process, but the organisation is seeking to learn from the HTAi Interest Group for Patient/Citizen Involvement in HTA and the work of other HTA bodies such as those in Canada and the UK.

The European Network for Health Technology Assessment (EUnetHTA) was established in 2006 to avoid duplication in HTA work, share information and methods and harmonize evidence requirements. The ultimate goal is to achieve timely access to appropriately evaluated health technologies, whilst ensuring health service sustainability. All this needs to be done in cooperation with regulators and other stakeholders. Patients are an important stakeholder and they have a particular role to play in harmonizing evidence requirements.

EUnetHTA is about to enter its third Joint Action (JA) of Member States, which will continue the work of previous JAs to support generation of the most appropriate evidence to inform HTA. This is particularly important for rare diseases, where the small populations, lack of natural history data and heterogeneity of diseases and treatment effects means that demonstrating added value can be challenging.

Between 2012 and 2015, 23 Early Dialogue processes were undertaken between several HTA bodies and medicine and device manufacturers, with some instances of parallel advice with EMA. These discussed evidence generation plans for specific products in relation to HTA. Twelve were conducted as part of the EUnetHTA JA2 and eleven in the Shaping European Early Dialogues (SEED)[5] project. Eight of the SEED processes were for medicines and three were for rare diseases.

These Early Dialogues were based on the principle that "improving and anticipating the collection of clinical evidence before licensing (i.e. at the end of phase II of a clinical trial for a medicinal product) would enable easier and quicker HTA processes after licensing, leading to quicker decisions on uptake of new products. Early Dialogues are therefore supposed to bring benefit to HTA authorities, regulators and individual volunteering companies"[6].

As patients acknowledge the need to reduce the risk of inadequate data and increase the speed of decision-making, they wanted to contribute to these Early Dialogues. So in partnership with EURORDIS (a member of the EUnetHTA Stakeholder Forum), a process was developed to involve patients in each SEED meeting. Reflections on patient

[5] http://www.earlydialogues.eu/has/#

[6] SEED project documentation: http://ec.europa.eu/chafea/documents/health/tenders/2013/EN/EAHC_2013_09_Specifications.pdf

engagement in Early Dialogues were fully reported at HTAi 2015[7]. Key findings were that patient engagement enriched the dialogues and provided important insights on issues such as the diversity of healthcare provision in Europe, the clinical trial population, possible impact of the medicine and important outcomes. There were issues relating to the resources required, limited time to identify appropriate patients and read papers, development of support and training needed to ensure patients could participate in the technical discussions of the Early Dialogue and questions about impact of involvement. Patients' input was particularly important when discussing the choice of endpoints and practical aspects about treatment administration.

The Early Dialogue process, and patient engagement in it, developed as experience was gained during the SEED project and these learnings will be used to develop new Early Dialogue processes in EUnetHTA JA3 that started in June 2016. The other important area of new work in JA3 will be to coordinate collection of post-launch data across several countries after an HTA finds uncertainty for a promising health technology. Cooperation will start with an agreement on the definition of the common research question, and go further with an agreement on protocols defining common core outcome datasets. For data collection, the use of registries will be particularly considered. This will link in with EMA work such as pilots on adaptive pathways pilots on the use of registries and EUnetHTA will learn from their processes for patient engagement. Consequently, it is hoped that meaningful patient engagement will also be developed in this field of EUnetHTA's work.

6. Multi-stakeholder Approaches to Improve Evidence-based Decisions in Rare Diseases: Engagement of Patients and Patient Organizations – Patient Perspective

Durhane Wong-Rieger PhD, President and CEO, Canadian Organization for Rare Diseases

This panel session has presented the best of best practices in the US and Europe. Unfortunately this isn't what generally happens for rare diseases – most patients don't know what's being developed, how it is developed or how it is assessed. The great promise of the various initiatives to encourage medicine development for rare diseases is not being delivered; then when a product gains a marketing authorization, challenges to access arise as a result of HTA as shown in Table 3.

Table 3. Challenges of HTA for rare disease products

Patient population may be small (rare conditions, subtypes) so outcomes are less robust
Cost of testing unaffected patients means that there is a low overall return on investment.
Regulatory approval may be based on less definitive outcomes (surrogate, biomarkers, short-term measures) that aren't sufficient for HTA
Tend to have high R&D costs, high uncertainty, high cost of product
Incremental value added (effectiveness, side effects, tolerability, improved quality of life) may not be sufficiently demonstrated for the incremental cost
Reimbursement strategies may be established to reduce uncertainty in safety, clinical effectiveness, appropriate use and budget impact that restrict patient access

7 http://www.htai.org/fileadmin/HTAi_Files/ISG/RegulatoryInteractions/HTAi_SEED_Panel_Report_final.pdf

When considering challenges of fair access to treatment, there is no universal rule of justice, it depends on values, which may vary widely (egalitarian, utilitarian, libertarian, socialist, capitalist etc), so patient input is crucial.

Patient engagement is essential at all levels to optimize patient and system outcomes by:

- helping individual patients to make appropriate treatment choices and adhere to optimal use
- ensuring patient relevant outcomes, real-world benefits and adverse effects are addressed in healthcare and medicine development
- agreeing values and rules at healthcare policy level that will ensure equitable and sustainable resource allocation.

The challenge is that such meaningful engagement rarely happens and patients feel on the outside of decision-making. If they are invited to join in multi-stakeholder meetings, they don't feel that they are respected or a partner. To achieve such partnership requires substantial training for patients to explain the role of the committee, its processes and what they will be expected to contribute, but also other members of the committee need training to understand how they can facilitate patients to contribute. Furthermore many activities require substantial resources from a patient group and although most regulatory and HTA bodies reimburse travel expenses, few provide payment for the time taken to prepare or provide input.

There are some emerging good practices as outlined in this panel by the PFDD and early and continuous dialogue initiatives. Other companies are also engaging rare disease patient groups to provide advice on clinical study design and PRO development. Regulators are including patients on advisory committees and seeking patient testimonials and input from patient groups. Some HTA bodies are including public partners on appraisal committees, encouraging patient group submissions and using citizens' councils to advice on social value judgements as shown in Table 4.

Table 4. Examples of optimal representation of patients in HTA

Consultee, Informant Input through Citizens Council, Task Force Collect Information: Survey, Poll, Focus Group Form of Information: Answers, Opinions, Deliberation Impact: Advise, Discretionary Examples: NICE Citizens Council, IQWiG, Ontario Citizens Council	**Patient Representative** Input through Committee, Board, Council Collect Information: Experts, Deliberation Form of Information: Analytical, Guidelines Impact: Varied, Based on Guidelines Examples: NICE, AU MASC, CEDAC, pERC Ontario CED
Individual Patients Input through Clinical Trials, Testimony Collect Information: QoL, PROs, Impact Statement Form of Information: Ratings, Qualitative Impact: Varied, Emotional Suasion Examples: SMC, IQWiG Quebec conseil, BC Pharmacare,	**Patient Groups** Input through Submissions Collect Information: Written, Oral, Meetings Form of Information: Qualitative Statement Degree of Impact: Response Examples: NICE, SMC AU MASC, CADTH, pCODR, Ontario CED

In reality the picture of patient engagement in HTA is patchy internationally, with no engagement in Mexico and South Africa. In Brazil, Poland, Netherlands and South Korea, patients are invited to provide comment on draft HTA reports, whereas in Taiwan and Thailand patients can be invited to participate in committees that select topics or appraise products. In Scotland and Canada, patient groups can make submissions that are presented to the appraisal committee by a public partner. In Germany and England patients are involved in the scoping of the HTA research and participate in the appraisal process, but do not have a vote in the final decision.

The really disappointing aspect of this picture of patient engagement in HTA is that it has changed little over the past five years, despite efforts by the HTAi Interest Group for Patient/Citizen Involvement in HTA to share good practices internationally and promote Values and Quality Standards for Patient Involvement in HTA[8].

Patients can provide valuable input over the whole life cycle of product development, evaluation and optimization of use, but they need to be fully informed and prepared. Continuous dialogue is needed with patients about the processes of patient engagement. Patients need training on technical aspects of medicine development, regulation and HTA. Manufacturers, regulators and HTA staff and all their committee members need training on how to engage patients. This will develop productive partnerships that can promote fair, transparent decision-making.

7. Discussion

Marleen Kaatee stressed the importance of training for patients and noted the value of the EUPATI course[9]. She encouraged developers to consider rare diseases that have no treatments and noted that it is important to consider a wide range of patients' perspectives, particularly across countries. She highlighted the lack of public knowledge about the process of clinical trials and the benefits of being involved. She ended by stressing the challenge of funding a patient group given the potential conflicts of interest that are perceived if money is taken from product developers.

As there was limited time for discussion, a follow-up meeting was held with rare disease patient representatives attending HTAi, who were given the opportunity to present good practice examples of patient engagement.

8. Case Studies from Patient Representatives

8.1 Making a real difference to the development of a new medicine Marleen Kaatee, PSC Patients Europe

Primary sclerosing cholangitis (PSC) is a rare liver disease, currently without a cure. Here's a personal story of how I engaged with the patient community to understand their issues and used these to influence a medicine developer.

Nor-ursodeoxycholic acid (norUDCA): In the PSC community, many had heard of the name of this potential new medicine, but what is this new medicine and how does it work? Is it similar to the already available UDCA (aka "urso"), as the name sure looks similar? PSC Patients Europe decided to contact one of the members of Team norUDCA to see if an interview was possible to hear more about it and to address some of the questions within the PSC Community. Prof. Dr. Michael Trauner, M.D. and researcher at Chair of Gastroenterology and Hepatology at the Division of Gastroenterology and Hepatology at Medical University of Vienna (Austria), immediately responded and invited me to come to Vienna for an interview.

[8] http://www.htai.org/interest-groups/patient-and-citizen-involvement/pcig-home/values-and-standards.html
[9] http://www.patientsacademy.eu/index.php/en/edu

Beforehand, PSC Patients Europe checked what PSCers exactly wanted to know about norUDCA (aka “nor-urso”), by giving over 3.000 PSC forum members worldwide the opportunity via various Facebook forums to post any questions they had about nor-urso. There were 60 voters from UK, NL, USA and Australia, 7 posts and many likes, resulting in ten added questions to the interview. Shall we call them patient-reported questions (PRQs)? Much to my surprise, approx. 20% of the questions were related to the actual taking the existing medicine, to be more precise: the swallowing of UDCA. Personally I don’t have any trouble taking the meds and would never have guessed it to be an issue for so many.

After collecting the questions and also making a ‘wish list’ from PSC patients, I flew to Vienna to have the interview at the Vienna Medical University. Prof. Trauner and Dr. Emina Halilbasic, busy as always, gave me a warm welcome and gave me the pitch on norUDCA. Complicated stuff at times, yet very interesting to hear about the in’s & out’s. Once finished, Prof. Trauner gave me the opportunity to ask the questions from the PSC Community. My first question was if the new medicine would be available in liquid form. It hadn’t crossed his mind to do so and he was curious about the reasoning behind it. After explaining the swallowing problems quite a few PSCers indicated, he immediately explained to me why norUDCA wasn’t going to be available in liquid form: due to shelf life and because of the formulation (not every substance can be available as a liquid).

The next question was if Prof. Trauner had ever tried the medicine himself. I admit, it might be a weird question, but the pills can be so bitter, many don’t like taking them. The taste is also due to the fact we are dealing with synthetic bile, not much could be done about that, most probably. Last but not least, I asked him why the current pill was “sandpaper”, meaning the large pills are hard to swallow due to the exterior texture of the pill. “That can be solved”, Prof. Trauner said immediately, “There can be a coating on the pill, which will cost 1 to 2 Eurocents per pill extra. Let me take care of that”.

8.2 The Patient Reported Outcomes, Burden and Experiences (PROBE) study – Phase 1 results show PROBE study methodology feasible, Mark W Skinner PhD, Institute for Policy Development Ltd

Government and healthcare payers increasingly value data based on patient-centered outcomes research as part of the overall evaluation of value for high-cost care and treatment of diseases, such as hemophilia. This emerging dimension of the healthcare environment presents a significant opportunity and urgent need to improve patient organizations' ability to collect and interpret relevant outcomes data.

When the first new products for hemophilia were assessed by an HTA body in Sweden, patient groups were not sufficiently prepared to present information that could influence the decision making. It was recognized that more robust patient reported data would improve advocacy efforts to build comprehensive care programs, promote home treatment and implement preventative treatment regimen. This would enable advocacy to move beyond emotion and anecdote to be grounded in real-world patient experiences and evidence.

So the PROBE study was initiated; a global team of investigators leading an international study that will develop a structured mechanism to investigate outcomes that patients deem relevant to their care. PROBE is an independent, investigator-led, research project supported by the National Hemophilia Foundation and with grant / research support from a range of funders.

The Patient Reported Outcomes, Burdens, and Experiences (PROBE) study will develop a low cost, easily administrable inventory for collecting patient self-reported outcomes, burdens and experiences of living with hemophilia. It is hoped that this robust tool will enhance the patient voice in health care decision-making.

The PROBE questionnaire incorporates EQ5D-5L, with additional domains identified as important by patients, including pain, independence, schooling, employment, relationships and activities of daily living. Disease characteristics are also collected including treatment, bleeding history and joint status. The questionnaire is currently being refined and tested for face validity, relevance, clarity and completeness.

The phase I fieldwork is complete, with 704 responses received from 430 hemophilia patients (stratified as mild, moderate and severe) and 274 controls in 17 countries. More than 70% of patients could complete the questionnaire in less than 15 minutes. Interesting findings are emerging about important patient outcomes, such as range of motion and how that links to clinical definitions of target joints.

Phase I has shown the feasibility of patient-centered generation of health outcome data and the value of using questionnaires developed with patients to collect information about their disease in language that they would use.

The next phases of this research will be to assess the reproducibility, discrimination and responsiveness of PROBE by comparing different treatment delivery modalities, regimens and outcomes. The aim is that the PROBE questionnaire will provide valuable global perspectives of patient reported health outcomes and experiences in hemophilia.

8.3 Investing in research for Neuroendocrine Tumours. Simone Leyden, CEO Unicorn Foundation

Neuroendocrine tumours (NETs) is the umbrella term for a group of unusual, often slow-growing cancers. These tumours develop from secretory cells found throughout the body, which are concentrated in the gastrointestinal system, lung, pancreas, ovary and testes. As the early symptoms mirror symptoms of more common conditions diagnosis is often delayed for many years, by which time more than 50% of patients have secondary cancer.

In a relatively small country like Australia, patient representatives have good relationships with clinicians, so this is a good building block for collaboration.

There are several treatments for neuroendocrine tumours (NETs) but none are curative. One effective treatment for slowing, and in some cases reducing tumor growth is Peptide Receptor Radionuclide Therapy (PRRT). Although this treatment has been used with varied success in some Australian centres for over 10 years, funding is still varied and not guaranteed due to the lack of clinical trial data. As with most countries the Australian HTA system relies on clinical trial data and sponsor submissions for listing of treatments for reimbursement. Currently patients can access PRRT in some states of Australia only if all other listed treatments have failed. The discrepancy in access means that some patients pay in excess of $30,000 for 4 cycles of treatment whilst other patients in other states can access the treatment at no charge. This creates inequity in the health system and causes great apprehension amongst the patient community.

With the absence of a sponsor for PRRT, the Unicorn Foundation (patient advocacy group) set about gathering the trial evidence needed by seed funding the CONTROL NETs clinical trial through the Australasian Gastro Intestinal Trials Group (AGITG). With the help of patients, fundraising events and corporate donations the trial is currently recruiting 100

patients in three states. In order to continue recruitment to the trial, government funding is being sought through the National Health and Medical Research Council (NHMRC). This trial was the result of the Unicorn Foundation working directly with clinicians to find out what the need and the barriers were to access of this treatment for NET patients, with the results of the trial eagerly awaited by NET cancer experts around the world.

9. Roundtable discussion

The presentations in the panel have demonstrated that it is important to develop systematic, learning processes for patient engagement over the whole life cycle of medicine development and evaluation/assessment.

The discussions with patient representatives have given a range of practical examples of not just how patients can be engaged in clinical research, but how they can lead research in collaboration with clinicians and researchers.

Issues

- The guidelines for industry to support patient engagement (in protocol development, PRO development etc) are not clear and codes of conduct are interpreted differently by different companies. The regulatory position on the direct engagement of patients in medicine development needs to be better understood.
- The case of repurposing treatments for an unlicensed condition could be an ideal candidate for adaptive pathways, avoiding phase I and perhaps phase II, to expedite approval.
- It is unclear how HTA works (or does not work) for rare disease treatments.
- Patient groups need to know how they can develop reliable information/evidence that can be used by a range of stakeholders (manufacturers, regulators, HTA bodies).

10. Conclusion

The panel and subsequent presentations from patient representatives demonstrated the value of patient engagement throughout the life cycle of medicine development and assessment to provide insights into the burden of the condition, treatments and outcomes that matter to them. There were several examples of good practice, but these are not widespread or consistent. More needs to be done to build the capacity of patients to contribute to medicine development, regulation and HTA and to train other stakeholders in good practices in patient engagement.