Integrating the patient perspective in the assessment of benefits and risks of medicines

WORKSHOPS - SESSION III
Wednesday, 12 November 2014
15:00-16:00

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Risk Benefit in Medical Product Development

ISPOR, Amsterdam, 12th November 2014

Presented by:
Donald L. Patrick, PhD, MSPH, University of Washington, Seattle, WA, USA

Disclaimers

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What is Benefit Risk?

• Balancing the desired effects or benefits of a medical product against undesired effects or risks
• Key issues of benefit include results of clinical trials and clinical meaning of primary and secondary endpoints
• Key issues of risk include adequacy of safety database, severity and reversibility of adverse events, and potential for sub-optimal management

Patient Perspective

• “Of the 7,000 known rare conditions, only five percent have a disease-specific treatment. Many patients and families affected by rare diseases are willing to accept greater risk. Creating an opportunity for patients to contribute to benefit-risk assessments will foster increased research and therapy development.”
• How best to do this? Structured preference studies, qualitative research, case studies, survey data?
FDA Perspective

- "Patients who live with a disease have a direct stake in the outcome of FDA's decisions and are in a unique position to contribute to the understanding of their disease" (FDA Notice in the federal register, April, 2013)

- "There are currently few venues in which the patient perspective is discussed outside a specific product’s marketing application review" (FDA- Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making, February 2013)

FDA’s Benefit-Risk Framework

<table>
<thead>
<tr>
<th>Decision Factor</th>
<th>Evidence and Uncertainties</th>
<th>Conclusions and Reasons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analysis of Condition</td>
<td></td>
<td></td>
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<tr>
<td>Current Treatment Options</td>
<td></td>
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<tr>
<td>Benefit</td>
<td></td>
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<tr>
<td>Risk</td>
<td></td>
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<tr>
<td>Risk Management</td>
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<tr>
<td>Benefit-Risk Summary Assessment</td>
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</tbody>
</table>
EMA Perspective

“As patients live with their condition on a day-to-day basis, their views on the therapeutic effect of a medicine and its impact on their quality of life - particularly when these are balanced against the risks - may differ from those of other stakeholders,” says Guido Rasi, EMA Executive Director. “Involving patients in CHMP discussions brings the patients’ voice into the decision-making process and ultimately contributes to the safe and rational use of medicines.”

Payor Perspective

• Unlike regulators, payors must consider cost
• Methods include budget impact, cost benefit, cost effectiveness
• Evidence weighed by the payor to balance benefit-risk and determine reimbursement
• Transparency differs for differ payors
• Many HTA methods used to assist payors
Challenges

- Patient-centered benefit risk assessment: not straightforward how or when to engage patients and which patients to engage
- Increasing use of quantitative methods requires simple communication
- Increased transparency desirable
- Benefit risk assessment only as good as the evidence weighed using patient, provider and payor perspectives and communicated to providers
The patient voice in the benefit-risk assessment of medicines

ISPOR, Amsterdam, 12th November 2014

Presented by:
Carla Dias Barbosa, Associate Research Director, Patient-Centered Outcomes Mapi HEOR

Patient’s role is changing

- Traditional benefit-risk (B-R) assessment of medicines relied primarily on expert opinion and evidence based medicines
- Patients today have more knowledge and influence than before
- Shift in the product development paradigm
- Patient voice is a critical component of B-R assessment during new drug development
Patient involvement in drug development process

- Assessment of a drug’s benefits and risks (B-Rs) involves analysis of the medical condition in question and the current range of available treatment alternatives
- Patients are the final users; taking into consideration their point of view should avoid drug development failure or to miss expected market penetration
- Traditional approach to patient input generally relied on feedback received at regulatory committee meetings
- Appraisal process could benefit from a more broader and systematic approach to obtaining patient viewpoint on their medical condition and unmet medical need by therapeutic or disease areas (Bi-directional exchange – dialogue not monologue)

FDA initiative
FDA’s Benefit-Risk Framework*

<table>
<thead>
<tr>
<th>Decision Factor</th>
<th>Evidence and Uncertainties</th>
<th>Conclusions and Reasons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analysis of Condition</td>
<td>Sets the context for the weighing of benefits and risks:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• How serious is this indicated condition, and why?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• How well is the patient population’s medical need being met by currently available</td>
<td></td>
</tr>
<tr>
<td></td>
<td>therapies?</td>
<td></td>
</tr>
<tr>
<td>Current Treatment</td>
<td>Characterize and assess the evidence of benefit:</td>
<td></td>
</tr>
<tr>
<td>Options</td>
<td>• How compelling is the expected benefit in the post-market setting?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• How clinically meaningful is the benefit, and for whom?</td>
<td></td>
</tr>
<tr>
<td>Benefit</td>
<td>Characterize and assess the safety concerns:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• How serious are the safety signals identified in the submitted data?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• What potential risks could emerge in the post-market setting?</td>
<td></td>
</tr>
<tr>
<td>Risk Management</td>
<td>Assess what risk management (e.g., labeling, REMS) may be necessary to address the</td>
<td></td>
</tr>
<tr>
<td></td>
<td>identified safety concerns</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Benefit-Risk Summary and Assessment</td>
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</table>

Presented at DIA meeting October 29-30, 2014 Washington, DC, USA
« Patient Engagement throughout the Full Spectrum of Drug Development »
Patient Focused Drug Development (PFDD) initiative under PDUFA V*

- Patients are uniquely positioned to inform FDA’s understanding of the disease impacts and current treatment options
  - Patient perspective helps inform FDA understanding of the therapeutic context for the benefit-risk assessment
  - Input can inform FDA’s oversight both during drug development and during FDA review of a marketing application

- PFDD offers a more systematic way of gathering patient perspective on their condition and treatment options
  - FDA is convening at least 20 meetings on specific disease areas in Fiscal Years (FY) 2013-2017
  - Meetings can help advance a systematic approach to gathering input

*Fifth authorization of the Prescription Drug User Fee Act

PFDD meetings for FY2013-2015

**FY 2013 (Conducted)**
- Chronic fatigue syndrome/myalgic encephalomyelitis
- HIV
- Lung cancer
- Narcolepsy

**FY 2014 (Conducted)**
- Sickle cell disease
- Fibromyalgia
- Pulmonary arterial hypertension
- Inborn errors of metabolism
- Hemophilia A, B, and other heritable bleeding disorders
- Idiopathic pulmonary fibrosis

**FY 2015 (Conducted)**
- Female sexual dysfunction

**FY 2015 (to be announced)**
- Alpha-1 antitrypsin deficiency
- Breast cancer
- Chronic Chagas disease
- Functional gastrointestinal disorders
- Parkinson’s disease and Huntington’s disease

http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm347317.htm
Patient Focused Drug Development (PFDD) Meeting format

- Meetings follow similar design, but tailored to disease context
  - Takes into account current state of drug development, specific interests of the FDA review division, needs of the patient population

- Discussion elicits patients' perspectives on their disease and on treatment approaches

- Patient input is generated in multiple ways:
  - Patient panel comments followed by facilitated discussion with patients in the audience
  - Web participants can submit comments and respond to poll questions
  - A FDA facilitator leads the discussion and a panel of FDA staff ask follow-up questions

Key outcomes from FDA’s PFDD meetings

- After each meeting, FDA prepares a « Voice of the Patient » report which captures key patient inputs/viewpoints on their individual personal perspectives, experiences, disease symptoms, impacts and treatment approaches
  - Chronic Fatigue Syndrome /Myalgic Encephalomyelitis, lung cancer, HIV, Sickle Cell, Narcolepsy reports have been published*
  - *http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm368342.htm

- Each individual meeting report serves to support FDA staff in conducting B-R assessments for products under review and advising drug sponsors on their drug development programs

- Patient input can also serve to identify specific areas of unmet need in the specific patient population under investigation and potentially identify clinical outcome measures which may be developed for clinical trials
EMA initiative

EMA - Benefit Risk Methodology Project (1)

- EMA began the B–R Methodology Project in 2009
- Purpose: To develop and test tools and processes for balancing multiple benefits and risks as an aid to informed regulatory decisions about medicinal products
- Goal: Enhance transparency and consistency of the B–R assessment decision-making process, and facilitate the communication of the rationale for each decision, both within the regulatory system and to the public.
EMA - Benefit Risk Methodology Project (2)

- The project consists of five consecutive work packages (4 completed to date)

<table>
<thead>
<tr>
<th>Work Package</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Describing the BRA models already being used in the European Union’s regulatory network</td>
<td>✓</td>
</tr>
<tr>
<td>2) Assessing the suitability of the current tools and processes used in BRA</td>
<td>✓</td>
</tr>
<tr>
<td>3) Field-testing the most appropriate models in five European medicine regulatory agencies</td>
<td>✓</td>
</tr>
<tr>
<td>4) Refining the most suitable models for use in medicines regulation to create a new benefit-risk tool</td>
<td>✓</td>
</tr>
<tr>
<td>5) Training module for European assessors to use the final tool</td>
<td>Started March 2012</td>
</tr>
</tbody>
</table>

Pilot project to involve patients in assessing B-Rs of medicines (1)

- New pilot project announced in September 2014 (EMA/372554/2014 – rev. 1)
- Patients put at the heart of B-R discussion for marketing authorization evaluation
- Patients invited to present their views on drugs for which there is an unmet medical need and where CHMP still have concerns or doubts
- Patients will be invited to give their views on whether to recommend the withdrawal, suspension or revocation of a marketing authorization, or a restriction of indication of an authorized medicine
- The pilot project will run for 1 year
Pilot project to involve patients in assessing B-Rs of medicines (2)

- The first medicine to be included in the pilot project is the orphan drug afamelanotide; It is intended for the treatment of erythropoietic protoporphyria (EPP), a rare genetic blood disorder which causes an absolute intolerance to light
  - An estimated 5,000-10,000 patients worldwide have EPP
  - No authorized medicine for this condition

- At the CHMP’s September meeting in 2014, two patients with EPP shared their experiences of living with this condition and answered specific questions

- On 27th October, 2014 Australia’s Clinuvel Pharmaceuticals Ltd announced their drug SCENESSE® (afamelanotide) received its first approval from the EMA

- First time patients were invited to participate directly on B-R, though patient representatives are already involved in many other EMA related activities, including their Pharmacovigilance Risk Assessment, Paediatric and Advanced Therapies committees.

Initiative from one patient advocacy organization

Patient advocacy organization for Duchenne muscular dystrophy (DMD)
Benefit-Risk Assessments in Rare Disorders

- In 2013 Parent Project Muscular Dystrophy (PPMD) – a leading patient advocacy organization for Duchenne muscular dystrophy (DMD) proposed a collaboration with the FDA to initiate a rare disease B-R pilot program using DMD as the initial therapeutic area
- The PPMD led a study to measure caregiver preferences for potential benefits and risks of emerging therapies and proactively inform the FDA’s B-R assessments (Peay HL et al., Clin Ther. 2014)
- The PPMD produced a whitepaper entitled ‘Benefit-Risk Assessments in Rare Disorders: The case for therapeutic development in Duchenne Muscular Dystrophy as the prototype for new approaches’
- To facilitate future clinical trials in DMD, the PPMD drafted a policy guidance for FDA (June 2014) (first guidance drafted by patient advocacy organization)

Final Comments

- Patient voice is important, yet the decision in the drug approval process rests with the regulators
- Informed patients are able to provide invaluable feedback
  - Bi-directional exchange – dialogue not monologue
- Patient opinion of “acceptable risk” is subjective thus it can and does often vary from physician or indeed regulators opinions
- Movement from an ad hoc to systematic involvement throughout drug development life-cycle
  - How to integrate the patient’s voice with maximum importance?
  - How best to adjust regulatory procedures and practices to support this amalgamation?
  - How best to exhibit the supplementary value of assimilating the patient’s voice in regulation?
- Patients experience the B & Rs so their preferences should be paramount if decisions are to be patient-centered and in their best interest
IMI PROTECT WP5:
What has been our experience in integrating the patient perspective in the benefit-risk assessment of medicines?

ISPOR, Amsterdam, 12\textsuperscript{th} November 2014

Presented by:
Kimberley Hockley, MPH, PhD

\textbf{IMI PROTECT}
\textbf{Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium}

Led by the EMA with 31 public and private partners, 2009-2014 (www.imi-protect.eu)

\textbf{Aim}: to strengthen the monitoring of the benefit-risk of medicines.

\textbf{Work Package 5}:
Develop methods for continuous benefit-risk monitoring of medicines, by \textit{integrating data on benefits and risks} from clinical trials, observational studies and spontaneous reports.
The licensing challenge

- Task of regulators: to make good and defensible decisions on best available evidence
- How to justify and explain these decisions to stakeholders?

Two important questions:
- Can more formal approaches of decision-making help regulators do these better?
- Can formal approaches of decision-making be used to elicit preferences from patients and the public in a regulatory setting?

Perception on benefit-risk of medicines
Decision makers – who are they?

Patients
- Make decisions for themselves

Healthcare providers
- Make decisions based on prescribing lists

NICE
- Makes decisions on cost-effectiveness

EMA/MHRA etc.
- Makes decisions on quality, safety, efficacy and benefit-risk balance to individuals and public health

Pharmaceutical companies
- Makes decisions on what to develop for which licenses to apply

Patient and public involvement

Patient and public:
Clinical trial participants, patients and potential patients, disabled people, parents and guardians, people who use health and/or social care services, carers, members of the public, and the organisations who represent the interests of these consumers.

Involvement:
An active partnership between stakeholders in the research process, rather than the use of people as ‘subjects’ of research. Public involvement in research is often defined as doing research ‘with’ or ‘by’ the public, rather than ‘to’, ‘about’ or ‘for’ them.

Source: NHS INVOLVE
Classification of B-R methods

Source: Mt-Isa et al. (2014)

Varying degrees

- How much of an active role patients and the public should take in the decision-making process?
  - Consultation: health professionals elicit the patient and public perspective to inform the decision-making stage or entire decision-making process
  - Collaboration: health professionals and patients and the public form an active partnership and jointly participate in the decision-making stage or entire decision-making process

- Potential differences between an individual versus population level perspective:
  - Would I take this treatment?
  - Should a patient population with this indication take this treatment?
### Varying stages

- Where can PPI be applied to benefit-risk decision-making methodologies?
  - What might be necessary or facilitate its application, what potential barriers may exist, and how can involvement can be most meaningful and valid?
- A) All the way through
  - Desirable, but: few methodological guidelines, feasibility, and/or a lack of time and resources
- B) Specific stages
  - Systematically approach each step of the benefit-risk pathway in turn; and investigate where it would be most meaningful and beneficial to involve patients
  - E.g. (a) the selection, inclusion and exclusion of relevant outcome measures, or (b) the ranking and weighting of outcome measures

### Challenges with formalised preference elicitation and benefit-risk assessment

- Whose preferences?
- Which methodology or methodologies?
- Which favourable and unfavourable effects?
- How to communicate?
Whose preferences?

Patient and public:
Clinical trial participants, patients and potential patients, disabled people, parents and guardians, people who use health and/or social care services, carers, members of the public, and the organisations who represent the interests of these consumers.

Which methodology or methodologies?

- Testing the elicitation of patient preferences through two case studies:
  - Rimonabant
    - Discrete choice experiment
  - Natalizumab
    - Discrete choice experiment
    - Analytic hierarchy process
    - Swing-weighting
    - MACBETH
Which favourable and unfavourable effects?

- Which outcome measures to use?
  - Reduction in relapse rate
  - Slowdown in disability progression
  - PML
  - Reactivation of serious herpes viral infections
  - Seizures
  - Abortion or congenital abnormalities
  - Transaminase elevation
  - Infusion or injection site reactions
  - Hypersensitivity reactions
  - Flu-like reactions

Benefit-risk balance

Benefits
- Reduction in relapse rate
- Slowdown in disability progression

Risks
- PML
- Reactivation of serious herpes viral infections
- Seizures
- Abortion or congenital abnormalities
- Transaminase elevation
- Infusion or injection site reactions
- Hypersensitivity reactions
- Flu-like reactions

Serious side effects

Mild side effects
- Transaminase elevation
- Infusion or injection site reactions
- Hypersensitivity reactions
- Flu-like reactions

How to communicate?

- Communicating benefits and risks through text
  - “This is not patient worded.”
  - Frequency, severity, duration, reversibility, vignettes, impact on quality of life

- Communicating through visualisations
Conclusions

- Eliciting patient preferences in regulatory assessment can add value and lead to more clinically relevant decisions
- Many different formal methods of benefit-risk assessment can be used to elicit patient preferences
- Benefit-risk assessment methodologies support decision-making and are not intended to replace medical or regulatory expertise
- There isn’t a right or wrong or one-size-fits-all answer

Disclaimers

“The processes described and conclusions drawn from the work presented herein relate solely to the testing of methodologies and representations for the evaluation of benefit and risk of medicines.

This report neither replaces nor is intended to replace or comment on any regulatory decisions made by national regulatory agencies, nor the European Medicines Agency.”
Acknowledgements

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• The PROTECT project has received support from the Innovative Medicine Initiative Joint Undertaking (www.imi.europa.eu) under Grant Agreement n° 115004, resources of which are composed of financial contribution from the European Union’s Seventh Framework Programme (FP7/2007-2013) and EFPIA companies’ in kind contribution.

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Private: Merck KGaA (co-leader), AMGEN, AstraZeneca, Bayer, GSK, Lilly, Lundbeck, Novartis, Novo Nordisk, Pfizer, Roche, Sanofi-Aventis, Takeda

Resources: http://www.imi-protect.eu/results.shtml#

Recommendations of the IMI-PROTECT Benefit-Risk
Hughes et al, Recommendations for the methodology and visualisation techniques to be used in the assessment of benefit and risk of medicines, Nov 2013

Review of methodologies
Mt-Isa et al, Review of methodologies for benefit and risk assessment of medication, May 2013

Visualisation methods for representation of benefit risk assessment of medicine
Review of methods
Part one
Mt-Isa et al, Review of visualisation methods for the representation of benefit risk assessment of medication, Feb 2013

Part two
Mt-Isa et al, Review of visualisation methods for the representation of benefit risk assessment of medication, April 2013

Click or scan me!
Resources:  http://www.imi-protect.eu/results.shtml#

Wave 1 Case Studies
Rimonabant
Juhaeri et al, Benefit Risk Wave 1 Case study report Rimonabant, Oct 2011
Mt-Isa et al, Supplement to Wave 1 Case study report Rimonabant, Oct 2011
Telithromycin
Quartey et al, Benefit Risk Wave 1 Case study report Telithromycin, Feb 2012
Efalizumab
Micaleff et al, Benefit Risk Wave Case study Report Efalizumab, Feb 2013
Micaleff A et al, Supplement 1 to Wave 1 case study report Efalizumab, Feb 2013
Phillips et al, Supplement 2 to Wave 1 case study report Efalizumab, Feb 2013
Natalizumab
Nixon et al, Benefit Risk Wave 1 Case study report Natalizumab, May 2013

Wave 2 Case Studies
Rimonabant
Juhaeri et al, Benefit Risk Wave 2 Case study report Rimonabant, Jan 2013
Rosiglitazone
Phillips et al, Benefit Risk Wave 2 Case study report Rosiglitazone, Feb 2013
Natalizumab
Nixon et al, Benefit Risk Wave 2 Case study report Natalizumab, March 2013
Warfarin
Hallgreen et al, Benefit Risk Wave 2 Case study report Warfarin, March 2013

Benefit-Risk Assessment at individual level in real world
Treatment Acceptance

ISPOR, Amsterdam, 12th November 2014

Presented by:
Benoit Arnould, PhD, Senior Director, Global, Patient-Centered Outcomes Mapi HEOR
Benefit Risk Assessment is Multilevel

Perspective of the patient is not necessarily the same as scientific/technical experts and their view of “acceptable risk” may differ from others’ views

- **FDA** evaluates benefits/risks for the population
- **Provider** evaluates benefits/risks for a patient
- **Patient** evaluates benefits/risks in terms of personal values

Image Source: http://www.fda.gov/Safety/SafetyofSpecificProducts/ucm180528.htm

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Case study: Treatments of chronic iron overload

- **Deferasirox/Exjade** - Object of case study
  - Once daily oral iron chelation therapy
  - Licensed in 2006

- **Deferoxamine (DFO)** - Previous treatment
  - Previous gold standard therapy
  - Requires subcutaneous infusion over 8-12 hours, 5-7 times per week
Impact of DFO on HRQL and poor compliance have been documented

- DFO has a detrimental impact on many domains of HRQL (Abetz, 2006)
- Parenteral administration of DFO and associated AEs hinder optimal compliance. (Neufeld, 2006)
- Many young patients allow iron load to rise because infusion is too burdensome for full compliance. ≈ 50% of UK β-thalassaemia patients die before age 35 (Modell, 2000)
- Association between compliance with iron chelation therapy and improved survival (Modell, 2000)

Market access decisions for deferasirox

Implicit use of HRQL and patient satisfaction evidence in public domain

<table>
<thead>
<tr>
<th>Country</th>
<th>Specifics</th>
</tr>
</thead>
<tbody>
<tr>
<td>FR</td>
<td>Reference was made to HRQL benefits of mode of administration, and better management of patients (poor compliance with DFO) ASMR ratings high (II and III), and price premium achieved</td>
</tr>
<tr>
<td>NL</td>
<td>Oral therapy associated with improvement in HRQL Believability of utilities</td>
</tr>
<tr>
<td>UK</td>
<td>The message of HRQL impact and patient satisfaction with administration appears to have been considered. Clinical significance of linking HRQL to compliance and outcomes Utility was explicitly considered due to effect on cost effectiveness. Consistency between utility and HRQL. HRQL/convenience/preference mentioned in UK guidance</td>
</tr>
</tbody>
</table>
Is there a better gold standard to assess patient’s view on B/R ratio in real world than adherence and persistence?

Health Beliefs Model
Horne’s necessity-concerns model

Studies across range of illnesses, countries and cultures indicate that the **Necessity–Concerns Framework** is useful for explaining low adherence

- Renal dialysis (Horne et al. 2001)
- Renal transplantation (Butler et al. 2004)
- Asthma (Horne & Weinman 2002)
- Cancer (Horne & Weinman 1999)
- Coronary heart disease (Horne & Weinman 1999)
- Hypertension (Ross et al. 2004)
- HIV/AIDS (Gonzalez et al., 2006; Horne et al. 2007, 2001)
- Haemophilia (Llewellyn et al. 2003)
- Bipolar disorder (Clatworthy et al. 2007)
- Rheumatoid arthritis (Neame & Hammond 2005)
- General practice — new meds (Clifford 2008)

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**Acceptance in Health Beliefs Model**

Marant 2011

- Socio-demographic (Age, sex, Social category, …)
- Individual psychosocial characteristic (personality, cognitive characteristic …)
- Perceived Susceptibility
- Perceived Severity
- Health value
- Perceived benefit
- Perceived barriers

Acceptance

Behaviour
Accept Questionnaire

- 25 items
- 6 dimensions
  - Acceptance/Medication Inconvenience (5 items)
  - Acceptance/Long-term Treatment (3 items)
  - Acceptance/Regimen Constraints (5 items)
  - Acceptance/Numerous Medications (1 item)
  - Acceptance/Side Effects (5 items)
  - Acceptance/Effectiveness (3 items)
  - Acceptance/General (3 items)
- Answer choice
  - Acceptance/general eg Q24: Given the advantages and disadvantages of your medication, do you consider it to be an acceptable solution?

<table>
<thead>
<tr>
<th>Not at all acceptable</th>
<th>Not very acceptable</th>
<th>Somewhat acceptable</th>
<th>Totally acceptable</th>
<th>I don’t know</th>
</tr>
</thead>
</table>

  - Other dimensions eg Q1: Do you find it inconvenient to prepare your medication?

<table>
<thead>
<tr>
<th>Yes, and I don’t find this easy to accept</th>
<th>Yes, but I find this easy to accept</th>
<th>No</th>
<th>My medication doesn’t need any preparation</th>
</tr>
</thead>
</table>

Application in real-world: assessing acceptance in a large sample of patients suffering from a variety of diseases accessed through Carenity, an online patient community
Patient disposition

A unique population of patients:
- Population size: data on more than 4,000 patients analyzed
- Variety of diseases: more than 270 chronic diseases, among which 19 including more than 30 patients

- Type 2 diabetes (N=669)
- Multiple sclerosis (N=426)
- Type 1 diabetes (N=251)
- Ankylosing spondylitis (N=297)
- Fibromyalgia (N=248)
- Rheumatoid arthritis (N=215)
- Arthrosis (N=163)
- Bipolar disorder (N=143)
- Breast cancer (N=137)
- Depression (N=104)
- Lupus (N=100)
- Crohn’s disease/Ulcerative colitis (UC) (N=98)
- Chronic obstructive pulmonary disease (COPD) (N=74)
- Psoriasis (N=68)
- Parkinson’s disease (N=65)
- Hypertension (N=64)
- Asthma (N=51)
- Epilepsy (N=45)
- Myocardial infarction (N=33)

How do patients accept their treatment?
Score « Acceptance/General »

Box = interquartile (Q3-Q1); + = mean; — = median; upper and lower bars = observed max – min values. Boxplots are ranked based on mean Acceptance/General score.
### Dimension « Acceptance/Effectiveness »

<table>
<thead>
<tr>
<th>Dimension Score</th>
<th>ACCEPT Item- % response &quot;I don't find this easy to accept&quot;</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20 (effective)</td>
<td>21 (protecting enough)</td>
</tr>
<tr>
<td>Type 2 diabetes (N=669)</td>
<td>7.2</td>
<td>8.8</td>
</tr>
<tr>
<td>Type 1 diabetes (N=251)</td>
<td>8.5</td>
<td>7.6</td>
</tr>
<tr>
<td>Multiple sclerosis (N=426)</td>
<td>8.7</td>
<td>8.7</td>
</tr>
<tr>
<td>Fibromyalgia (N=248)</td>
<td>24.6</td>
<td>19.4</td>
</tr>
<tr>
<td>Breast cancer (N=137)</td>
<td>6.6</td>
<td>5.1</td>
</tr>
</tbody>
</table>

### Dimension « Acceptance/Side Effects »

<table>
<thead>
<tr>
<th>Dimension Score</th>
<th>ACCEPT Item- % response &quot;I don't find this easy to accept&quot;</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>15 (side effects)</td>
<td>16 (unpleasant side effects)</td>
</tr>
<tr>
<td>Type 2 diabetes (N=669)</td>
<td>32.3</td>
<td>35.4</td>
</tr>
<tr>
<td>Type 1 diabetes (N=251)</td>
<td>37.1</td>
<td>39.0</td>
</tr>
<tr>
<td>Multiple sclerosis (N=426)</td>
<td>40.6</td>
<td>40.8</td>
</tr>
<tr>
<td>Fibromyalgia (N=248)</td>
<td>58.5</td>
<td>58.9</td>
</tr>
<tr>
<td>Breast cancer (N=137)</td>
<td>75.9</td>
<td>73.7</td>
</tr>
</tbody>
</table>
Correlations between the Acceptance/General dimension and other ACCEPT dimensions

<table>
<thead>
<tr>
<th></th>
<th>Medication inconvenience</th>
<th>Long-term Treatment</th>
<th>Regimen Constraints</th>
<th>Side Effects</th>
<th>Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2 diabetes (N=669)</td>
<td>0.18</td>
<td>0.23</td>
<td>0.25</td>
<td>0.37</td>
<td>0.52</td>
</tr>
<tr>
<td>Type 1 diabetes (N=251)</td>
<td>0.20</td>
<td>0.28</td>
<td>0.34</td>
<td>0.23</td>
<td>0.65</td>
</tr>
<tr>
<td>Multiple sclerosis (N=426)</td>
<td>0.29</td>
<td>0.28</td>
<td>0.26</td>
<td>0.34</td>
<td>0.50</td>
</tr>
<tr>
<td>Fibromyalgia (N=248)</td>
<td>0.19</td>
<td>0.21</td>
<td>0.24</td>
<td>0.44</td>
<td>0.63</td>
</tr>
<tr>
<td>Breast cancer (N=137)</td>
<td>-0.06</td>
<td>0.26</td>
<td>0.22</td>
<td>0.35</td>
<td>0.48</td>
</tr>
</tbody>
</table>

Pearson correlation coefficients, in white <0.20; in grey 0.20-0.39; in blue 0.40-0.59; in purple 0.60-0.79

Ultimately, individualized Benefit Risk assessment can’t be disconnected from life
“the right treatment for the right person at the right time”

Thank you