ISSUE PANEL: PROVE IT WITH PROS
Yvonne-Beatrice Böhler
Stefan Holmstrom
Finn Boerlum Kristensen
Anke van Engen

Introduction
Anke van Engen
There is a drive to incorporate the patient experience of treatment into healthcare decision making.

What do we mean by the patient experience?

<table>
<thead>
<tr>
<th>Concept</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health-Related Quality of Life (HRQoL) (incl. health status)</td>
<td>HRQoL is multi-dimensional and represents the patient’s evaluation of a health condition and its treatment on daily life: physical function, psychological function, social function, role function, emotional function, well-being, vitality, health status, etc</td>
</tr>
<tr>
<td>Health-Related Quality of end of life</td>
<td>Same as HRQoL at the end of life</td>
</tr>
<tr>
<td>Patient satisfaction</td>
<td>Evaluation of treatment, patients preference, health care delivery systems and professionals, patient education programs and medical devices</td>
</tr>
<tr>
<td>Physical functioning</td>
<td>Physical limitations and activity restrictions, e.g. self-care, walking, mobility, sleep, sexual disability</td>
</tr>
<tr>
<td>Psychological functioning (incl. coping)</td>
<td>Positive or negative affect and cognitive, e.g. anger, alertness, self-esteem, sense of well-being, distress, coping</td>
</tr>
<tr>
<td>Signs and symptoms</td>
<td>Reports of physical and psychological symptoms or sensations not directly observable, e.g. energy and fatigue, nausea, irritability</td>
</tr>
<tr>
<td>Social functioning (incl. work)</td>
<td>Limitations in work or school, participation in community</td>
</tr>
<tr>
<td>Treatment adherence</td>
<td>Reports or observations of actual use of treatments</td>
</tr>
<tr>
<td>Utility</td>
<td>Generic measures of HRQoL with societal reference weights for their classification systems that can help to inform health-care resource allocation. Utilities provide a useful summary index of overall QoL relative to full health (utility = 1) and death (utility = 0)</td>
</tr>
</tbody>
</table>

Source: ISPOR HTA Training material, 2018
PRO instruments should capture symptoms that are meaningful to patients

“I just overall didn’t have a lot of energy for doing the kind of things that I was normally used to doing, like playing sports and things like that. Even just doing activities around the house, I got to be kind of a couch potato, just didn’t have a lot of energy to do things.” – Prostate cancer patient

“PRO instruments should capture symptoms that are meaningful to patients”

FACT-P (Version 4)

Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

<table>
<thead>
<tr>
<th>PHYSICAL WELL-BEING</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>I have a lack of energy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I have nausea</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Because of my physical condition, I have trouble meeting the needs of my family</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I have pain</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I was bothered by side effects of treatment</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I feel ill</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am fearful spending time in bed</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

In regulatory decision-making, the science and requirements for PRO evidence have matured

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Stringent requirements
- Emphasis on disease symptoms
- Historically fewer PRO-based label claims
- Legislation is driving rapid change (21st Century Cures Act & PDUFA V and VI)
- Change already being felt by industry
- New disease guidance
- Additional data requests
- Innovative labels

- More open to distal concepts
- More flexible
- Historically more PRO-based label claims
- Evolution through pilots (voice of the patient) and collaboration (FDA and EMA on patient engagement)
- Adopting similar standards as FDA
- New disease guidance
- Deeper scrutiny of PRO evidence
Consequently, the last decade has shown a marked increase in PRO data included in oncology labels, particularly in Europe.

**Oncology & rare diseases PRO label claims**

- **Key drivers**
  - Rise of patient-centricity
  - Effect on overall survival may be difficult to detect
  - Improved outcomes with standard of care raising the bar for traditional endpoints
  - Safety profile of chemotherapies
  - Technology enablers

**EMA label claim:** “Osimertinib improved patient-reported lung cancer symptoms compared to chemotherapy by demonstrating a statistically significant difference in mean change from baseline vs. chemotherapy for all 5 pre-specified primary PRO symptoms.”

Although PRO evidence is increasingly collected, the use of PRO evidence varies across therapy areas.

**HTA submissions with PRO data**

- **Oncology**: 70%
- **Rare diseases**: 48%
- **Diabetes**: 27%

Submissions in France include PRO data less frequently than submissions to the other three HTA bodies

Products with PRO data do not necessarily receive a more favourable recommendation

Source: IQVIA HTA Accelerator.
Scope: Single drug assessments (original, extension of indication, resubmissions) for oncology w/ a recommendation from Jan 2011 to Dec 2016 from 4 HTA bodies (G-BA, HAS, NICE, SMC)
Evidence that PRO data influenced the decision was most clear in Germany

Source: IQVIA HTA Accelerator. Scope: Single drug assessments (original, extension of indication, resubmissions) for oncology w/ a recommendation from Jan 2011 to Dec 2016 from 4 HTA bodies (G-BA, HAS, NICE, SMC)

The German perspective

Yvonne-Beatrice Boehler
Agenda

- Setting the scene – General process
- Facts – Methodology to assess PROs
- Case studies – Data driven
- In a nutshell – Learnings
General process

1 year – free pricing & reimbursement

Assessment 3 months
Institute for Quality & Efficiency in Health Care (IQWiG)

Appraisal 3 months
Federal Joint Committee (G-BA)

Pricing 6 months
National Association of Statutory Health Insurance Funds (GKV-SV)

✓ First 6 month – methodological viewpoints on PROs

Focus

Last 6 months – strategic viewpoints on PROs

Agenda

- Setting the scene – General process
- Facts – Methodology to assess PROs
- Case studies – Data driven
- In a nutshell – Learnings
PROs may qualify for an added benefit against the appropriate comparator therapy in several outcome categories.

Social Code Book V § 35b
- Increase in life expectancy
- Improvement in health status
- Reduction in disease duration
- Reduction in adverse effects
- Improvement in quality of life

IQWiG methods
- Mortality
- Morbidity
  - Symptoms
  - Complications
  - Adverse events (AEs)
- Health-related quality of life (HRQoL)

Dimensions of added benefit

Probability
- Proof
- Indication
- Hint

Extent
- Major
- Considerable
- Minor
- Non-quantifiable added benefit
- No added benefit proven
- Benefit of drug smaller than benefit of appropriate comparator therapy

Indicating certainty of conclusions

<table>
<thead>
<tr>
<th>Benefit category</th>
<th>All-cause mortality</th>
<th>Serious (or severe) symptoms (or late complications) &amp; AEs, HRQoL</th>
<th>Non-serious (or non-severe) symptoms (or late complications) &amp; AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major</td>
<td>0.85</td>
<td>0.75 &amp; risk ≥5%</td>
<td>N/A</td>
</tr>
<tr>
<td>Considerable</td>
<td>0.95</td>
<td>0.90</td>
<td>0.80</td>
</tr>
<tr>
<td>Minor</td>
<td>1.00</td>
<td>1.00</td>
<td>0.90</td>
</tr>
</tbody>
</table>

b: Risk must be at least 5% for at least 1 of the 2 groups compared.

References 7

Inferential statistical thresholds for relative effect measures

a: Precondition (as for all patient-reported outcomes): use of a validated or established instrument, as well as a validated or established response criterion.
Implications

- Validation of instruments applied & response criteria to be addressed in the dossier (module 4, methods section 4.2.5.2)
  - Requires validated or established response criterion (e.g., individual minimally important difference [MID])
- If results are dichotomous (responders/non-responders, relative effect measures)
  - Clinical relevance of effects is addressed
  - Extent criteria for added benefit can be applied

  MID is key...otherwise...

- Clinical relevance
  - Use of standardized mean difference (SMD expressed as Hedges’ g)
  - Irrelevance threshold of 0.2, confidence interval of e.g. change from baseline effect estimate must lie completely above

- Extent criteria
  - Only non-quantifiable

Examples in upcoming case studies

References 7-9
**Dulaglutide (2015)**
- × Disease-specific instruments (APPADL, IW-SP, LBSS), IQWiG/G-BA: Questionnaires not accepted, validated populations did not correspond to the target population (e.g., diabetes type 1)

**Sofosbuvir/Velpatasvir/Voxilaprevir (2018)**
- × Used disease-specific instruments (CLDQ-HCV, FACIT-F), IQWiG/G-BA: Questionnaires not accepted, validated populations did not correspond to the target population, CLDQ-HCV content validity questionable
- ~ However SF-36 was accepted, MCS with statistically significant advantage (mean difference, no responder analysis), Hedges’g not completely above irrelevance threshold: No added benefit for this endpoint

**Abiraterone (03/2018)**
- ✓ A real treasure of examples, negatively & positively
- ✓ EQ-5D VAS health status, FACT-P & one of many BPI-SF item response criteria accepted
- × BFI and many BPI-SF response criteria & sensitivity analyses not accepted – mean difference applied: Hedges’g not completely above irrelevance threshold: No added benefit for these endpoints, before addendum

**Learnings**
- ✗ Negative
- ✖ Medium
- ✔ Positive
Case studies – Data driven

**Plan (2)**

**Bosutinib (08/2018)**

- EQ-5D (same response criteria as for abiraterone?!). FACT-Leu response criteria & sensitivity analyses not accepted (for both very long IQWiG argumentation lines) - mean difference applied: Hedges’g not completely above irrelevance threshold: No added benefit for these endpoints

**Cariprazine (2018 – indication field: relapse prevention)**

- ClinRO/PRO PANSS response criteria & sensitivity analyses not accepted - mean difference applied: Hedges’g not completely above irrelevance threshold: No added benefit for these endpoints

- PSP, response criteria & sensitivity analyses not accepted, mean difference applied: Hedges’g completely above irrelevance threshold: **Driver of added benefit**

**Learnings**

<table>
<thead>
<tr>
<th></th>
<th>Negative</th>
<th>Medium</th>
<th>Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bosutinib</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cariprazine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

References 16-19

12 NOV 2018

Yvonne-Beatrice Boehler – The German perspective

---

**Conduct**

**Regorafenib (2015)**

- EORTC QLQ-C30 (symptom scales – morbidity – non-serious) & EORTC QLQ-C30 (functional scales – HRQoL), **ITT problem** in 2013 assessment (>30% missing), in re-assessment 2015 MMRM still not accepted

**Learnings**

<table>
<thead>
<tr>
<th></th>
<th>Negative</th>
<th>Medium</th>
<th>Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Regorafenib</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

References 20-21

12 NOV 2018

Yvonne-Beatrice Boehler – The German perspective

---
Analyse

Abiraterone (03/2018)

~ EQ-SD VAS health status responder analysis was assessed as “non-serious” & statistically significant difference did therefore not qualify for an added benefit according to IDWG methods
✓ After addendum: BFI Item 3 response criteria (many staggered sensitivity analyses, robust effects) accepted
✓ FACT-P, BFI Item 3 & BPI-SF Item 3 responder analysis resulted in added benefit, however overall survival data was available and convincing...

Cariprazine (2018 – indication field: relapse prevention)

~ PSP mean difference data was assessed as “non-serious” & not as HRQoL-measure (difference in added benefit thresholds), however, non-quantifiable anyway due to Hedges’g
✗ After addendum: ClinRO/PRO BARS response criteria accepted - no statistically significant differences, no change of initial assessment

Dabrafenib (2015)

✓ EORTC QLQ-C30 (symptom scales – morbidity – non-serious) & EORTC QLQ-C30 (functional scales – HRQoL), time to deterioration of 10 points responder analyses accepted – added benefit based on HRQoL
✓ After addendum: EQ-SD VAS responder analyses & sensitivity analyses (also for subgroups) accepted – positive change for added benefit for men

References 12, 15, 17, 19, 22, 23

Agenda

- Setting the scene – General process
- Facts – Methodology to assess PROs
- Case studies – Data driven
  - In a nutshell – Learnings

Learnings

- Negative
- Medium
- Positive
### PROs Plan
- Choose or develop validated instruments (content validity & psychometric properties)
  - Validated in Disease/subgroup
  - Subscale/Item validation
  - MID available
- Consider validated generic &/or disease-specific instruments
- Consider blinded endpoint assessors for ClinROs in open-label trials
- Pre-specify analyses, e.g.
  - Responder-Analyses with different cut-offs
  - Subscale & Item-Analyses according to validation
- Consider early dialogues to inform your viewpoints on your PROs

### PROs Conduct
- Implement the data collection correctly
  - Close monitoring avoiding missing data & collecting robust data
  - Consider effective ePRO implementation
- Consider amendments of analysis plans once more validation data is published, available etc. (blinded!)
- Follow ITT principle
- Deliver (even if staggered and posthoc) responder & sensitivity analyses, also for relevant subgroups
- Deliver an argumentation on severity of measured symptoms/concepts (relevant for extent category severe vs. non-severe)
- Support these with change from baseline data
- Address sources of bias
- Prepare for potential data submissions in hearing procedure – and therewith for possible addendum

### PROs Analyse
- Be ready to: PROVE it with PROs!

---

**The industry perspective**

*Stefan Holmstrom*
HTA GUIDANCE IS NOT DETAILED AND CONSISTENT ENOUGH FOR THE INDUSTRY TO BE ABLE TO IMPLEMENT IT

PRO guidance available

PRO guidance in development

No published PRO guidance

In Germany, HTA bodies use specific criteria to assess PRO evidence and it can be very influential in the reimbursement decision (positively and negatively).

EUnetHTA’s 2017-2020 work plan includes the development of a joint position on the principles for development and validation of patient reported outcomes.

Ex-HAS: “Quality of life is a nice-to-have but it would only have a very minor impact on the ASMR rating.”

EQ5D is preferred as a utility measure for cost-effectiveness analysis, but no guidance on e.g. data collection.

CASE STUDY: XTANDI IN MEN WITH MCRPC NOT YET INDICATED FOR CHEMOTHERAPY

PREVAIL study overview:
A Phase 3 trial of enzalutamide after progression on ADT in men with mCRPC

Patient population:
• 1717 men with progressive mCRPC
• Asymptomatic/mildly symptomatic
• Chemotherapy-naïve
• Steroids allowed but not required

RANDOMIZED 1:1

Enzalutamide
160 mg/day (capsules)
n=872

Placebo
n=845

Co-primary endpoints:
• OS
• rPFS

ADT=androgen deprivation therapy; mCRPC=metastatic castration-resistant prostate cancer; OS=overall survival; rPFS=radiographic progression-free survival.

Source: Beer TM, et al. ASCO GU 2014; Oral presentation; ClinicalTrials.gov identifier: NCT01212991.
MULTIPLE PRO INSTRUMENTS WERE INCLUDED IN THE PREVAIL STUDY

PRO instruments assessment schedule

<table>
<thead>
<tr>
<th>PRO instrument</th>
<th>Screening</th>
<th>Week 1</th>
<th>Week 5</th>
<th>Week 13</th>
<th>Week 25</th>
<th>Week 37 and every subsequent 12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>BFI</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BPI</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>EQ-5D</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>FACT-P</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

BFI: Brief Fatigue Inventory  
BPI: Brief Pain inventory  
EQ-5D: European Quality of Life 5-Domain Scale  
FACT-P: Functional Assessment of Cancer Therapy - Prostate

THE PRO RESULTS WERE GENERALLY POSITIVE

Adjusted mean change from baseline in FACT-P and EQ-5D at week 61 and BPI-SF worst pain at week 25

FACT-P  
The between-group differences regarding decreases in most scores at week 61 were significantly in favour of enzalutamide

EOQ-5D  
Enzalutamide had a beneficial effect versus placebo on general health utilities measured by EQ-5D visual analogue scale

BPI-SF  
BPI-SF worst pain deteriorated to a lesser extent in the enzalutamide

Source: Loriot et al, 2015, Effect of enzalutamide on health-related quality of life, pain, and skeletal-related events in asymptomatic and minimally symptomatic, chemotherapy-naive patients with metastatic castration-resistant prostate cancer (PREVAIL): results from a randomised, phase 3 trial
XTANDI SHOWED A DELAY IN THE TIME TO DETERIORATION IN HRQOL

FACT-P Total Score

Prostate Cancer Subscale

EQ-5D Index

EQ-5D VAS

Source: Loriot et al, 2015. Effect of enzalutamide on health-related quality of life, pain, and skeletal-related events in asymptomatic and minimally symptomatic, chemotherapy-naïve patients with metastatic castration-resistant prostate cancer (PREVAIL): results from a randomised, phase 3 trial

THE PRO EVIDENCE PACKAGE SUBMITTED DIFFERED BY HTA BODY

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Submitted PRO data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HAS</td>
</tr>
<tr>
<td>FACT P</td>
<td></td>
</tr>
<tr>
<td>Median time to deterioration in FACT P total score</td>
<td></td>
</tr>
<tr>
<td>FACT P total score (w13 + w25)</td>
<td></td>
</tr>
<tr>
<td>Change from baseline FACT P total score (w13 + w25)</td>
<td></td>
</tr>
<tr>
<td>Change from baseline FACT P total score (w61)</td>
<td></td>
</tr>
<tr>
<td>EQ5D</td>
<td></td>
</tr>
<tr>
<td>Median time to deterioration in EQ-5D index</td>
<td></td>
</tr>
<tr>
<td>Median time to deterioration in EQ-5D VAS</td>
<td></td>
</tr>
<tr>
<td>EQ-5D VAS (w13 + w25)</td>
<td></td>
</tr>
<tr>
<td>Change from baseline EQ-5D VAS (w13 + w25)</td>
<td></td>
</tr>
<tr>
<td>Change from baseline EQ-5D index (w61)</td>
<td></td>
</tr>
<tr>
<td>Change from baseline EQ-5D VAS (w61)</td>
<td></td>
</tr>
<tr>
<td>BPI</td>
<td></td>
</tr>
<tr>
<td>Median time to progression of pain at its worst</td>
<td></td>
</tr>
<tr>
<td>Pain severity and pain interference at (w13 + w25)</td>
<td></td>
</tr>
<tr>
<td>Change in pain severity and pain interference (w25)</td>
<td></td>
</tr>
<tr>
<td>Progression of pain at its worst (w25)</td>
<td></td>
</tr>
</tbody>
</table>

Data submitted in dossier
Acceptance and impact of PRO data in HTAs

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>HAS</th>
<th>G-BA</th>
<th>NICE</th>
<th>SMC</th>
</tr>
</thead>
<tbody>
<tr>
<td>FACT P</td>
<td>+</td>
<td>✓</td>
<td>?</td>
<td>+</td>
</tr>
<tr>
<td>Median time to deterioration in FACT P total score</td>
<td>+</td>
<td>✓</td>
<td>?</td>
<td>+</td>
</tr>
<tr>
<td>FACT P total score (w13 + w25)</td>
<td>?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline FACT P total score (w13 + w25)</td>
<td>?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline FACT P total score (w61)</td>
<td>+</td>
<td>?</td>
<td></td>
<td>?</td>
</tr>
<tr>
<td>EQ5D</td>
<td>?</td>
<td></td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Median time to deterioration in EQ-5D index</td>
<td>?</td>
<td></td>
<td></td>
<td>?</td>
</tr>
<tr>
<td>Median time to deterioration in EQ-5D VAS</td>
<td>?</td>
<td></td>
<td></td>
<td>?</td>
</tr>
<tr>
<td>EQ-5D VAS (w13 + w25)</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline EQ-5D VAS (w13 + w25)</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline EQ-5D index (w61)</td>
<td>?</td>
<td>?</td>
<td></td>
<td>?</td>
</tr>
<tr>
<td>Change from baseline EQ-5D VAS (w61)</td>
<td>?</td>
<td>?</td>
<td></td>
<td>?</td>
</tr>
<tr>
<td>BPI</td>
<td>?</td>
<td></td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Median time to progression of pain at its worst</td>
<td>?</td>
<td></td>
<td></td>
<td>?</td>
</tr>
<tr>
<td>Pain severity and pain interference at (w13 + w25)</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in pain severity and pain interference (w25)</td>
<td>x</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Progression of pain at its worst (w25)</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data submitted in dossier: ✓ Data not mentioned in report: ? Data not accepted: x Data acknowledged: + Data was a decision driver: ✓

The critique of the PRO data was mixed

- There are indications of significant added benefit for serious / severe symptoms / adverse events and health-related quality of life.

- The median time until decline in the FACT-P global score was also significantly extended by 5.7 months relative to placebo. These outcomes may have particular importance to patients.

- The difference in collection of BPI data was more than 15% between the two treatments, so no valid statement could be derived.

- Available data are inconclusive as to the effect of the treatment.

- It is challenging to convince HTA bodies of patient-relevant improvements, and better guidance from HTA bodies is needed.
HOWEVER, THE INDUSTRY MUST ALSO PRESENT EVIDENCE IN A MORE USER-FRIENDLY FORMAT

Time to deterioration in HRQoL based on FACT-P total score

Transposed scores for items of the physical well-being domain of the FACT-P

A total score can indicate an overall trend but can be confusing and hard to interpret

Item-level analysis can demonstrate where patients may be performing well or if there are any areas with a significant deterioration


PROs, the HTA Core Model and European HTA

Finn Børılm Kristensen
Professor, University of Southern Denmark
EUnetHTA developed the HTA Core Model, which contains nine HTA domains

**Domains of HTA**

| Health problem and current use of technology | Developed by EUnetHTA within the HTA Core Model® |
| Technical characteristics | Builds on international consensus on what HTA should consider to assess |
| Safety | Promotes the wide scope and multidisciplinary nature of HTA |
| Clinical effectiveness | |
| Costs and economic evaluation | |
| Ethical analysis | |
| Organizational aspects | |
| Patient and social aspects | |
| Legal aspects | |

PROs may be used to assess the clinical value of new technologies in HTAs

**Domains of HTA**

| Health problem and current use of technology | Clinical value (REA) |
| Technical characteristics | PROs |
| Safety | |
| Clinical effectiveness | |
| Costs and economic evaluation | |
| Ethical analysis | |
| Organizational aspects | |
| Patient and social aspects | |
| Legal aspects | |

**Acceptance of PRO data**

- Yes: 36 (75%)
- No: 2 (4%)
- Don’t know: 10 (21%)

Patient reported endpoints are generally accepted when estimating effectiveness or safety in assessments.

Source: EUnetHTA. www.eunethta.eu

Source: Kristensen FB. Mapping of methodologies in EU and Norway, 2018
And in assessing the overall value, HRQoL plays an even larger role.

<table>
<thead>
<tr>
<th>Domains of HTA</th>
<th>Acceptance of HRQoL data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health problem and current use of technology</td>
<td>5 (4%)</td>
</tr>
<tr>
<td>Technical characteristics</td>
<td></td>
</tr>
<tr>
<td>Safety</td>
<td>2 (16%)</td>
</tr>
<tr>
<td>Clinical effectiveness</td>
<td></td>
</tr>
<tr>
<td>Costs and economic evaluation</td>
<td></td>
</tr>
<tr>
<td>Ethical analysis</td>
<td></td>
</tr>
<tr>
<td>Organizational aspects</td>
<td></td>
</tr>
<tr>
<td>Patient and social aspects</td>
<td></td>
</tr>
<tr>
<td>Legal aspects</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall value</td>
<td></td>
</tr>
<tr>
<td>PROs</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HRQoL is one of the main categories of endpoints in the EUnetHTA Guidelines for Clinical Endpoints.

Source: European Network for Health Technology Assessment, EUnetHTA
www.eunethta.eu
EUnetHTA guidelines also touch upon the need for HRQoL in cost-effectiveness analyses

A general recommendation applicable to all types of REA, irrespective of their particular purpose, is to require the inclusion of a disease- or population specific and a generic HRQoL measure for most adequately capturing the impact of a disease on daily life. In case there is a need for the calculation of QALYs, a utility measure (Time Trade-Off or Standard Gamble) or generic HRQoL, instrument associated with a reference set of utility values (generic utility instrument) is recommended.

The majority of recent EUnetHTA assessments included PRO data and lack of PRO data was regretted

EUnetHTA guideline on HRQoL for REA and utility measures

Source: European Network for Health Technology Assessment, EUnetHTA
www.eunethta.eu

Inclusion of PRO data in EUnetHTA assessments

Results were inconsistent across studies, probably due to differences in types of outcomes or survey tools. The certainty of the evidence for these outcomes varied from low to very low.

- EUnetHTA assessment of Continuous glucose monitoring and flash glucose monitoring as personal, standalone systems in patients with diabetes mellitus treated with insulin

Source: IQVIA HTA Accelerator
www.scienceandpolicy.dk
Evidence generation for HTA should take place throughout the technology lifecycle

PROVE IT WITH PROs

- PROs are generally accepted by HTA bodies in assessment of clinical value – the degree to which they are decisive differs by HTA body and therapeutic value
- A sound PRO strategy is needed to generate PRO evidence with impact: PROs are not consistently included as endpoint in clinical trials, or data is not adequately collected
- Guidance from HTA bodies should be more clear on the distinction between PROs as outcomes and as utility measures for health economic evaluation
- Industry must present PRO evidence in a more insightful way
- The new EU joint HTA structure provides an opportunity for more consistency and more guidance for collecting PRO data and inclusion of PROs in HTA submissions

Thank you for your attention!
Any comments or questions?