ISSUE PANEL: PROVE IT WITH PROS

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Introduction

Anke van Engen

There is a drive to incorporate the patient experience of treatment into healthcare decision making

IQVIA 3

What do we mean by the patient experience?

Concepts measured in PROs

Concept	Description
Health-Related Quality of Life (HRQoL) (incl. health status)	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
Health-Related Quality of end of life	Same as HRQoL at the end of life
Patient satisfaction	Evaluation of treatment, patients preference, health care delivery systems and professionals, patient education programs and medical devices
Physical functioning	Physical limitations and activity restrictions, e.g. self-care, walking, mobility, sleep, sexual disability
Psychological functioning (incl. coping)	Positive or negative affect and cognitive, e.g. anger, alertness, self-esteem, sense of well-being, distress, coping
Signs and symptoms	Reports of physical and psychological symptoms or sensations not directly observable, e.g. energy and fatigue, nausea, irritability
Social functioning (incl. work)	Limitations in work or school, participation in community
Treatment adherence	Reports or observations of actual use of treatments
Utility	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)

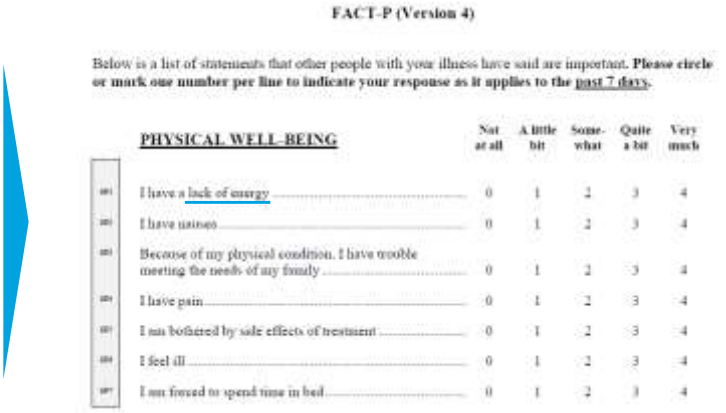
- *How a patient feels and functions in the context of their disease or condition*
- *How a patient feels and functions in the context of their treatment*

Source: ISPOR HTA Training material, 2018

IQVIA 4

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



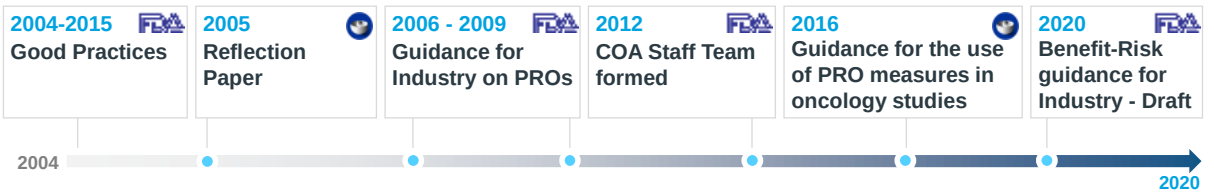
FACT-P (Version 4)

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.**

PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
I have a lack of energy	0	1	2	3	4
I have nausea	0	1	2	3	4
Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
I have pain	0	1	2	3	4
I am bothered by side effects of treatment	0	1	2	3	4
I feel ill	0	1	2	3	4
I am forced to spend time in bed	0	1	2	3	4

Source: IQVIA research; http://www.facit.org/LiteratureRetrieve.aspx?ID=42292

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

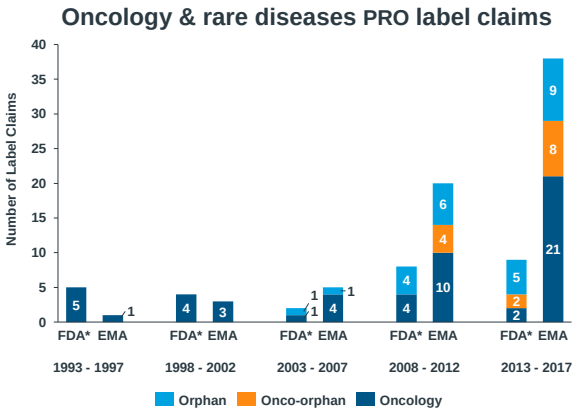


FDA
- Stringent requirements
- Emphasis on disease symptoms
- Historically fewer PRO-based label claims
- Legislation is driving rapid change (21st Century Cures Act & PDUFA V and VI)
- Change already being felt by industry
  - New disease guidance
  - Additional data requests
  - Innovative labels

EMA
- 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

European Medicines Agency US Food and Drug Administration

Consequently, the last decade has shown a marked increase in PRO data included in oncology labels, particularly in Europe



*Note: The FDA labels only include PRO label claims, FDA descriptive labelling was excluded from the analysis

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."*

Sources: ePROVIDE PROLABELS.- analysis of oncology drugs and drugs with EMA orphan drug status
https://eprovide.mapi-trust.org/advanced-search?form%5BtypeOfContent%5D=drug&form%5Bdrug_status%5D=Approved

IQVIA 7

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

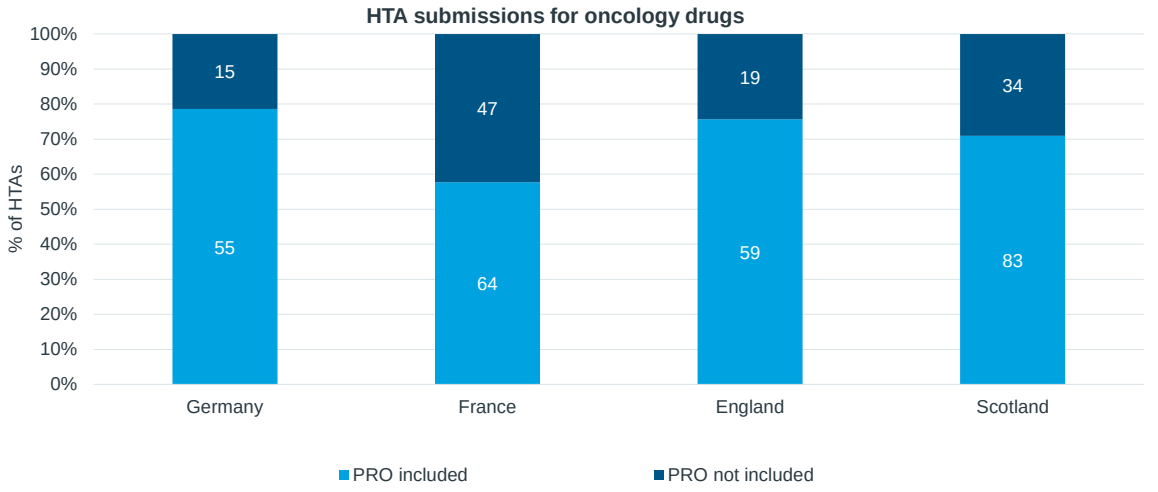
	Oncology	Rare diseases	Diabetes
HTA submissions with PRO data[1]	70%	48%	27%
Significant HRQoL burden	●	◕	◑
Significant therapy AE burden	●	◑	◑
"Hard" endpoints poorly defined	○	●	○
"Hard" endpoints hard to achieve	●	◑	◑
Demand for patient-relevant endpoints	◕	●	◔

● High relevance ◑ Medium relevance ○ Low relevance

Source: [1]IQVIA HTA Accelerator.
Scope: Single drug assessments (original, extension of indication, resubmissions) in oncology and diabetes published by HAS, G-BA, NICE and SMC between Jan 2011 and Dec 2016

IQVIA 8

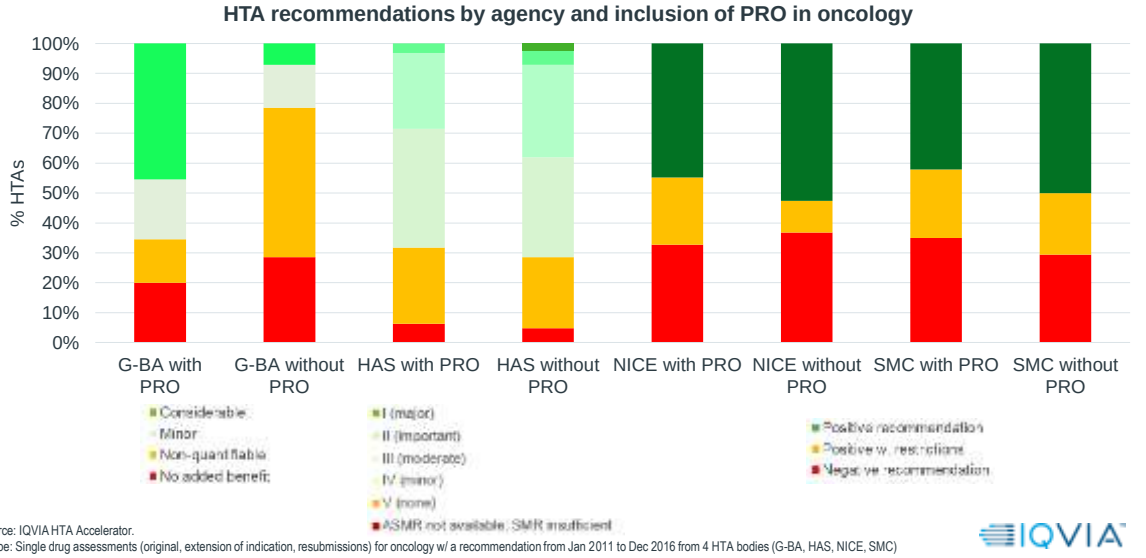
Submissions in France include PRO data less frequently than submissions to the other three HTA bodies



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)

IQVIA 10

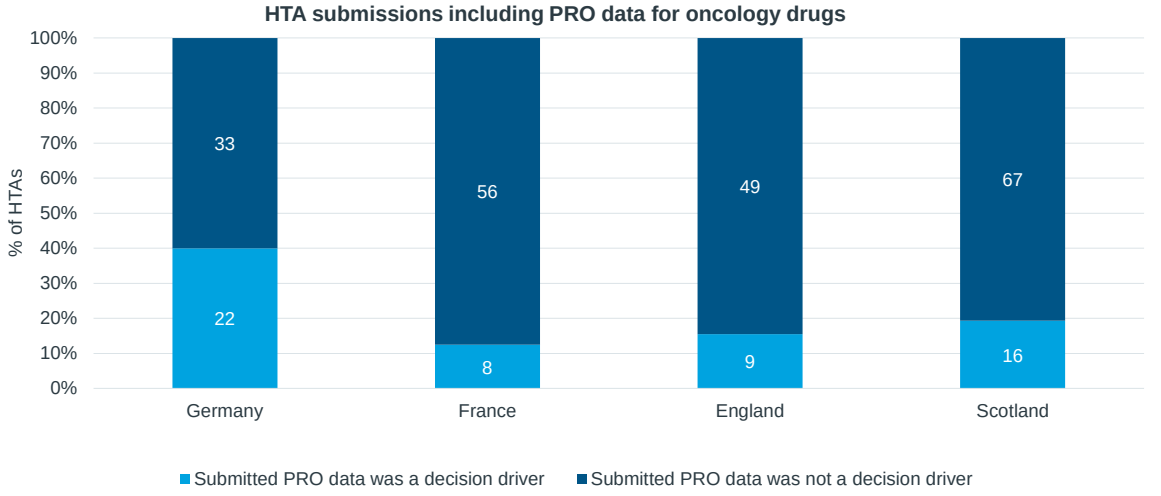
Products with PRO data do not necessarily receive a more favourable recommendation



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)

IQVIA 11

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)

IQVIA 12

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

Agenda

- **Setting the scene – General process**
- Facts – Methodology to assess PROs
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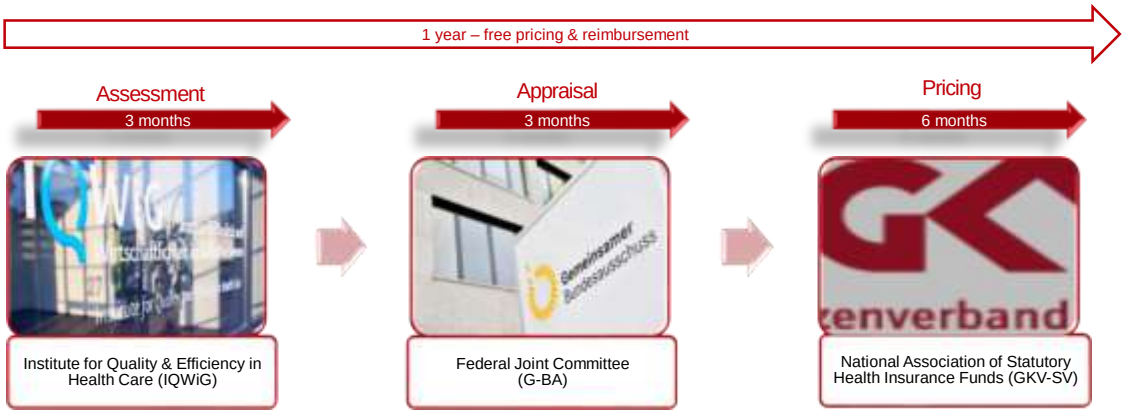
Setting the scene – General process

General process



✓ **First 6 month – methodological viewpoints on PROs** Focus **Last 6 months – strategic viewpoints on PROs**

References 1-6

Agenda

- Setting the scene – General process
- **Facts – Methodology to assess PROs**
- Case studies – Data driven
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Facts – Methodology to assess PROs

Patient-relevant benefit – Outcome categories

Social Code Book V § 35b	IQWiG methods
✓ Increase in life expectancy	✓ Mortality
✓ Improvement in health status	✓ Morbidity
✓ Reduction in disease duration	✓ Symptoms (PROs)
✓ Reduction in adverse effects	✓ Complications (PROs)
✓ Improvement in quality of life	✓ Adverse events (AEs) (PROs)
	✓ Health-related quality of life (HRQoL) (PROs)

PROs may qualify for an added benefit against the appropriate comparator therapy in several outcome categories

References 7

Facts – Methodology to assess PROs

Dimensions of added benefit

Probability ← Indicating certainty of conclusions

- ✓ Proof
- ✓ Indication
- ✓ Hint

Extent

- ✓ Major
- ✓ Considerable
- ✓ Minor

Depending on…

- ✓ Non-quantifiable added benefit
- ✓ No added benefit proven
- ✓ Benefit of drug smaller than benefit of appropriate comparator therapy

Inferential statistical thresholds for relative effect measures

Benefit category	Outcome category		
	All-cause mortality	Serious (or severe) symptoms (or late complications) & AEs, HRQoL[a]	Non-serious (or non-severe) symptoms (or late complications) & AEs
Major	0.85	0.75 & risk ≥5%[b]	N/A
Considerable	0.95	0.90	0.80
Minor	1.00	1.00	0.90

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

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

References 7

Facts – Methodology to assess PROs

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])[8]
- ✓ 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[9]
- ✓ **Extent criteria**
  - ✓ Only non-quantifiable

Examples in upcoming case studies

References 7-9

Agenda

- ○ Setting the scene – General process
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- ○ **Case studies – Data driven**
- ○ In a nutshell – Learnings

PRO Plan (1)

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

References 10-15

Case studies – Data driven

PRO 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

- ⊗ Negative
- ~ Medium
- ✓ Positive

References 16-19

Case studies – Data driven

PRO 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

- ⊗ Negative
- ~ Medium
- ✓ Positive

References 20-21

Case studies – Data driven

PRO Analyse

Abiraterone (03/2018)

- ~ EQ-5D VAS health status responder analysis was assessed as “non-serious” & statistically significant difference did therefore not qualify for an added benefit according to IQWiG 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-5D VAS responder analyses & sensitivity analyses (also for subgroups) accepted – positive change for added benefit for men

Learnings

⊗ Negative
~ Medium
✓ Positive

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**

In a nutshell – Learnings

PRO 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

PRO 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!)**

PRO Analyse

- ✓ 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

Be ready to: PROVE it with PROs!

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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

Gemeinsamer Bundesausschuss
IQWiG Institute for Quality and Efficiency in Health Care

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

PRO guidance in development

eunethta

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

No published PRO guidance

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

NICE National Institute for Health and Care Excellence
Scottish Medicines Consortium

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

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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

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

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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

PRO instrument	Screening	Week 1	Week 5	Week 13	Week 25	Week 37 and every subsequent 12 weeks
BFI		X				
BPI	X	X		X	X	
EQ-5D		X		X	X	X
FACT-P		X	X	X	X	X

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

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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

	Enzalutamide	Placebo	Treatment difference*	p value
FACT-P				
FACT-P total score	-5·08 (-6·87 to -3·28)	-10·87 (-13·49 to -8·25)	5·80 (3·18 to 8·41)	<0·0001
Physical wellbeing	-2·61 (-3·08 to -2·14)	-3·53 (-4·24 to -2·82)	0·92 (0·21 to 1·63)	0·011
Functional wellbeing	-1·95 (-2·49 to -1·41)	-3·11 (-3·92 to -2·30)	1·16 (0·35 to 1·97)	0·0050
Emotional wellbeing	0·19 (-0·18 to 0·57)	-1·03 (-1·63 to -0·43)	1·23 (0·62 to 1·84)	<0·0001
Social or family wellbeing	0·57 (0·08 to 1·07)	-0·26 (-0·98 to 0·46)	0·84 (0·13 to 1·54)	0·021
Prostate cancer subscale	-1·99 (-2·63 to -1·35)	-3·18 (-4·17 to -2·18)	1·19 (0·19 to 2·19)	0·020
Prostate cancer subscale pain related	-1·37 (-1·77 to -0·98)	-1·87 (-2·49 to -1·26)	0·50 (-0·12 to 1·12)	0·11
EQ-5D				
Utility index	-0·07 (-0·09 to -0·05)	-0·10 (-0·14 to -0·06)	0·03 (-0·00 to 0·07)	0·080
VAS score	-5·19 (-7·14 to -3·23)	-9·76 (-12·61 to -6·92)	4·58 (1·85 to 7·31)	0·0010
BPI-SF				
Worst pain	0·90 (0·64 to 1·17)	1·30 (1·00 to 1·61)	-0·40 (-0·66 to -0·15)	0·0022

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

EQ-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

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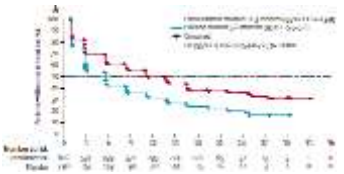
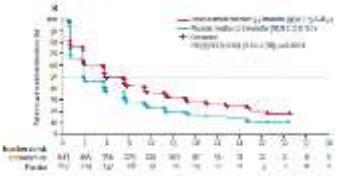
Source: Loriot et al, 2015, Effect of enzalutamide on health-related quality of life, pain, and skeletal-related events in asymptomatic and minimally symptomatic, chemotherapy-naive patients with metastatic castration-resistant prostate cancer (PREVAIL): results from a randomised, phase 3 trial

XTANDI SHOWED A DELAY IN THE TIME TO DETERIORATION IN HRQOL

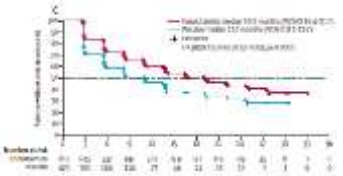
FACT-P Total Score



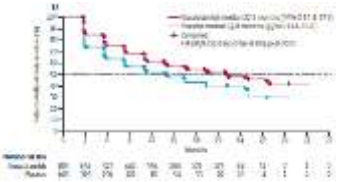
Prostate Cancer Subscale



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-naive patients with metastatic castration-resistant prostate cancer (PREVAIL): results from a randomised, phase 3 trial

THE PRO EVIDENCE PACKAGE SUBMITTED DIFFERED BY HTA BODY

Submitted PRO data

	Endpoint	HAS	G-BA	NICE	SMC
FACT P	Median time to deterioration in FACT P total score				
	FACT P total score (w13 + w25)				
	Change from baseline FACT P total score (w13 + w25)				
	Change from baseline FACT P total score (w61)				
EQ5D	Median time to deterioration in EQ-5D index				
	Median time to deterioration in EQ-5D VAS				
	EQ-5D VAS (w13 + w25)				
	Change from baseline EQ-5D VAS (w13 + w25)				
	Change from baseline EQ-5D index (w61)				
	Change from baseline EQ-5D VAS (w61)				
BPI	Median time to progression of pain at its worst				
	Pain severity and pain interference at (w13 + w25)				
	Change in pain severity and pain interference (w25)				
	Progression of pain at its worst (w25)				

Data submitted in dossier

ACCEPTANCE OF PRO DATA VARIED BY HTA BODY AND OFTEN NO CLEAR ASSESSMENT WAS REPORTED

Acceptance and impact of PRO data in HTAs

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

Data submitted in dossier
? Data not mentioned in report
x Data not accepted
+ 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

Gemeinsamer Bundesausschuss

IQWiG Institute for Quality and Efficiency in Health Care

Scottish Medicines Consortium

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

HAS HAUTE AUTORITÉ DE SANTÉ

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

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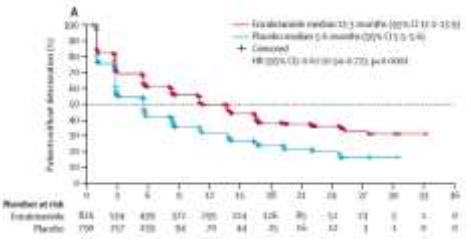
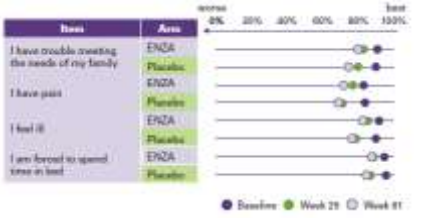
HOWEVER, THE INDUSTRY MUST ALSO PRESENT EVIDENCE IN A MORE USER-FRIENDLY FORMAT

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



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

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



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

Sources: 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 Naidoo et al, 2018 Effect of enzalutamide on specific symptoms and functional areas in metastatic castration-resistant prostate cancer: a novel analytic approach

PROs, the HTA Core Model and European HTA

Finn Børlum Kristensen
Professor, University of Southern Denmark

EUnetHTA developed the HTA Core Model, which contains nine HTA domains

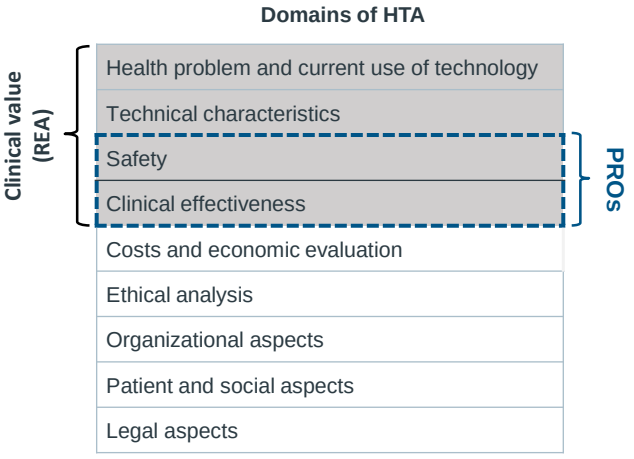
Domains of HTA
Health problem and current use of technology
Technical characteristics
Safety
Clinical effectiveness
Costs and economic evaluation
Ethical analysis
Organizational aspects
Patient and social aspects
Legal aspects

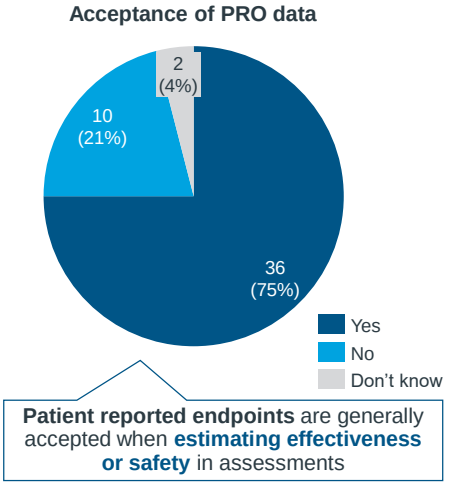
- Developed by EUnetHTA within the HTA Core Model®
- Builds on international consensus on what HTA should consider to assess
- Promotes the wide scope and multidisciplinary nature of HTA

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

Finn Børlum Kristensen | Science & Policy | www.scienceandpolicy.dk

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





Source: Kristensen FB. Mapping of methodologies in EU and Norway, 2018

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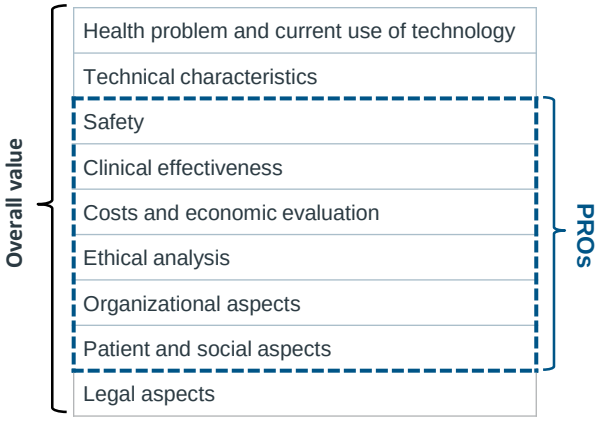
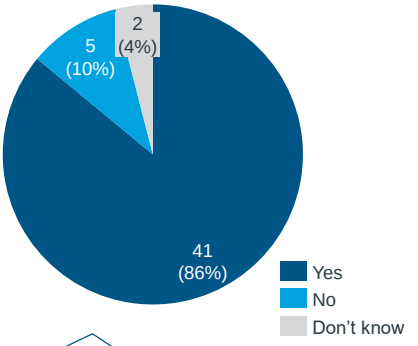
And in assessing the overall value, HRQoL plays an even larger role

Domains of HTA



Acceptance of HRQoL data

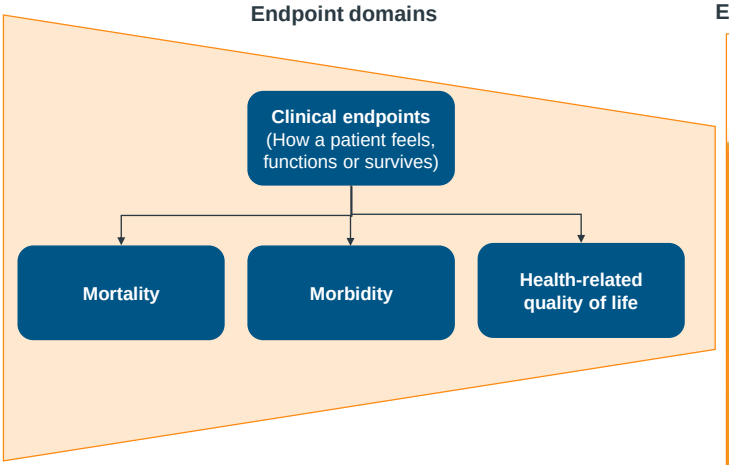


Health-Related Quality of Life measures (HRQoL) are used **in assessments**

Source: Kristensen FB. Mapping of methodologies in EU and Norway, 2018

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

Endpoint domains



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

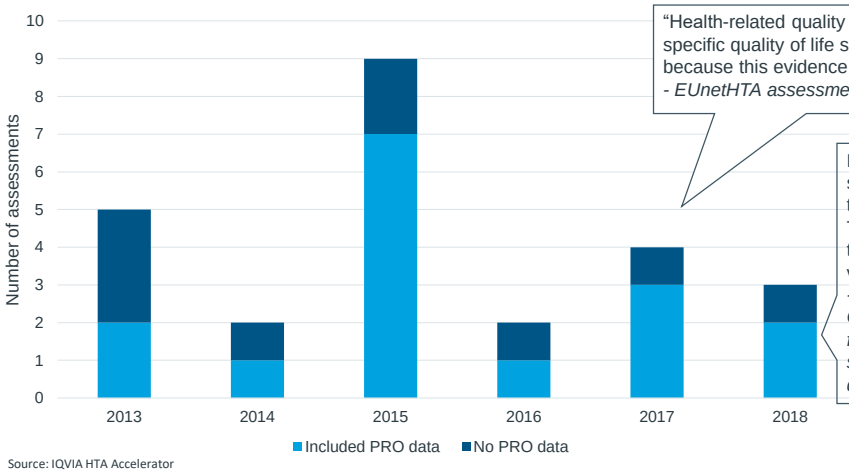
EUnetHTA guideline on HRQoL for REA and utility measures

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.

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

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

Inclusion of PRO data in EUnetHTA assessments

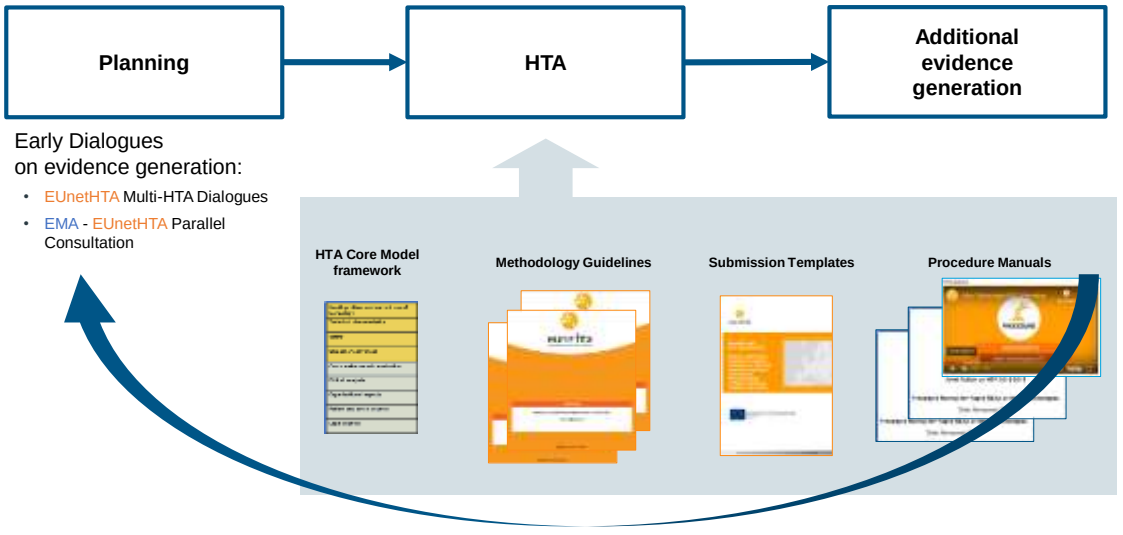


"Health-related quality of life and disease-specific quality of life should be studied, because this evidence is currently lacking
- EUnetHTA assessment of midostaurin

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

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?