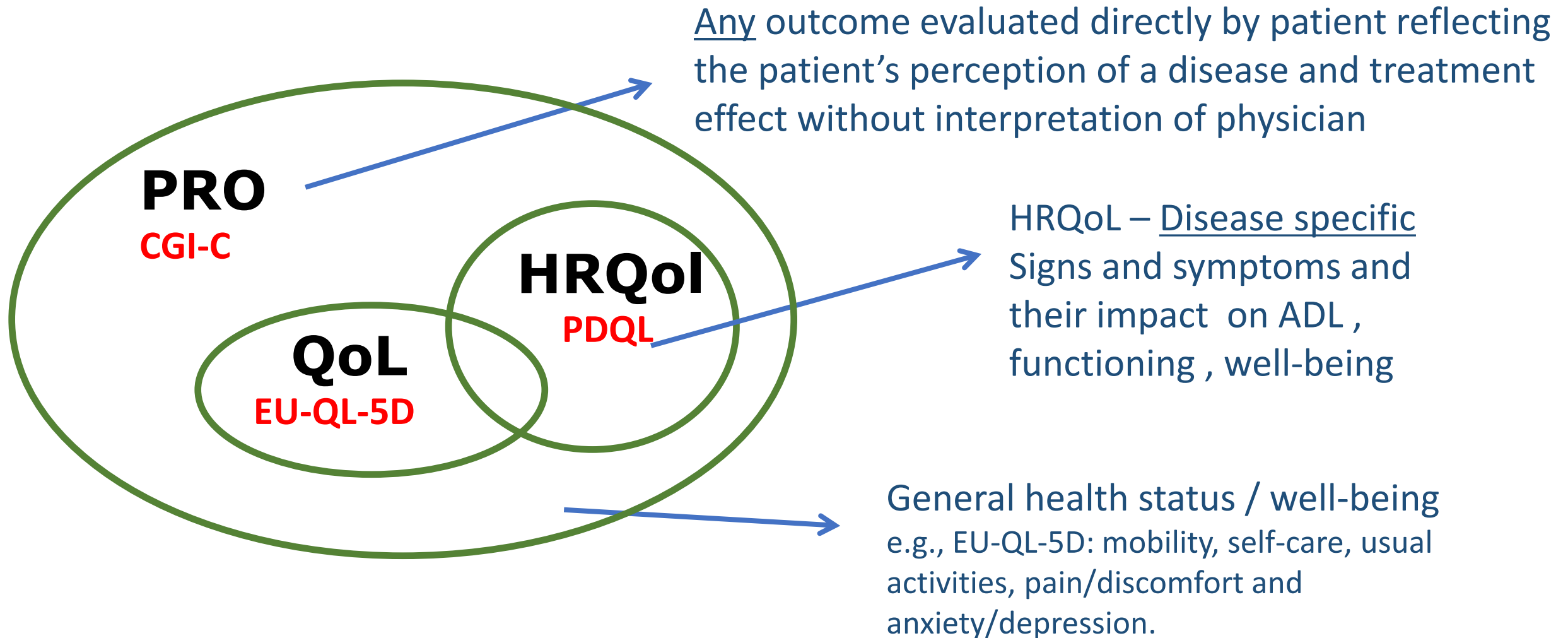


# Patient's Reported Outcomes

*Role in clinical development and approval decisions*

GOOD  
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- What is a Patient Reported Outcome ?
- Pro's and Con's
- Requirements
- Role in Decision making



# PRO's are not rare, but are diverse

Examples:

Pain scale

Dyspepsia Symptom Severity Index

Fatigue Severity Scale (FSS)

Patient Global impression of change (PGI-C)

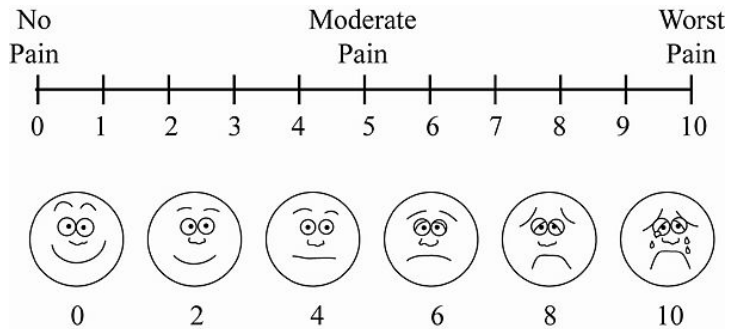
Multiple Sclerosis Walking scale (MSWS-12)

Crohn's Disease Activity Index

Parkinson Quality of Life (PDQL/PDQ-37)

European Qol scale (EU-QOL-5D) ..... Ect

# Pain / MSW-12 / PGI-C



## PGI-C: Clinical Global Impression of Change

- 1 Very much improved
- 2 Much improved
- 3 Minimal improved
- 4 No change
- 5 Minimal worse
- 6 Much worse
- 7 Very much worse

**Table S1** The 12-item Multiple Sclerosis Walking Scale (MSWS-12)

- These questions ask about *limitations to your walking* due to MS during the past 2 weeks.
- For each statement, please circle the one number that best describes your degree of limitation.
- Please answer *all* questions even if some seem rather similar to others, or seem irrelevant to you.
- If you cannot walk at all, please tick this box.

In the past two weeks, how much has your MS ...	Not at all	A little	Moderately	Quite a bit	Extremely
1. Limited your ability to walk?	1	2	3	4	5
2. Limited your ability to run?	1	2	3	4	5
3. Limited your ability to climb up and down stairs?	1	2	3	4	5
4. Made standing when doing things more difficult?	1	2	3	4	5
5. Limited your balance when standing or walking?	1	2	3	4	5
6. Limited how far you are able to walk?	1	2	3	4	5
7. Increased the effort needed for you to walk?	1	2	3	4	5
8. Made it necessary for you to use support when walking indoors (eg, holding on to furniture, using a stick, etc.)?	1	2	3	4	5
9. Made it necessary for you to use support when walking outdoors (eg, using a stick, a frame, etc.)?	1	2	3	4	5
10. Slowed down your walking?	1	2	3	4	5
11. Affected how smoothly you walk?	1	2	3	4	5
12. Made you concentrate on your walking?	1	2	3	4	5

Please check that you have circled ONE number for EACH question

**Note:** Reprinted with permission from Hobart JC, Riazi A, Lamping DL, Fitzpatrick R, Thompson AJ. Measuring the impact of MS on walking ability: the 12-item MS Walking Scale (MSWS-12). *Neurology*. 2003;60(1):31–36. Promotional and commercial use of the material in print, digital or mobile device format is prohibited without the permission from the publisher Wolters Kluwer Health. Please contact [healthpermissions@wolterskluwer.com](mailto:healthpermissions@wolterskluwer.com) for further information.

# PDQL-HR 37 items

## Appendix 1. The modified Parkinson's Disease Quality of Life questionnaire

This questionnaire has 37 questions, which will help us to know how you are feeling. Please do not leave out any questions, it is important that they are all answered. Place a tick ✓ in the box that you feel shows how much of a problem each one has been for you *in the past 3 months*.

How often in the last 3 months have you had trouble with	All the time	Most of the time	Some of the time	A little of the time	Never
1. Stiffness?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. Feeling generally unwell?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. Feeling that you are no longer able to do your hobbies?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. Being tense?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. Feeling insecure of yourself due to your physical limitations?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. Shaking of your hand(s)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7. Feeling worn out or having no energy?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. Difficulties in doing sport or leisure activities?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9. Clumsiness?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10. Feeling embarrassed about your illness?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Appendix 2. Scoring of the Parkinson's Disease Quality of Life questionnaire: the questionnaire consists of 37 items, which provide an overall total score, and can be combined to give four sub-scales

Sub-scale	Item numbers
Parkinsonian symptoms (14 items)	1, 4, 6, 11, 14, 16, 20, 22, 25, 27, 30, 32, 35
Systemic symptoms (7 items)	2, 7, 13, 19, 24, 28, 33
Social functioning items (7 items)	3, 8, 12, 17, 23, 29, 37
Emotional functioning (9 items)	5, 10, 15, 18, 21, 26, 31, 34, 37

The responses to the items are scored for the total score and the sub-scales. Higher scores are indicative of better quality of life.

# EuroQOL (EQ-5D-3L)

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

## Mobility

- I have no problems in walking about
- I have some problems in walking about
- I am confined to bed

## Self-Care

- I have no problems with self-care
- I have some problems washing or dressing myself
- I am unable to wash or dress myself

## Usual Activities (e.g. work, study, housework, family or leisure activities)

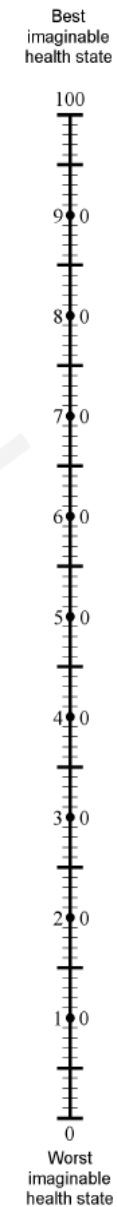
- I have no problems with performing my usual activities
- I have some problems with performing my usual activities
- I am unable to perform my usual activities

## Pain/Discomfort

- I have no pain or discomfort
- I have moderate pain or discomfort
- I have extreme pain or discomfort

## Anxiety/Depression

- I am not anxious or depressed
- I am moderately anxious or depressed
- I am extremely anxious or depressed



# Pros'

- Patient-centered
- Independent from physician
- Perceived Benefit
- What matters

# Cons'

$$\frac{C \quad B \quad G}{M \quad E \quad B}$$

- Subjective → Double blind studies
- Can be driven by one sign/symptom
- Not very sensitive to change
- Not always disease specific
- (HR) QoL not interchangeable
- High variability



## PRO are clinical outcome measurements and thus need to be validated

- Face validity
  - Is the scale reliable
  - Content Validity
  - Sensitive to change
  - Can we determine which xx points change would be of clinical relevance
  - Sensitive to detect a treatment effect
  -
- } Validation of a PRO is a research discipline**

# Role in decision making/ labelling

$\frac{C \ B \ G}{M \ E \ B}$

## Example: Parkinson's disease

Non-PRO	PRO	HRQoL	QoL	Approval	PRO in labeling ?
UPDRS	CGI-I	PDQL	EQ-QoL-5D		
+	+	+	+	Yes	PRO yes (HR)QoL case by case
+	+	+	-	Yes	Idem
+	+	-	-	Yes	PRO yes QoL not applicable
+	-	-	-	Yes	Not applicable
-	-	+	+	No!	Not applicable

- PROs are certainly being utilized to support claims made by Marketing Authorization holders in product assessment and for labeling
- **Play essential role for the approval/refusal products**
  - autoimmune conditions, respiratory conditions, pain, neurological conditions and psychiatric conditions.
- **PRO Result blinding and randomized are more trustworthiness,**
  - open-label studies also contribute to patient-care decision making

**Conclusion:** Overall, PRO integration into the assessment of the benefit-risk and approval/refusal of products is gradually increasing.



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MEDICINES  
USED  
BETTER**

## Internal study MEB by Nora Al-Mugoter

Mentioning of PRO's as primary/secondary endpoint in European Public Assessment reports of 149 new products assessed between 2018-2020 .

- EPAR
- Benefit risk assessments
  - Discussion
  - Effect Table



SmPC PRO's in the labelling



Increasing influence in decision making

May affect patent-care decision making

# Role in decision making/ labelling

Description	number
PROs utilized as primary and/pr secondary endpoints and/or contributed to benefit-risk, effect table and product labeling	84 (56.4%)
PROs utilized as a primary endpoint	11 (7.10%)
PROs utilized as a secondary endpoint	74 (49.66%)
PROs mentioned in the benefit-risk balance	55 (36.9%)
PROs mentioned in the Effect table	37 (25.0%)
PROs mentioned in the SmPC	41 (29.5%)

## Type of treatment and PRO use/contribution

