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Health Related Quality of life Questionnaires a Regulatory Perspective

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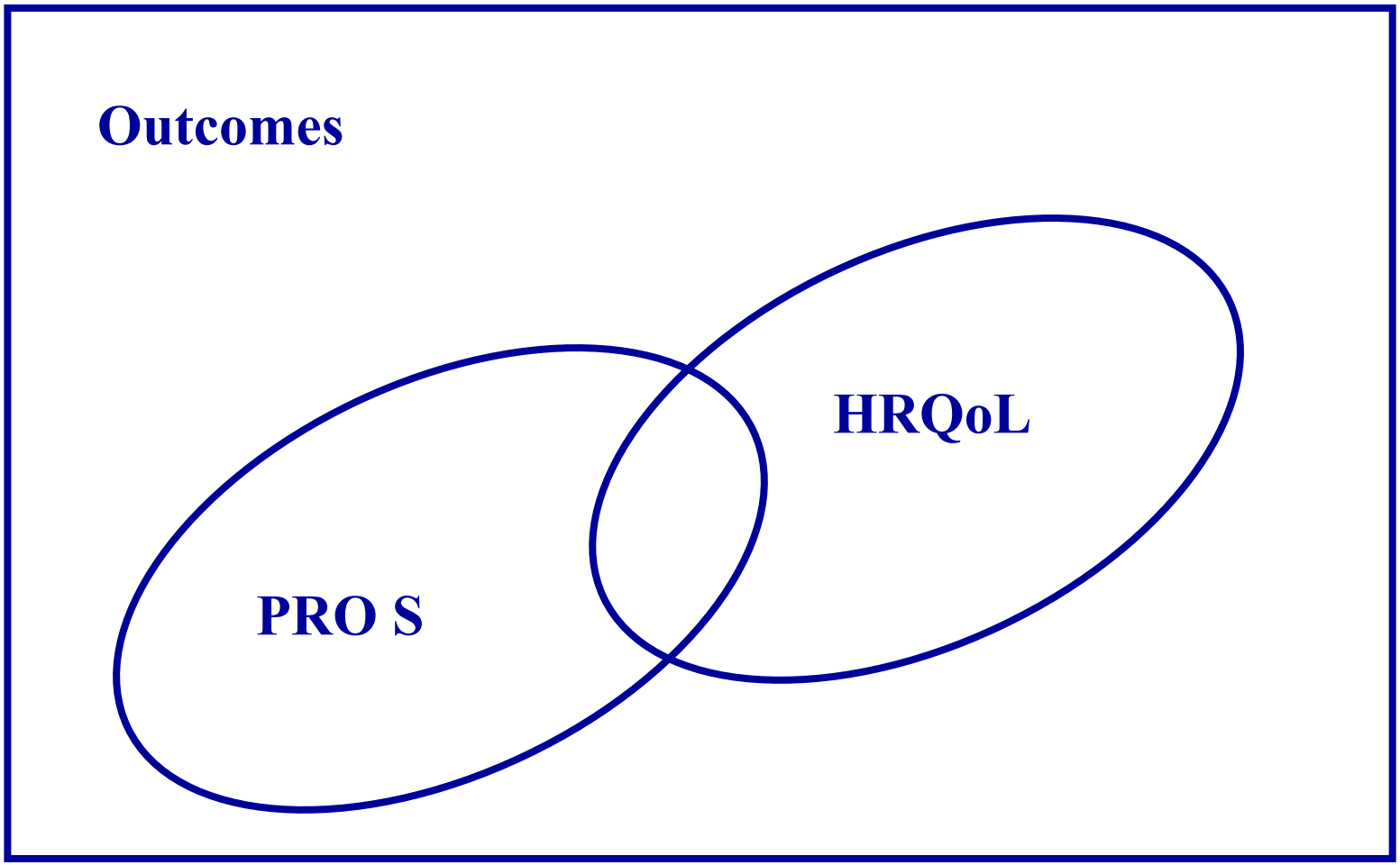
Patient reported outcomes (1)

Any outcome based on reports and/or ratings of a disease and its treatment(s) provided by the patient.

Usually are patient's self-evaluation of symptoms/signs, activities of daily life, functional status, well-being, satisfaction.

Range form Symptoms/signs <> HRQoL



Patient reported outcomes (2)

Well-accepted endpoints in clinical trials e.g.

Primary:

Migraine, Pain, Allergic rhinitis, Asthma, Parkinson's disease

Secondary:

CGI, ADL, functional status, well-being, satisfaction

Patient reported outcomes (2)

As secondary endpoints, PROs, may add to the interpretation of the observed effect on the primary endpoint .

e.g. FEV versus symptom score

VAS pain vs. ADL

Health related quality of life (1)

Focuses on the assessment of broad multidimensional concepts of health (e.g. physical, emotional, social).

Specific case of PRO.

Health related quality of life (2)

- **May provide insight in the interpretation of the observed effect on the primary endpoint in terms of consequences for in daily life and social functioning.**

- **However, its value in terms of added value to the traditional/clinical endpoints from a regulatory viewpoint is still under discussion.**

Approval of a product

Balance efficacy/safety

Claim oriented - Indication

- Symptoms/sign

e.g. Disease oriented.

Approval of a product

Focus on core symptoms of the underlying disease

=> as expressed in for instance, in symptoms and signs score.

=> If a clinically relevant effect is shown a SPC claim can be defined relatively easy.

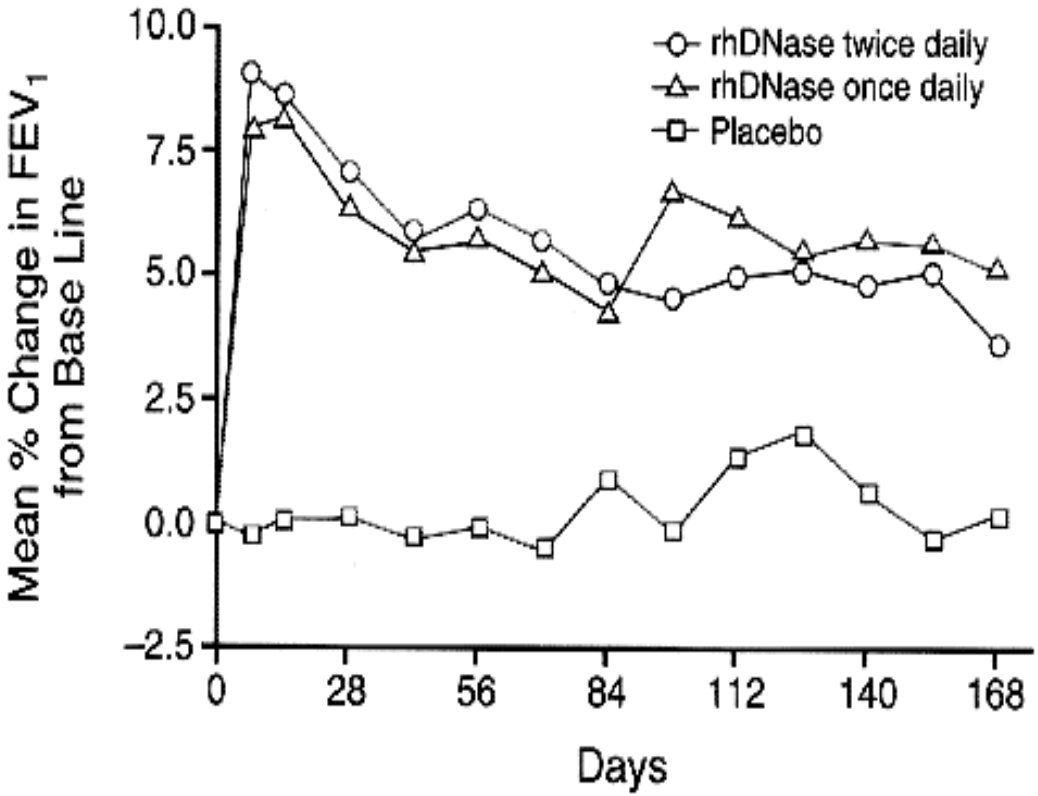
Approval & HR-Quality of life (1)

Would approval of be justified if

- **A major improvement in HRQL is observed but not in the core symptoms/signs of the disease ?**
- **If major improvement on symptoms and signs is observed but none on the HRQL ?**
- **HRQL as primary efficacy variable in clinical trials ?**

Improvement in HRQL & Improvement in symptoms/signs

- **Example rhDNase in cystic fibrosis.**



Effect of Aerosolized Recombinant Human DNase on Exacerbations of Respiratory Symptoms and on Pulmonary Function in Patients with Cystic Fibrosis, Henry J. Fuchs, et al, NEJM; 1994: 331:637-642.

VARIABLE	PLACEBO (N = 325)	RHDNASE	
		ONCE DAILY (N = 322)	TWICE DAILY (N = 321)
Dyspnea scale (100-mm scale) — change from base line	0.4±0.6	−2.1±0.7†	−0.8±0.7
Overall well-being score (5-point scale) — change from base line	−0.058±0.22	0.019±0.024†	−0.004±0.026
Cystic fibrosis–related symptom score (5-point scale) — change from base line	−0.001±0.022	0.126±0.025‡	0.112±0.025‡
Hospital days — mean no.	6.9	5.6§	5.9¶
Parenteral-antibiotic days — mean no.	11.2	8.5¶	9.0¶
Days at home due to illness — mean no.	4.8	3.3¶	4.5
Mean cost of care for an exacerbation	$6,443	$4,761	$5,629
Cost of rhDNase‖	—	$4,536	$9,072

*Plus–minus values are means ±SE.

†$P \leq 0.05$ for the comparison of rhDNase with placebo.

‡$P < 0.01$ for the comparison of rhDNase with placebo.

§$P = 0.06$ for the comparison of rhDNase with placebo, by the Wilcoxon rank-sum test.

¶$P < 0.05$ for the comparison of rhDNase with placebo, by the Wilcoxon rank-sum test.

‖Based on the factory cost of rhDNase ($27 per ampule). Does not include the cost of the PulmoAide compressor ($95) or that of the T-Updraft nebulizer ($235, based on a cost of $1.40 per unit).

Improvement in symptoms and signs, not in HRQoL

- **Example Parkinson disease**

Table 4. Mean Changes From Baseline to Month 23.5 in Unified Parkinson's Disease Rating Scale (UPDRS) Scores*

Variable	Pramipexole (n = 151)	Levodopa (n = 150)	Difference in Treatments (95% CI)†	*P* Value
Total UPDRS	4.5 (12.7)	9.2 (10.8)	−5.0 (−7.6 to −2.4)	<.001
Motor	3.4 (8.6)	7.3 (8.6)	−3.9 (−5.7 to −2.1)	<.001
ADL	1.1 (4.5)	2.2 (3.2)	−1.4 (−2.2 to −0.5)	.001
Mental	0.0 (1.6)	−0.2 (1.2)	0.1 (−0.2 to 0.3)	.72

*Values are expressed as mean (SD). Positive values indicate improvement. ADL indicates activities of daily living.
†Difference in treatment is the difference in mean change between the groups (pramipexole minus levodopa) and is adjusted for investigator effects and the baseline value of the outcome variable in an analysis of covariance model.

Pramipexole vs Levodopa as Initial Treatment for Parkinson Disease A Randomized Controlled Trial , Parkinson Study Group, JAMA. 2000;284:1931-1938.

Improvement in symptoms and signs, not in HRQoL

- **Example Parkinson disease**

Table 2. Treatment Effects on Dopaminergic End Points*

End Points	No. (%) Pramipexole (n = 151)	No. (%) Levodopa (n = 150)	HR (95% CI)†	*P* Value
First dopaminergic complications‡	42 (27.8)	76 (50.7)	0.45 (0.30-0.66)	<.001
Wearing off	36 (23.8)	57 (38.0)	0.57 (0.37-0.88)	.01
Dyskinesias	15 (9.9)	46 (30.7)	0.33 (0.18-0.60)	<.001
On-off fluctuations	2 (1.3)	8 (5.3)	0.27 (0.06-1.32)	.11

*All analyses are stratified by enrolling investigator.
†HR indicates hazard ratio; CI, confidence interval. The HR is the ratio of the risk of reaching the end point per unit of time for patients assigned to initially receive pramipexole treatment to the corresponding risk for patients assigned to initially receive levodopa treatment.
‡Defined as first occurrence of wearing off, dyskinesia, or on-off fluctuations.

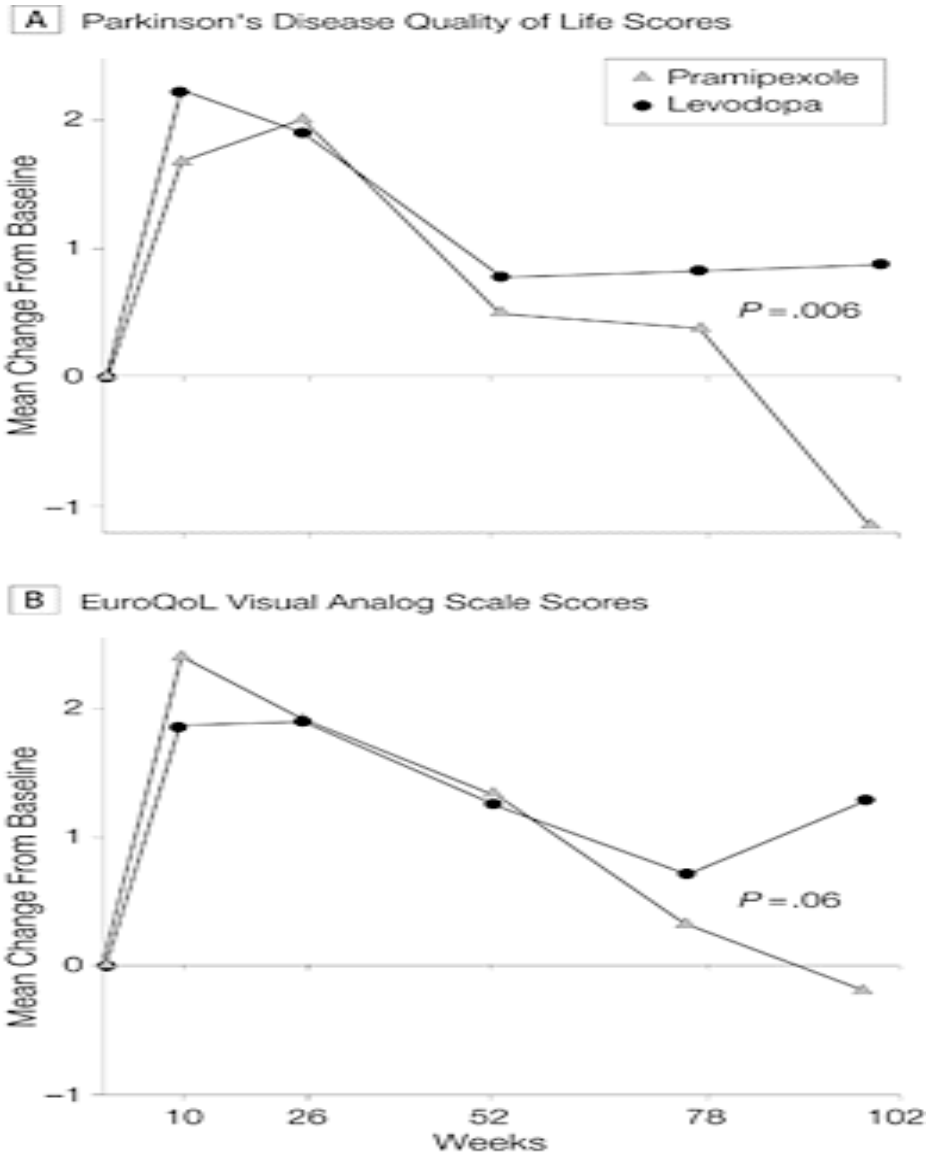


Figure 4.
Mean Changes in Quality-of-Life Scores Over the Course of the Trial

Quality-of-life scores improved by approximately 2 units during the first 6 months of the trial.

At the end of the trial (23.5 months), the group difference in the mean change was statistically significant (*P* = .006) for the Parkinson's Disease Quality of Life Scale and marginally significant for the EuroQol (*P* = .06), with the scores higher for those in the levodopa group. Differences in mean changes were not significant at any other time points.

HRQL driven by one dimension

- **Example Pain**

Example Eight placebo controlled studies in pain (anonymised);

SF-36 Quality of life results								
SF36-subscale	Study 1	Study 2	Study 3	Study 4	Study 5	Study 6	Study 7	Study 8
Physical functioning	-	-	<0.05	-	-	-	-	-
Physial Role limitations	-	-	-	-	-	-	-	-
Social Functioning	-	<0.05	<0.05	-	-	-	-	-
Bodily pain	<0.05		<0.05	<0.05	-	-	<0.05	<0.05
Mental Health	-	<0.05	<0.05	-	-	-	<0.05	-
Emotional Role Limitations	-	-	-	-	-	-	-	-
Vitality<0.05	-	<0.05	-	-	-	-	<0.05	-
General Health Perception	-	-	<0.05	-	-	-	-	<0.05

HRQL as variable in clinical trials

- Chronic conditions e.g. osteoarthritis, asthma.
- Diseases with no symptoms e.g. Hypertension ?
- (Oncology: Survival balanced against HRQOL).

HRQL as variable prerequisites

- **HRQL should be assessed in stable disease i.e. during an exacerbation of disease.**

- **HRQL instruments should be valid, reliable, responsive and interpretability in the condition /setting studied**

  => A lot to do.

Conclusions (1)

PRO's :

- **Accepted as primary and secondary endpoint in clinical trials for many conditions**

  => No regulatory issue .

- **Not always possible e.g. psychiatric conditions.**

Conclusions (2)

HR- Quality of Life:

- **Efficacy first should be shown on well-established traditional/clinical outcomes relevant for the condition studied => A New product will rarely be approved only on the basis of an improvement Health related Quality of Life .**

- **Health related Quality of Life may be of interest to the patient and prescriber provided efficacy has been shown on the core symptom/sign of a disease**

  => Occasionally this may lead to a claim in the SPC.

Conclusions (3)

HR- Quality of Life:

- **Not mandatory as an effect on the core symptom/sign of a disease forms a sufficient legal basis for approval.**

- **Value as primary endpoint on a case by case basis e.g. chronic conditions.**

- **Quality of life assessments usually does not discriminate sufficiently between efficacy and safety.**

  => HRQoL cannot replace the usual package with respect to safety data of a dossier.

Conclusions (4)

HR- Quality of Life:

- **HRQoL cannot replace the usual package with respect to safety data of a dossier.**
- **A major improvement in HRQoL may not be accepted if the improvement is mainly driven by one specific dimension.**
- **The role of HRQoL variables may be more prominent in chronic conditions.**

Thus

In most situations Quality of life will go beyond the usual efficacy and safety assessment which are the basis for an approval.