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Allergy: a global problem. Quality of life

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The importance of quality of life issues in health care practice and research is steadily growing. This growing interest fits into the definition of health as proposed by the World Health Organization (WHO) in 1948 (1). The WHO defines health as 'a state of complete physical, mental and social well-being and not merely the absence of disease and infirmity'. The attention to health-related quality of life is reflected in the increase in the use of quality-of-life evaluation as a technique of clinical research since 1973, when only five articles listed 'quality of life' as a reference key word in the Medline data base; during the subsequent five-year periods there were 195, 273, 490, and 1252 such articles (2).

Also in the field of allergy it has been recognized that allergic disease comprise more than the classical signs and symptoms being part of physical disorders such as allergic rhinitis, asthma and the atopic eczema/dermatitis syndrome (AEDS) (3). In the last decades an increasing effort has been made to understand the socioeconomic burden of atopic disease in terms of effects on health-related quality of life (HRQL) and healthcare costs. It has been acknowledged in several consensus reports that rhinitis and asthma are associated with impairments in the patients' functioning in day-to-day life at home, at work and at school (4–8). With the introduction of questionnaires designed to measure asthma- (9–11) and rhinitis-associated impairments of quality of life (12) it is clear that patients may be bothered by sleep disorders, emotional problems, impairment in activities and social functioning. Also, in general terms, patients with asthma (13) and allergic

rhinitis (14) are impaired in their physical and mental functioning, including vitality and the perception of general health. From daily medical practice it can be easily understood that AEDS has a major impact on HRQL. In a way, the use of questionnaires focused on skin disease (15–17) formally confirms this association.

Assessment of quality of life

Quality of life, QOL, has divergent meanings for different people. Also, HRQL may be considered as ill-defined. More agreement has been reached about the four domains of QOL which are considered to be important:

- 1) physical status and functional abilities;
- 2) psychological status and well-being;
- 3) social functioning;
- 4) economic and/or vocational status and factors (18).

As the true quality of life value cannot be measured directly, researchers and clinicians have to resort to series of questions (items) to measure this construct indirectly. Combinations of items yield scores referring to physical, mental and social domains.

An HRQL instrument must meet several criteria. It should address each component (symptom, condition) that is important to the patient. Attributes of an instrument are described in Table 1.

It will be clear that the construction of quality of life questionnaires is a complex task, drawing from the fields of clinimetrics, psychometrics and clinical decision-making (2). Differences in approach, for instance item selection using factor analysis vs the impact method

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which select items that are most frequently perceived as important by patients – yields different questionnaires (19).

Instruments measuring HRQL

In general two types of instruments, generic and specific, have been used in allergy research.

Generic questionnaires

Generic questionnaires measure physical, psychological and social domains in all health conditions irrespective of the underlying disease. A frequently used generic instrument is the Medical Outcomes Survey Short Form 36 (SF-36) (20). The SF-36 was developed as part of the Medical Outcomes Study and analyzes health status using 36 questions to measure nine different health dimensions. It has been used to characterize patients with asthma. Bousquet (13) compared the FEV₁ and a clinical score of asthma severity for 252 asthmatic patients. There was a significant positive correlation between all nine quality of life domains of the SF-36 and the clinical score of Aas. Eight of the nine domains also correlated with the FEV₁.

Also in perennial rhinitis there was a significant impairment in eight of nine QOL dimensions in patients compared with healthy subjects (14). Furthermore, the SF-36 is used to evaluate the effects of a non-sedating antihistamine on quality of life. In this study all of the nine quality of life dimensions improved significantly after one and six weeks of cetirizine treatment compared with placebo (21).

Other generic instruments that have been used in allergy research are the Sickness Impact Profile (SIP) (22) and the Nottingham Health Profile (NHP) (23). The 136 items in 12 categories of the SIP describe activities of everyday living. This instrument has been used to evaluate the effect of salmeterol on asthma (24). Salmeterol led to significant improvements over salbutamol on virtually all clinical outcomes. Although all four quality of life instruments used in this study showed the same trend in favor of salmeterol, only the disease-specific Asthma Quality of Life Questionnaire (AQLQ) and the Rating Scale utilities showed significantly greater improvement on salmeterol than on salbutamol. In severe AEDS it was shown, using the SIP, that cyclosporin improves quality of life significantly (25). In particular, the SIP has been used for comparison with disease-specific instruments (24, 26–28). The NHP, the only generic instrument derived entirely from lay people, has been used to validate a disease-specific instrument for patients with dermatitis and psoriasis (29). In asthma the NHP was not able to capture clinical improvement by treatment with pulmonary steroids (30).

The latter observations underline the disadvantage that the generic instruments miss depth and therefore

may not be responsive enough to detect changes in general health states in spite of important changes in disease-related problems (26). The advantage of generic instruments, however, is that the burden of illness across different disorders and patient populations can be compared. In a comparison between asthma and epilepsy the major finding was that children with epilepsy had a relatively more compromised quality of life in the psychological, social, and school domains (31). In contrast, children with asthma had a more compromised quality of life in the physical domain. These findings suggested that attention simply to seizure control in the clinical setting will not address the full range of quality of life problems in children with epilepsy.

Disease-specific questionnaires

Specific instruments have been designed by asking patients what kind of problems they experience from their disease. Both the frequency and the importance of impairments are measured by means of the questionnaires. These instruments have the advantage that they describe the disease-associated problems of the patients. As stated above, they seem to be more responsive to changes in HRQL than do the generic instruments.

Several instruments for patients with asthma have been developed. The Asthma Quality of Life Questionnaire of Juniper is focused on symptoms, emotions, exposure to environmental stimuli, and activity limitation (32). Modifications of this questionnaire have been published recently (33, 34). When using HRQL outcome in clinical trials, the question arises whether a change in HRQL is of clinical importance. For the AQLQ, which uses a seven-point scale, the minimal important difference of quality of life score per item is considered to be very close to 0.5 (35). A change of 1.0 in the score represents a moderate change and a change in score of greater than 2.0 represents a large change in HRQL. The minimal important difference as described by Juniper is based upon patient opinions. Measures such as the standardized response mean or the effect size can be used to standardize changes. These measures are based solely upon the distribution of the observed data, in particular upon the variance (36).

Recently, it has been shown that both the SF-36 and AQLQ were able to characterize a group of patients with moderate asthma very well, whereas the AQLQ domains were found to have the best discriminative properties (37).

The Asthma Quality of Life Questionnaire of Marks captures breathlessness, physical restrictions, mood disturbance and concerns for health (38). St. George's Respiratory Questionnaire (11) is designed for patients with asthma and chronic obstructive pulmonary disorder COPD. It can be applied in both reversible and fixed airway obstruction. In contrast to other

Table 1 Attitudes of an instrument

		Description	Interpretation and examples
Content validity	Refers to adequate representation of the content of an instrument		Are all items important for an asthma patient included and all irrelevant items excluded from an asthma specific questionnaire?
Criterion validity	Involves assessing an instrument against external criteria	Concurrent validity means agreement with a gold standard Predictive validity concerns the ability to predict future	Cave: In most diseases a gold standard is not available QOL scores may be predictive of subsequent survival time in cancer trials
Construct validity	Refers to the degree to which an instrument measures the construct that it was designed to measure	Known-groups validity refers to the ability to discriminate between groups in a predicted direction Convergent described in terms of high correlation with related constructs that are expected to be correlated Discriminant described in terms of low correlation with unrelated constructs	Comparison between subjects with severe symptoms and subjects with few symptoms Cross-sectional comparison between rhinitis specific questionnaires yields significant correlations with nasal symptom scores (12) Cross-sectional comparison between eczema specific questionnaires yields low correlation with anxiety (15)
Reliability	Concerns the random variability associated with measurements	Internal consistency is based upon item-to-item correlation and expressed as Cronbach's α , for example Test retest measures of repeatability are Pearson's r and the intraclass correlation coefficient (ICC) Inter-rater reliability concerns the agreement between two or more raters	Reliability coefficients should be above 0.7 (acceptable) or 0.8 (good) to be used in clinical trials and above 0.9 (excellent) for individual patient assessment (36). However, it has been stated, that reliability coefficients must amount to 0.90 for clinical trials and 0.95 for individual patient assessment (101)
Responsiveness	Relates to the ability to detect changes when a patient improves or deteriorates		Moderate mean Δ QOL of 1.06 in subjects whose asthma changed vs 0.11 change in stable asthma (9)

questionnaires, the Living with Asthma Questionnaire (10) does not include impairments experienced as a direct consequence of asthma symptomatology. Other instruments are presented in Table 2. The properties of the most frequently used questionnaire are described in Table 3.

Specific instruments have been developed for children and caregivers (Table 2). In addition, questionnaires have been constructed for different age-groups of patients with rhinitis (12, 39–41).

A simple practical questionnaire technique for routine clinical use, the Dermatology Life Quality Index (DLQI) has been introduced to characterize patients with skin disorders (15). This instrument has been used to compare patients with psoriasis and dermatitis (42). Also versions for children are available: the Children's Dermatology Life Quality Index (CDLQI) and the Infant's Dermatology Life Quality Index (IDLQI) (16). Other questionnaires are the Skindex (43) the Dermatology-Specific Quality of Life (DSQL) (17) and the patient-generated Dermatology Quality of Life Scales (DQOLS) (44).

Recently, a questionnaire has been developed to measure HRQL in patients with allergy to insect stings. Subsequently, this instrument has been used in the evaluation of venom immunotherapy (45). It appeared that venom immunotherapy resulted in a statistically and clinically significant improvement in HRQL.

Why should we measure quality of life?

Both in clinical practice and in research physicians and investigators rely on physiological and objective measures, whenever possible. However in asthma an increase in FEV₁ or a decrease in PC₂₀ histamine or methacholine may occur without any improvement experienced by the patient. Medical intervention may improve physiologic measures, whereas for instance side-effects of drugs or the cumbersome aspects of subcutaneous immunotherapy may unfavorably influence day-to-day life and compliance with treatment.

It has been put forward that the classical outcome variables may only partially characterize the disease of the patient. From that point of view it has been advocated to measure HRQL along with the conventional clinical indices (46).

In line with this reasoning is the weak association between classical asthma measures and the outcome of HRQL questionnaires. Comparison between de AQLQ of Marks with asthma symptoms and lung function variables revealed that a change in AQLQ score was weakly correlated with change in symptom score ($r=0.37$, 95% CI 0.04–0.64) and change in BHR ($r=0.38$, 95% CI 0.06–0.64). The association with change in peak flow variability was weak ($r=0.12$, 95% CI 0.26–0.47) (27). Similar observations have been reported by others (47–50).

An interesting study shows that the mere presence of

Table 2. Health-related quality of life questionnaires used in allergic disorders

Questionnaire	Reference	Scales	No. items	Category	Age group
Adults					
Nottingham Health Profile (NHP)	Hunt (23)	6	45	Generic	
Sickness impact profile (SIP)	Bergner (22)	12	136	—	
15D	Sintonen(102)	—	15	Generic	
Short Form 36 (SF 36)	Ware (20)	8	36	Generic	
Modified Marks Asthma Quality of Life Questionnaire (MAQLQ-M)	Adams (103)	4	22	Asthma	
AQ20	Barley (104)	—	20	Asthma	
Integrated Therapeutics Group Asthma Short Form (ITG-ASF)	Bayliss (105)	6	15	Asthma	
Life Activities Questionnaire for Adult Asthma	Creer (106)	7	70	Asthma	
Living with Asthma Questionnaire	Hyland (10)	11	68	Asthma	
Asthma Quality of Life Questionnaire	Juniper (32)	4	32	Asthma	
Asthma Control Questionnaire (ACQ)	Juniper (107)	—	7	Asthma	
Mini-Asthma Quality of Life Questionnaire	Juniper (96)	4	15	Asthma	
Asthma Quality of Life Questionnaire (standardized)	Juniper (34)	4	32	Asthma	
Perceived Control of Asthma Questionnaire (PCAQ)	Katz (108)	—	11	Asthma	
Asthma Impact Record Index (AIR)	Letrait (109)	3	63	Asthma	
Asthma Quality of Life Questionnaire	Marks (38)	6	20	Asthma	
Patient Satisfaction with Medication (PSAM)	Mathias (110)	4	77	Asthma	
Asthma Symptom Utility Index	Revicki (93)	—	11	Asthma	
St. George's Respiratory Questionnaire	Jones (11)	3	76	Asthma, COPD	
Quality-of-life for Respiratory Illness Questionnaire (QOL-RIQ)	Maille (111)	7	55	Asthma, COPD	
Skindex	Chren (43)	8	62	AEDS	
Dermatology Life Quality Index (DLQI)	Finlay (15)	—	10	AEDS	
Dermatology quality of life scales (DQOLS)	Morgan (44)	8	29	AEDS	
Questionnaire on Experience with Skin Complaints	Schmid-Ott (112)	5	34	AEDS	
Questionnaire of Coping with Skin Disease (QCSD)	Stangier (113)	5	42	AEDS	
Rhinoconjunctivis Quality of Life Questionnaire	Juniper (12)	7	28	Rhinitis	
Rhinoconjunctivitis Quality of Life Questionnaire (standardized)	Juniper (97)	7	28	Rhinitis	
Mini Rhinoconjunctivitis Quality of Life Questionnaire	Juniper (95)	5	14	Rhinitis	
Rhinitis Symptom Utility Index (RSUI)	Revicki (92)	—	10	Rhinitis	
Children					
Functional status II, parent version	Stein (114)	2	28	Generic	0–12
Exqol	Eiser (115)	—	12	Generic	6–12
Adolescent Asthma Quality of life Questionnaire (AAQOL)	Rutishauser (116)	6	32	Asthma	12–17
Paediatric Asthma Quality of Life Questionnaire (PAQLQ)	Juniper (117)	3	23	Asthma	7–17
Life Activities Questionnaire for Childhood Asthma	Creer (118)	7	71	Asthma	5–17
Childhood Asthma Questionnaire (CAQ)CAQA	Christie (119)/French (120)	2	14	Asthma	4–7
Childhood Asthma Questionnaire (CAQ)CAQB	Christie (119)/French (120)	4	22	Asthma	8–11
Childhood Asthma Questionnaire (CAQ)CAQC	Christie (119)/French (120)	5	—	Asthma	12–16
TACQOL	Theunissen (121)	7	56	Asthma	8–17
TACQOL parent-version	Vogels (122)	7	56	Asthma	6–15
Children's Health Survey for Asthma (CHSA)	Asmussen (123, 124)	5	48	Asthma	5–12
HAY (How Are You) child version	Le Coq (125)	8	34	Asthma	8–13
HAY (How Are You) parent version	Le Coq (126)	6	38	Asthma	8–12
Adolescent Asthma Quality of life Questionnaire (AAQOL)	Rutishauser (116)	6	32	Asthma	12–17
Children's Dermatology Life Quality Index (CDLQI)	Lewis Jones (16)	—	10	AEDS	3–16
Infants' Dermatitis Quality of Life Index	Lewis Jones (127)	—	10	AEDS	< 4
Adolescent Rhinoconjunctivitis Quality of Life Questionnaire	Juniper (40)	6	25	Rhinitis	12–17
Paediatric Rhinoconjunctivitis Quality of Life Questionnaire	Juniper (41)	5	23	Rhinitis	6–12
Caregivers					
Paediatric Asthma Caregivers Quality of Life Questionnaire (PACQLQ)	Juniper (128)	2	13	Asthma	7–17 <7(129)

respiratory symptoms or a (gradually) reduced lung function is insufficient reason for patients to seek medical help. Subjects are more likely to consult their general practitioner once their quality of everyday life is affected or they experience variability in lung function (51).

Also, rhinitis related quality of life appears to be moderately correlated to the more classical outcome variables used in clinical trials, such as daily symptom scores and nasal hyperreactivity (52).

Another argument to use quality of life instruments

lies in the headstart with respect to the knowledge of their validation, reliability and responsiveness compared to the common symptom scores or visual analogue scores (VAS) scales used at clinical trials. In the field of nasal allergy, validation or standardization of symptom scores has rarely been the subject of research. In asthma, even quite recently introduced measures, such as the number of symptom-free days, merit more attention in terms of standardization and validation (53).

Table 3. Clinimetric properties of some QOL questionnaires used in atopic disease

Questionnaire/reference	Validity	Comparison	Validity coefficient	Reliability	Reliability coefficient	Responsiveness
SF-36(13)	Construct	AAS scores	0.17–0.50	Cronbach α	0.91	
Living with Asthma Questionnaire (10)	Construct	SIP	0.17–0.66	Test-retest r	0.9	
Asthma Questionnaire (10)	Predictive	Steroid prescribing	0.35			
Asthma Quality of Life Questionnaire (9, 32)	Construct	Peak flow	–0.44			
		SIP	0.28–0.52	ICC	0.89–0.94	1.06 $\pm$ 0.78 change (on a 7-point scale) after steroid treatment
		SF36	0.09–0.81			
		FEV ₁	0.06–0.18			
		PC ₂₀	0.00–0.14			
		Asthma control	0.31–0.69			
		PEF	0.04–0.16			
Asthma Quality of Life Questionnaire (27, 38)	Construct	FEV ₁	–0.20	Cronbach α	0.92–0.94	Correlation δ QOL and δ symptoms: $r=0.37$; δ BHR: $r=0.38$; δ PEF: $r=0.12$; δ SIP: $r=0.18$
St. George's Respiratory Questionnaire (SGRQ) (11)	Construct	PD20	–0.16	ICC	0.80	Variance for linear regression between changes in SGRQ and reference measures. R^2 : 0.02–0.22
		Number of drugs	0.38			
		FEV ₁ , FVC, SaO ₂	0.1–0.2	Test-retest r	0.87–0.91	
		6-MWD	0.13–0.44			
		SIP	0.07–0.54			
		Anxiety	0.12–0.38			
		Depression	0.08–0.39			
Childhood Asthma Questionnaire (119, 120)	Construct	Parental rating of severity	0.50	Cronbach α	A: 0.59–0.63	
CAQ A; CAQ B; CAQ C		Doctors' rating of severity	0.46	Test-retest r	B: 0.44–0.82	
		PEF variation	–0.19–0.21	ICC	C: 0.50–0.80	
					A: 0.59–0.63	
					B: 0.73–0.75	
					C: 0.73–0.84	
					A: 0.59–0.63	
					B: 0.72–0.74	
					C: 0.68–0.84	
Paediatric Asthma Quality of Life Questionnaire (117)	Construct	FEV ₁	–0.37––0.61	ICC	0.84–0.95	δ QOL score of patients in whom asthma changed: 0.79 ($P<0.001$) on a 7-point scale
		PEF	–0.01––0.22			
		Asthma control	–0.26––0.34			
		β –agonist	–0.30––0.30			
		Feeling	0.36–0.53			
		Thermometer				
Paediatric Asthma Caregivers Quality of Life Questionnaire (PACQLQ) (128)	Construct	Caregiver burden of illness	0.26–0.70	ICC	0.84	δ QOL in subjects who changed in global ratings: 0.71–1.80 ($P<0.001$) on a 7-point scale
		FEV1	0.25–0.26			
		PEF	0.31–0.37			
		Asthma control	–0.29––0.30			
		β –agonist	–0.22––0.28			
Dermatology Life Quality Index (15)	Construct	SF36	–0.15––0.41	Test-retest r	0.99	
Children's Dermatology Life Quality Index (CDLQI) (16)	Construct	Eczema vs controls	Mean CDLQI: 7.7 $\pm$ 5.6 vs 0.38 $\pm$ 0.71	Test-retest r	0.86	
Infants' Dermatitis Quality of Life Index (127)	Construct	Clinical severity	0.58	Test-retest r	0.91	
Rhinoconjunctivitis Quality of Life Questionnaire (12)	Construct	FDI	0.87			
Adolescent Rhinocconjunctivitis Quality of Life Questionnaire (41)	Construct	Daily nasal symptoms	0.31–0.59	ICC	0.86	δ QOL between treatment groups in the hayfever season: 0.57 $\pm$ 0.39 ($p=0.009$)
		Changes in daily nasal symptoms and QOL	0.38–0.52			Repeated measures analysis of variance in patients treated with fluticasone or loratidine: treatment effect: $P=0.049$; time effect: $P=0.0001$
Paediatric Rhinocconjunctivitis Quality of Life Questionnaire (42)	Construct	Daily nasal symptoms	0.51–0.59	ICC	0.93	δ QOL in children in whom rhinoconjunctivitis changed: 0.57 ($P<0.01$)
		Physician global rating	0.45			

Other reasons to assess quality of life are conceivable. Measurement of quality of life can also be useful for screening purposes or for evaluation of therapy. Quality of life may be a determinant of effectiveness or efficacy of treatment. Moreover, its assessment might be relevant to striving for optimal decision-making.

Quality of life instruments in clinical trials

As the perception of patients is clearly important in the management of disease and patient compliance (Fig. 1), measurement of this 'dimension' by HRQL questionnaires in clinical trials may be justified. The emphasis on quality of life has sometimes resulted in a routine inclusion of HRQL questionnaires in clinical trials. The inclusion of such an instrument is valuable only if the changes can be interpreted by clinicians and contributes to optimal medical decision-making. In an editorial, criticism has been directed to the routine inclusion of such instruments when the structure of the evaluation and its rationale appears ill-defined (54).

Generally in clinical trials the effect of treatment or intervention on HRQL runs parallel with the effect on conventional medical outcome measures. However, in some studies differences can be found. In a study evaluating the combined effect of steroids and antihistamines no differences were demonstrated between patients treated with antihistamine and steroids *vs* steroids alone in terms of quality of life, whereas for some patient-rated symptoms the combination turned out to be superior (55). In a large multicenter study comparing budesonide and fluticasone it was found that both drugs were equally effective in suppressing symptoms (56), although budesonide had a better effect on general quality of life (57). This might indicate that patients perceive differences not captured by conventional symptom scores. The reverse situation, i.e. significant effects on classical outcomes (symptom scores, medication use, peak flow or FEV₁) without important change in two generic and two specific HRQL measures has been described in a study on the effect of formoterol, a long-acting α_2 -agonist, in mild to moderate asthmatic patients (58). The latter discrepancies can be explained by a limited performance of HRQL measures in mild asthmatic patients. Alternatively, it is possible that the minor changes in symptom scores and lung function due to the intervention are not perceived by patients as relevant. Moreover, patients with a chronic condition may adapt themselves to their disease.

Limitations

The strength of HRQL questionnaires, that is the patient-centred approach, is also one of its weaknesses. Perceptions of quality of life experienced by persons may shift in time. It is easy to understand that a dramatic personal accident or a serious disease will not

only cause deterioration in quality of life but will eventually also influence the patient's values and internal standards. For instance, in a study of quality of life after radiotherapy for laryngeal cancer, a temporary deterioration of physical functioning and symptoms was reported, mostly caused by side-effects of treatment. Despite physical deterioration, there was an improvement of emotional functioning and mood after treatment, probably as a result of psychological adaptation and coping processes (59). It is possible also that in less dramatic circumstances, disease and treatments will induce shifts in perception due to changes in the patient's values. Such subjective changes in patients' perception are known as *response shift*.

Socioeconomic status is an additional important independent factor influencing HRQL. In a recent study with asthmatic patients it was shown that socioeconomic status attributes to HRQL. More importantly, in this study it was difficult to separate out the unique effects of socioeconomic status and race/ethnicity (60). Recently, a significant relationship between the mental health of children with asthma and family functioning has been shown (61). These findings suggest that the domains comprising the HRQL of children with asthma are related to both disease and non-disease factors.

Psychological functioning influences the burden of a specific disease. A study designed to assess the effects of depressive symptoms on asthma patients' reports of functional status and health-related quality of life revealed that asthma patients with more depressive symptoms reported worse health-related quality of life than asthma patients with similar disease activity, but fewer depressive symptoms (62). Interestingly, these findings were seen not only in generic (SF-36) but also in specific (AQLQ) instruments. This means that a disease-specific instrument may be also influenced by phenomena such as fear and depression.

Finally, patients may either intentionally or unconsciously mask their symptoms or trivialize their diseases. They may tend to ignore or discount those problems which they believe are unrelated to their illness. Others may tend to give socially desirable answers. Response shifts and illusory mental health (63) are not easily captured with HRQL instruments, but they will certainly influence the outcome of a clinical trial, when HRQL is chosen as the primary endpoint.

In summary, one has to realize that the translation of clinical effects of treatment into perceived and reported changes in quality of life finds a place at the integration level of the patient and this is, in a way, a black box which is not easy to assess (Fig. 1).

For these reasons it is strongly recommended to use HRQL outcome measures in parallel with conventional physiological outcome measures.

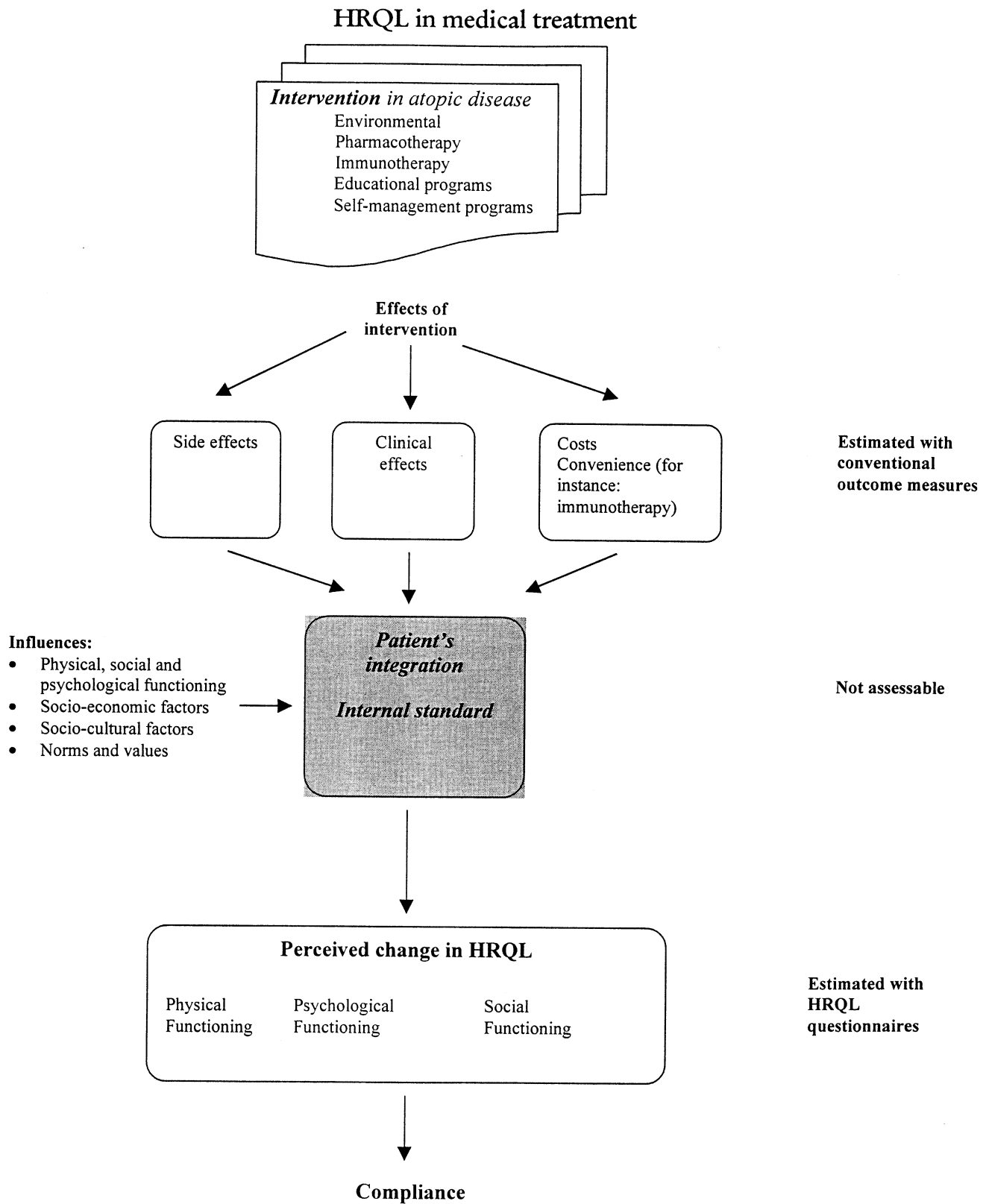


Figure 1. A model representing the relationships between clinical aspects of therapy, HRQL and factors influencing HRQL (adapted from Cramer and Spilker (17)).

Effects of comorbidity on HRQL

Asthma, allergic rhinitis and AEDS often coexist. The question to what extent concomitant allergic disease affects quality of life has infrequently been addressed. In a recent study the SF-36 questionnaire from 850 subjects recruited in two French centers participating in the European Community Respiratory Health Survey was evaluated. Both asthma and allergic rhinitis were associated with impairment in quality of life. However, 78% of asthmatics also had allergic rhinitis. Subjects with allergic rhinitis but not asthma were more likely to report problems with social activities, difficulties with daily activities as a result of emotional problems, and low mental well-being than subjects with neither asthma nor rhinitis. Patients with both asthma and allergic rhinitis experienced more physical limitations than patients with allergic rhinitis alone, but no difference was found between these two groups for concepts related to social/mental health (64). In another study focusing on asthma, rhinitis and AEDS, comprising 325 subjects allergic to house dust mites, it was found that patients did show impaired quality of life compared to normal groups, irrespective of the nature of the atopic disorder. Patients with the diagnosis of asthma did stand out in terms of physical impairments. In addition, asthma symptoms assessed with a visual analog scale had a major effect on social functioning, emotional functioning and vitality. Sleep disorders, particularly in patients with AEDS, appeared to be associated with bodily pain, physical functioning, decreased vitality, social functioning, mental health and general health (65).

It is not only concomitant atopic disease that has an impact on quality of life. Associated diseases such as rhinosinusitis, recurrent ENT (ear, nose and throat) infections and nasal polyps may bother patients with rhinitis and asthma. Using the SF-36 and a sinusitis-specific quality of life measure (the CSS: Chronic Sinusitis Survey) it has been shown that HRQL is impaired and that sinus surgery may improve quality of life for sinusitis patients undergoing surgery (66, 67). Recognizing that rhinosinusitis is a disabling disease, other specific instruments such as the Rhinosinusitis Disability Index (RDI) (68) and the 31-item Rhinosinusitis Outcome Measure (RSOM-31) (69) have been introduced. The impact of recurrent ENT infections on social life in children during the first four years of life is not easily captured. Indirect information can be obtained by use of a specific questionnaire, which measures the parental quality of life (70). Nasal polyposis is a frequent inflammatory chronic disease of the upper respiratory tract, which is frequently associated with lower respiratory disorders. Radenne (71) compared the HRQL profiles in patients with nasal polyposis with those of patients with perennial rhinitis and healthy subjects. It appeared that nasal polyposis impaired HRQL more than perennial allergic rhinitis

($P < 0.05$). The impairment of HRQL was greater when nasal polyposis was associated with asthma ($P < 0.05$). In addition, sequential evaluations of HRQL, nasal symptoms, and pulmonary function were performed 10 months after the first evaluation in 28 patients with nasal polyposis. These evaluations demonstrated that nasal polyposis treatment either with nasal steroids or endonasal ethmoidectomy significantly improved both nasal symptoms and QOL without significant changes in pulmonary function.

Comorbidity may constitute a bias if the clinician or investigator is interested in one particular disease. A recent study assessed the effects of comorbidity on the results of QOL measures through an analysis of longitudinal data from three double-blind, randomized, placebo-controlled clinical trials dealing with heartburn, asthma, and ulcer (72). The study results suggest that comorbid conditions significantly and extensively affect patients' scores on generic QOL measures and estimation of treatment effects, whereas their influence on disease-specific QOL scores and estimation of treatment effect is considerably smaller, although not absent.

These findings have significant practical implications for the estimation of true treatment effects, control of comorbidity effects, and the design of QOL trials.

Allergic disease and its impact on learning and school activities

The notion that atopic disease may have an unfavorable effect on daily functioning has been underlined by studies focused on school and absenteeism. Night time awakenings in children with asthma may affect school attendance and performance, as well as work attendance by parents (73). In a Dutch population study it was shown that of children with recent symptoms suggestive of asthma, 37% reported school absence for at least one week during the past 12 months, compared with 16% in children without respiratory symptoms. School absence because of respiratory illness was reported for 22%, and medicine use for respiratory problems for 38% of the children with recent symptoms suggestive of asthma (74). In another study students reported interference in their college activities and reported missing days of work and school because of asthma or allergies (75).

If nasal symptoms are not well controlled in patients with allergic rhinitis they may contribute to learning problems during school hours, either by direct interference or indirectly because of nocturnal sleep loss and secondary daytime fatigue (76, 77). Seasonal allergic rhinitis may be associated with reduced ability to learn. Treatment with sedating H_1 -antihistamines will aggravate these problems, whereas treatment with nonsedating H_1 -antihistamines will only partially reverse the limitations in learning (78, 79). Recently, in a single-blind study carried out over 6 months in 113 children with allergic perennial rhinitis and 33 children with

nonallergic perennial rhinitis, it was shown that beclomethasone or ipratropium bromide diminished the interference resulting from rhinorrhea on school attendance, concentration on school work, and sleep (80).

Allergic disease and work impairment

In assessments of the cost of illness, productivity losses potentially constitute a large proportion. Not unexpectedly it has been demonstrated that in adult asthma annual productivity loss days increased with increasing disease severity (81). The counterpart of the effect of asthma on work productivity comprises the effect of work on asthma. The prevalence of occupational asthma and work-related aggravation of asthma is increasing (82). It has been estimated that 5–15% of adult-onset asthma can be attributed to occupational exposures (83). Worsening of asthma at work occurs more commonly on the basis of aggravation of underlying asthma than on the basis of possible occupational asthma. It can be hypothesized that patients with occupational asthma may have a more severe impairment in quality of life because of the entanglement between work and disease. In a study designed to address this question a statistically significant difference was seen in the scores of the AQLQ (Juniper) obtained from a group of patients with occupational asthma and a control group of matched subjects with asthma of nonoccupational origin. The mean difference in the total score was 0.6 on a scale of 1 (no limitation or none of the time) to 7 (severe limitation or all the time) at the expense of the patient with occupational asthma (48). The absolute difference between both groups was small. Possibly, other more generic instruments focused on labor detect more profound differences.

Blanc et al. showed that both asthma and rhinitis negatively affect work productivity. Those with asthma are less likely to be employed at all, while among those remaining employed rhinitis is a more potent determinant of decreased work effectiveness (84). In the USA allergic rhinitis results in approximately 811 000 missed workdays, 824 000 missed school days, and 4230 000 reduced activity days per year (85). These data are derived from 38.9 million persons experiencing allergic rhinitis in 1987, with approximately 4.8 million persons seeking medical treatment.

These data indicate that allergic rhinitis may have an important impact on occupation and worker productivity. Patients are bothered by tiredness, with poor performance and concentration at work, and headache and malaise. Conjunctivitis may impair vision and vision-related activities. Not only disease but also medications may influence work productivity. It has been estimated that 50% of workers who treated their allergic rhinitis with first generation sedating antihista-

mines functioned at 75% efficiency for 14 days per year (86). Patients taking these sedating antihistamines are more likely to sustain occupational injuries (odds ratio 1.5). The type of occupational injuries include fractures, dislocations, open wounds, superficial injuries and burns (87). With the newer antihistamines these problems have been significantly reduced (88).

Health related quality of life and health care costs

Recent studies have estimated the costs for treatment of allergic rhinitis, asthma and associated diseases (85, 89, 90).

In 1998, asthma in the USA accounted for an estimated 12.7 billion dollars annually (89). A comparison of asthma costs in developed countries suggested an average annual societal burden ranging from \$326 to \$1315 per afflicted person (1991) (91). Approximately 40–50% of the total asthma costs were attributed to direct medical expenditures.

For the US it has been estimated that the costs when allergic rhinoconjunctivitis was the primary diagnosis were \$1.9 billion in 1996. The cost when allergic rhinoconjunctivitis was a secondary diagnosis to other disorders such as asthma and sinusitis was estimated at \$4.0 billion (90).

The high prevalence of allergic asthma and rhinitis and concerns about health care costs justify the increasing interest for cost-effectiveness studies. Not only does the efficacy of treatment have to be demonstrated, but also its cost-effectiveness. In these studies HRLQ measures must be incorporated in order to make comparisons across patient populations and for different disorders. It is, however, difficult to incorporate the generic SF-36 or disease-specific HRQL scores into cost-effectiveness analyses. For this purpose utilities such as the Standard Gamble, Feeling Thermometer have been developed, which measure the value that patients themselves place on their own health status. Alternatively some utilities measure the value that society places on various health states. Examples are the EuroQol and Multiattribute Health Utilities Index. An advantage of utilities is their ability to produce quality-adjusted life years (QALYs). QALYs associated with different medical therapies can easily be incorporated into cost-effectiveness studies.

Utility instruments are mostly generic. A recent rhinitis specific utility, the multiattribute Rhinitis Symptom Utility Index, has been developed as a patient outcome for clinical trials and for cost-effectiveness studies comparing medical treatments for rhinitis (92). The same group introduced an asthma specific instrument, the Asthma Symptom Utility Index (93). Also, disease-specific versions of the standard gamble and rating scale have been developed for patients with asthma (94).

Perspectives for the future

The interest in quality of life for patients with allergy emphasizes that allergy is characterized by a significant socioeconomic burden. Long before the introduction of HRQL outcome measures physicians were aware that patients cannot be fully characterized by physiological measures. In a way, HRQL outcome measures represent pieces of the history obtained from the patients, with which clinicians are already familiar in their day-to-day work. The formal presentation of these elements in the HRQL questionnaires makes it possible to include the patient perspective in clinical trials and cost-effectiveness studies. Ideally, the efforts in this field will improve medical decision-making and management of disease. Inclusion of these outcome measures in the evaluation and management of individual patients could be the next step.

However, HRQL questionnaires are still in the process of being refined in terms of revision and introduction of short forms of instruments (34, 95–97). Analysis of QOL data is usually based on the assumption that there are no measurement errors in the responses of items. Structural equation modelling (SEM) is an advanced statistical technique for identifying, estimating and testing models which takes measurement errors into account. An important feature of SEM is that it enables tests of whether a *prespecified* model fits the observed data. With this approach it has been shown that some changes in the analytical strategy of the SF-36 scale are needed when it is applied to evaluation of QOL for patients with intermittent claudication or peripheral arterial occlusive disease (98). SEM requires specialized software and collaboration with experienced statisticians.

Some criticism has been raised against the proliferation of instruments and the burgeoning theoretical literature devoted to the measurement of quality of life (99). It has been argued, that much attention has to be paid to better approaches for interpreting results, conceptualization of theoretical models and development of individualized measures, before these instruments will be routinely selected for use in clinical practice and for use as primary endpoints in large-scale clinical trials (100).

Also, in the field of allergy the number of outcome measures is growing. For the clinician and researcher it will be difficult to select among the wide variety of questionnaires. A researcher conducting a clinical trial is in need of an evaluative disease-specific questionnaire with a high responsiveness, whereas a decision-maker at the level of health politics requires a descriptive generic instrument measuring differences between subjects at a point in time, and utilities to assess cost-effectiveness of treatments.

In order not to overload patients with outcome measures research is needed to reveal redundancy between measurements.

In conclusion, further research needs to be focused on the selection and 'sharpening' of a limited number of valid and reliable patient-friendly instruments in order to better understand the patient with allergy and better interpret the results of clinical trials.

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