Review: Clinical Trial Methodology

CLINICAL INVESTIGATION

# Quality of life measures in patients on rhinosinusitis trials

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**Although rhinosinusitis is not a life-threatening condition, it impairs daily functioning and quality of life (QoL). The evaluation of rhinosinusitis patients must include a complete sinonasal history and nasal exploration, and in addition may include CT scan and the quantification of QoL. The burden of rhinosinusitis can be assessed and compared with controls using the available generic questionnaires. Specific questionnaires offer more sensitivity than generics in terms of details on distinct diseases such as rhinosinusitis when studying a selected population. This article is intended to provide a review of the available measurement instruments on QoL that have been used in clinical trials related to rhinosinusitis, both acute and chronic. The indexed English literature up to 2012 from PUBMED and EMBASE was reviewd. The studies suggest that the available instruments to quantify the impact of acute and chronic rhinosinusitis demonstrate impairment on QoL and the available treatments lead to a similar improvement.**

**Keywords:** acute rhinosinusitis • chronic rhinosinusitis • clinical trials • generic questionnaires • health-related quality of life • nasal polyposis • specific questionnaires

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In the last few decades, quality of life (QoL) has represented the development of patient-oriented assessment of health status, and it is being increasingly perceived by researchers and physicians as a significant outcome measure. Physical, social, emotional, psychological, sexual, cognitional, and economical aspects of life can be integrated in a general term of well-being, and it is commonly known as health-related QoL (HRQoL) [1,2], which entails two widely-accepted aspects: subjectivity and multidimensionality. All QoL dimensions are interrelated to such an extent that any disturbance influences the others as well as overall QoL [3].

HRQoL is measured from the patient's viewpoint rather than from that of outsider observers [4]. This enables the patient to indicate, emphasize and prioritize problems of potential relevance [5]. Patient Reported Outcome Measures (PROMs) are self-rated measures that are reported directly by the patient, reflecting multidimensionality in the process [6]. The suggestion is that the impact of a specific disease or its assessment can be achieved by comparing many patients' self-reported measures on health status. Questionnaires, visual scales, and grading systems are just some of the instruments used in quantitatively measuring HRQoL. Generally, questionnaires let the patient rate the impact of the disease alongside a number of other areas of healthcare interest. Every question is scored according to severity or repercussion of the disease, and individual domain scores are combined to produce an overall score. Although PROMs are self-reported by definition, children, the elderly, and the cognitively impaired patients can be assessed by proxy [7–11].

Some PROMs have been developed for particular conditions or treatments (disease-specific), while others are designed for use in patient groups and healthy

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individuals to measure the perception of their general health status (generic measures). In addition, generic instruments are also applicable to people with any medical illness or condition used to compare different illnesses, degrees of disease severity, or types of intervention [12].

Rhinosinusitis is a highly prevalent and poorly understood disease that can significantly affect HRQoL [13–17]. The current European Position Paper on Rhinosinusitis and Nasal Polyps, known as the EPOS guidelines, define rhinosinusitis as an inflammation of the nose and the paranasal sinuses characterized by two or more symptoms from the following: nasal blockage/obstruction/congestion, nasal discharge, postnasal drip, reduction or loss of smell, facial pain/pressure, endoscopic signs or a CT scan showing mucosal changes within the sinonasal cavities [6].

The cutoff duration time for defining acute or chronic rhinosinusitis (CRS) is 12 weeks, noting the following distinctions: acute rhinosinusitis (ARS) may be associated with upper and lower airway complications; CRS, with or without nasal polyposis (NP; CRSwNP and CRSsNP respectively) is often linked to asthma, cystic fibrosis, primary ciliary dyskinesia, or aspirin sensitivity [18]. The fact that the QoL scores do not always correlate with severity of nasal symptoms is key here [19]. Although CRS has been frequently cited in previous reviews, it is important to mention that, to date, details on ARS have not been included as part of reviews on QoL in connection with rhinosinusitis.

This article is therefore intended to provide a review of the validated measurement instruments available on QoL used in clinical trials in relation to rhinosinusitis, both acute and chronic. To this end, we reviewed the indexed English literature up to 2012 to identify studies of interest using the terms: QoL, rhinosinusitis, sinonasal and NP, from EMBASE and PUBMED. All the authors constituted the reviewer panel and agreed on the final documents.

## Psychometric characteristics of a QoL questionnaire

All psychometric assessment tools of QoL should meet certain quality criteria – validity, reliability and responsiveness – that determine whether these tools are effective or not.

### ■ Validity

Validity is defined as the degree to which evidence and theory support the interpretations of test scores. Thus, the validity of a measurement tool is considered to be the degree to which the tool measures what it claims to measure [20,21]. At least two types of validity have to be considered: convergent validity and discriminant validity.

#### Convergent validity

This refers to the degree to which two measures of constructs that are theoretically related are empirically related.

#### Discriminant validity

Discriminant validity evaluates whether concepts or measurements that are theoretically unrelated are, in fact, unrelated [22].

### ■ Reliability

Questionnaire reliability can take two forms: test–retest reliability and internal consistency reliability.

#### Test–retest

This approach sustains that there would not be substantial variations in measurements taken on two separate occasions. This is achieved by applying the same test following the same procedures on two different occasions. The time lapse between measurements is critical as this will determine the degree of correlation between constructs, depending on the period elapsed between the measurement occasions.

#### Internal consistency

Reliability is evaluated on one occasion with a single measurement instrument applied to a group of people. Internal consistency measures whether several items that propose to measure the same general construct produce similar scores. This is estimated by calculating Cronbach's $\alpha$ coefficient in a range of 0–1 [23]. When the scale has an $\alpha \geq 0.7$ it is considered to be reliable for group level comparison; likewise, it is considered reliable for evaluation at the individual level when a value of $\geq 0.9$ is observed [24]. Cronbach's $\alpha$ will generally increase as the intercorrelations among test items increase. This is referred to as an estimate of internal consistency of reliability for test scores. Cronbach's $\alpha$ is most appropriately used when the items measure different substantive areas within a single construct. When the set of items measures more than one construction, the hierarchical omega coefficient is deemed more appropriate [25].

### ■ Responsiveness

One definition of responsiveness refers to the capability of an instrument to accurately detect meaningful changes when they have occurred within a given time [26]. Like other measurement characteristics, responsiveness is not a constant characteristic of a measure; it can only be examined when a measure is used for a particular purpose with a particular group of subjects. Internal and external responsiveness have been recognized.

### Internal responsiveness

In a predefined timeframe, internal responsiveness reflects the ability of a measure to adapt. This type of responsiveness is often examined by measurement before and after a treatment of known efficacy.

### External responsiveness

External responsiveness indicates the proportion to which modifications in a measure relate to adaptation in other measures of health status.

#### ■ Assessment of instruments

There is an excellent scoring system described by van Oene *et al.* that comprehensively captures aspects of instrument validity, including construction of the questionnaire, description of the items and domains, feasibility and respondent burden, size of validation study and reliability in terms of internal consistency, test–retest reliability, content, convergent and discriminant validity, responsiveness, and calculation of the minimally important difference [27]. An instrument's implementation time will determine whether it is practicable or not. Furthermore, when an instrument is translated into different languages it should be done in both forward and backward directions to ensure the original meaning of items is retained, with this then being revalidated to ensure the retention of the same psychometric properties [6].

## QoL questionnaires

A variety of validated, reliable and revealing HRQoL questionnaires have been developed to suit the needs of various illnesses. The questionnaires can be generalized into three categories: generic health-status instruments, generic illness instruments, and disease-specific instruments [28,29].

#### ■ Generic questionnaires

Individuals with or without medical illness can complete generic health-status questionnaires. They are applicable to all populations. Such instruments enable comparisons of QoL impact in different diseases in healthy subjects alongside diseased subjects. They may also determine the relative cost utility of different interventions, and thereby inform commissioning decisions [6]. EuroQol 5D, McGill Pain Questionnaire (MPQ), Short Form-36 Health Survey (SF-46) and Short Form-12 Health Survey (SF-12) are some of the most often employed generic questionnaires in CRS (Table 1). All these questionnaires have been translated into several languages.

### EuroQol 5D

This questionnaire is intellectually unchallenging and takes just a few minutes to complete. Being generic, it is suitable for a wide range of health statuses and treatments. It is designed to be completed by respondents themselves and for use in face-to-face interviews and daily clinical practice, in addition to postal surveys. The EuroQol 5D describes some facets of health in terms of self-care, usual activities, mobility, anxiety/depression, and pain/discomfort. Each of these facets comprises three possible levels of intensity: extreme problems, some/moderate problems, or no problems. A visual analogue score record is used, which sees participants rate health status on a vertical graduated scale (0–100 mm) [30].

### MPQ

The MPQ was created to measure clinical pain in such a way that it can then be statistically analyzed [31]. It aims to capture descriptions of affective, sensory, and evaluative spheres used by subjects in detailing their subjective pain experience. The MPQ contains 20 word categories describing qualities of pain, which subjects use to express which option applies best to their circumstances. It also contains a severity scale to clarify the qualities of pain situation. MPQs must be delivered by interviewers. In turn, this entails some practical difficulties. As such, a shorter form of the MPQ (SF-MPQ) contains 11 questions instead of 20. With both the MPQ and the SF-MPQ each descriptor is positioned on a four-point intensity scale, where zero indicates no pain at all, and a score of 3 indicates severe pain.

### SF-36

Since 1991, SF-36 has been one of the most widely used generic questionnaires and has been included in more than 5000 publications [32]. It has also proven to be robust upon translation and adjustment to more than 120 languages [33,34]. This survey of 36 self-administered questions comprises eight areas related to mental and physical health components. The mental component summarizes four sub-areas: role emotional functioning, social functioning, vitality, and mental health. Likewise, the physical component comprises role physical functioning, physical functioning, bodily pain and general health. Scale scores range from 0 to 100 for each area and these are then collated into an overall percentage. High scores indicate better QoL than lower scores. Normative values for the general population are listed at the SF-36 website [101].

### SF-12

SF-12 takes 12 questions from the original SF-36 health survey and emulates the mental and the physical health elements scores this produces. The scoring of individual items is identical to the SF-36 [35].

**Table 1. Specific and generic quality of life questionnaires.**

| Questionnaire | Specific or generic | Type | Original language | Number of domains | Number of items | Score range | Fill-in time (mins) | Ref. |
|---|---|---|---|---|---|---|---|---|
| RSOM | Specific | Self-report | English | 7 | 31 | 0–155 | 15–20 | [40] |
| SNOT-22 | Specific | Self-report | English | - | 22 | 0–110 | <5 | [41] |
| SNOT-20 | Specific | Self-report | English | - | 20 | 0–100 | <5 | [42] |
| SNOT-16 | Specific | Self-report | English | - | 16 | 0–48 | <5 | [43] |
| RhinoQoL | Specific | Self-report | English | 3 | 17 | 0–100 | 5–10 | [45] |
| SN-5 | Specific | Self-report | English | - | 5 | 5–35 | <5 | [46] |
| SOQ | Specific | Self-report | English | 5 | 26 | 0–130 | 5–10 | [47] |
| RQLQ | Specific | Self-report/ Interviewer-administered | English | 7 | 28 | 0–168 | 10–15 | [48] |
| CSS | Specific | Self-report | English | 2 | 6 | 0–100 | <5 | [39] |
| EQ-5D | Generic | Self-report | Dutch, Swedish, English, Finnish, Norwegian | 5 | 15 | 0–100 | 5–10 | [30] |
| MPQ | Generic | Interviewer | English | 20 | 78 | 0–78 | 10–20 | [31] |
| SF-36 | Generic | Self-report | English | 8 | 36 | 0–100 | 10–20 | [32] |
| SF-12 | Generic | Self-report | English | 8 | 12 | 0–100 | 5–10 | [35] |
| GBI | Generic | Self-report | English | 3 | 18 | -100–100 | 5–10 | [36] |
| CHQ-PF50 | Generic | Self-administered by parent | English | 14 | 50 | 0–100 | 15–20 | [38] |

CHQ-PF50: Child health questionnaire parent form 50; CSS: Chronic sinusitis survey; EQ-5D: EuroQoL 5D; GBI: Glasgow Benefit Inventory; MPQ: McGill Pain Questionnaire; RhinoQoL: Rhinosinusitis quality of life questionnaire; RQLQ: Rhinoconjunctivitis quality of life questionnaire; RSOM: Rhinosinusitis outcome measure; SF-12/-36: Short form-12/-36 health survey; SN-5: Sinonasal-5; SNOT-16/-20/-22: Sinonasal outcome test-16/-20/-22; SOQ: Sinusitis outcomes questionnaire.

### Glasgow Benefit Inventory

The Glasgow Benefit Inventory contains 18 validated questions categorized according to three subscales. In total, 12 questions measure general benefit, three questions measure the amount of social support the subject has access to, and three questions measure changes in the overall physical health status of subjects [36,37]. The answers to each question are based on a five-point Likert scale, which spans extensive improvement in health status to significant decline.

To help control for response bias, half of the questions have the answers ranging from a large improvement to a large deterioration, whereas the other half range the other way.

### Child health questionnaire

The child health questionnaire (CHQ) provides a parent proxy-reported form comprised of 50 items (CHQ-PF50), together with a second form that can be filled by the child, depending on his/her age. The latter consists of 87 items (CHQ-CF87). The CHQ contains two summary element scales that represent physical and psychosocial aspects of health. The CHQ-CF87 or CHQ-PF50 can be also administered by interview [38].

## ■ Generic illness questionnaires

Some questionnaire types have been designed for populations with medical illnesses that can be used to compare differences between conditions as well as the severity of the disease, or indeed types of interventions. Being generic, these survey instruments evaluate the individual's perception of the functional impact of the illness or disability. The Sickness Impact Profile [28] and the Functional Assessment of Chronic Illness Therapy [29] are examples of such generic illness questionnaires. Although often used in cancer trials, to our knowledge no studies in relation to rhinosinusitis are available. In the future these types of questionnaire may well feature prominently in the assessment of chronic diseases such as CRSwNP and CRSsNP.

## ■ Specific questionnaires

Since generic questionnaires often lack sensitivity in detecting small but important QoL changes in specific diseases, specific QoL questionnaires can be much more useful. Specific questionnaires are focused on a selected population in one particular area such as a disease status or a certain function or problem.

Several rhinosinusitis-specific instruments are available, and these differ in terms of their aims, the

number of items included, setting, and ease of use. There is a direct relationship between the number of items and the task–completion burden on participants, and this has to be considered when selecting an instrument for use [6]. In addition, the choice of instrument will depend upon the aim of outcome measurement. At present, rhinosinusitis Disability Index, Chronic Sinusitis Survey Score and Sinonasal Outcome Test-20, -16 and -22 are some of the most widely used specific questionnaires for evaluating QoL in patients with rhinosinusitis.

### Rhinosinusitis disability index

This is a specific, validated, and reliable questionnaire indicated for patients with rhinosinusitis. It contains 30 items relative to sinus and nasal manifestations that can lead to specific restrictions on daily role. The rhinosinusitis disability index (RSDI) comprises three domains: physical (11 items), functional (nine items) and emotional (ten items). Each item is rated on a five-point Likert scale ranging from never (scored as 0) to always (scored as 4). The total score possible ranges from 0 to 120, with higher scores reflecting poorer HRQoL [5].

### Chronic Sinusitis Survey

Specifically designed for CRS, this instrument measures the health status and the effectiveness of treatment in adults. The Chronic Sinusitis Survey (CSS) is frequently used in many trials [1]. It is a duration-based questionnaire that generates a total sinusitis symptom score, and two subscale scores: symptom and medication. At symptom subscale, the patient must respond to questions in relation to maxillary headache, frontal headache, mucus production, stuffy nose, ability to smell, and feelings of being unwell. The first four items apply to scores on a Likert scale, with the response alternatives ranging from none (0) to very much (4). The fifth item has the response alternatives ranging from none (4) to normal (0). The last item has the response alternatives ranging from very ill (3) to healthy (0). The medication subscale score is reflective of medical treatment options (antibiotics, nasal spray, and antihistamines) for CRS. Survey total and subscale scores are transformed on a scale that ranges from 0 to 100, where the maximum value means the possible HRQoL [39].

### Rhinosinusitis outcome measure

Rhinosinusitis outcome measure (RSOM) is a well-validated questionnaire of 31 items divided into seven domains. It measures severity and significance to the patient relative to nasal, ear, eye, sleep, emotional, functional, and general manifestations and symptoms. General reports suggest patients do not find it easy to respond to these severity and importance scales [40].

### Sinonasal Outcome Test

The Sinonasal outcome test-20 (SNOT-20) is a validated questionnaire that has demonstrated sensitivity to changes. It comprises 20 nose, sinus and general items. To complete the questionnaire, patients indicate the extent to which they note the severity of each reported problem, and subsequently select the five most relevant items [41]. To calculate the overall score, items selected as the most relevant reflect a higher percentage than the items not highlighted [1]. The current EPOS guidelines do not recommend SNOT-20 for CRS surveys, due to the lack of items related to loss of smell or nasal obstruction. These items have been incorporated in SNOT-22 [6].

The SNOT-16 is a brief survey instrument of 16 items that was initially designed for the quantification of CRS manifestations in longitudinal studies. SNOT-16 can be completed by both face-to-face and telephone interviews. As with SNOT-20, it seeks to rate the intensity of sinonasal manifestations, and the emotional or social consequences of CRS. In regards to severity and frequency, patients rate how much each item bothers them using a four-point scale. The SNOT-16 has demonstrated its validity, responsiveness and reliability, and is therefore worth considering as an effective survey instrument in the measurement of HRQoL related to rhinosinusitis [42]. The questionnaire has been reported as easy to use, with a typical completion times of 5 min or less [43].

The SNOT-22, validated in 2009, is a modified form of SNOT-20 and the RSOM, containing 22 nose, sinus and general items [44]. It was revised to make the importance scale easier to use than the original. In contrast to SNOT-20, it contains one question on nasal obstruction and another on loss of smell and taste. The patient is asked to identify the five most important items. A large volume of published studies provide comparative data on the implementation of SNOT-20 and SNOT-22 [6]. In all SNOT questionnaires greater scores indicate greater QoL problems.

### Rhinosinusitis QoL survey

The Rhinosinusitis QoL questionnaire measures symptom frequency and shows impact scales. It consists of a 17-item rhinosinusitis-specific questionnaire divided into three areas developed by Atlas *et al.* [45]. All subareas of the instrument have shown distinction and quality when compared with previous versions. The values range from 0 to 100, with 0 indicating the worst possible health status and 100 the best.

### Sinonasal-5 QoL survey

Sinonasal-5 is specifically designed for pediatric populations with continuous sinus and nasal symptoms.

It measures longitudinal changes in HRQoL and includes five symptom-cluster items covering the terms related to nasal obstruction, sinonasal infection, allergy symptoms, emotional distress, and activity limitations [46]. This practical questionnaire shows a severity scale that ranges from one, when the symptom does not present at any time, to seven, when it presents every time. The caregiver completes a visual analogue scale of QoL with a maximum of ten, which means the best possible QoL for their children.

### Sinusitis outcomes questionnaire

The sinusitis outcomes questionnaire contains 26 items separated into five sections, devised for completion within 5 min [47]. The sections include general and specific sinonasal manifestations, eyes, and chest problems. In its last few questions, and in contrast to other instruments, it explores the economic burden of the sinonasal disease by calculating loss of school days or work, outpatient visits or hospitalization, sinonasal surgery or ear surgery, treatment used for rhinosinusitis or bronchitis or otitis. Overall scores vary between 0 and 130, where higher scores indicate greater symptomology.

### Rhinoconjunctivitis QoL questionnaire

The Rhinoconjunctivitis QoL questionnaire (RQLQ) is a fully validated questionnaire that shows strong attributes [1]. It was created to measure nose and eye symptoms experienced by people with allergic rhinoconjunctivitis. It has 28 questions divided into seven areas, which comprise sleep problems, activity limitations, nose or eye symptoms, non-nose/eye symptoms, practical problems, and emotional function [48]. Juniper *et al.* have developed a version of this questionnaire in which activities are standardized for all patients with this problem. Although created for allergic rhinoconjuctivitis, the RQLQ have also been inadequately used in rhinosinusistis.

## QoL in acute rhinosinusitis

In contrast to CRS, only a few studies consider HRQoL in relation to ARS. There may be a number of reasons for this. ARS is by definition a short-term disease and as such, impairment in QoL should, theoretically, also be transient, with QoL recovering to previous levels once the disease has been overcome. Moreover, due to some variations in the definitions used, most trials reveal heterogeneous groups of patients [6].

### ■ Generic questionnaires

One study reported the systematic use of SF-36 to measure general status in 184 patients suffering ARS and CRS between 18 and 78 years of age compared with healthy individuals of similar characteristics. Significant differences were shown between all groups ($p < 0.001$). Patients with ARS had poorer HRQoL (mean score 60.8) than healthy individuals (51.8), but less reduction than those with CRS (75.5) [49].

### ■ Specific questionnaires

Using SNOT-20 to assess symptom severity, a prospective randomized, and double-blind, placebo-controlled trial contrasted the effect of antibiotics and topical steroids with placebo in ARS [50]. The most important symptoms were post-nasal discharge, need to blow nose, nasal discharge and tiredness. This study demonstrated significant improvement in HRQoL from day zero to day 15 with topical steroids, producing a significantly greater improvement in the SNOT-20 ($p = 0.047$).

A recently published French survey requested physicians to report symptom frequency and severity prospectively in patients diagnosed with ARS [51]. The most common presenting signs and symptoms were nasal obstruction (80.4%) followed by pain on sinus palpitation (76.8%) or facial pain (74.5%), rhinorrhoea (70.4%), and headache (63.6%). All symptoms were indicated as having a significant effect on QoL areas, including daily-life activities (71.6% of patients), leisure (63.1%) and professional or school activities (59.2%).

Garbutt *et al.* validated SNOT-16 in 166 patients with ARS [44]. Their study showed Cronbach's $\alpha$ ranging from 0.82 to 0.91, thereby demonstrating high internal consistency and subsequently a good construct-related validity. There was a statistically significant decrease in SNOT-16 scores with time. The mean scores declined steadily from 1.71 (standard deviation [SD]: 0.5 at onset of illness) to 1.13 (SD: 0.54) at day 3, 0.74 (SD: 0.5) at day 7, falling to 0.49 (SD: 0.44) by day 10. When the use of amoxicilin (randomly prescribed in 85 patients) was tested against the placebo ($n = 81$), the mean change in SNOT-16 score was not significantly different between groups on day 3 (decrease of 0.59 in the amoxicillin group and 0.54 in the control group) or on day 10. SNOT-16 helped to conclude that, when ARS patients on a course of amoxicillin are compared with placebo, symptoms did not diminish over the first 3 days [52].

## QoL in CRS with/without NP

### ■ Generic questionnaires

CRS imposes a considerable health burden as clearly noted by the available survey instruments implemented to date (Table 2). Using SF-36, many surveys have shown that CRS has an important impact on every questionnaire domain [53–57]. Social functioning is impaired to a greater extent in CRS than in other illnesses considered as severe, such as chronic

**Table 2. Generic quality of life questionnaires in chronic rhinosinusitis with and without nasal polyposis.**

| Study | Disease | Number of patients (n) | Treatment | Treatment duration (months) | QoL questionnaire | Impact on QoL | Level of evidence | Ref. |
|---|---|---|---|---|---|---|---|---|
| Newton *et al.* | CRS† | 50 | Surgery | 6, 12, 24 | GBI | Before treatment: decreased<br>After treatment: improved | IIb | [37] |
| Alobid *et al.* | CRSwNP | 78 | Oral and intranasal steroids | 3, 6, 12 | SF-36 | Before treatment: decreased<br>After treatment: improved | Ib | [1] |
| Videler *et al.* | CRS† | 23 | Surgery | 12, 24 | SF-36, MPQ | Before treatment: decreased<br>After treatment: improved | IIb | [61] |
| Atlas *et al.* | CRS† | 50 | Surgery | 3 | SF-12 | Before treatment: decreased<br>After treatment: improved | IIb | [45] |
| Alobid *et al.* | CRSwNP | 130 | Not defined‡ | N/A | SF-36 | Negative impact of asthma and allergy | III | [13] |
| Alobid *et al.* | CRSwNP | 109 | Steroids vs surgery | 6, 12 | SF-36 | Before treatment: decreased<br>After treatment: improved | Ib | [14] |
| Baumann and Blumenstock | CRS† | 123 | Surgery | 3 | SF-36, EQ-5D | Before treatment: decreased<br>After treatment: improved | III | [55] |
| van Agthoven *et al.* | CRS† | 56 | Filgrastim | 6 | EQ-5D, SF-36, MPQ | Before treatment: decreased<br>After treatment: improved | Ib | [60] |
| Radenne *et al.* | CRSwNP | 49 | Steroids vs surgery | 6, 12 | SF-36 | Before treatment: decreased<br>After treatment: improved | IIa | [15] |
| Winstead and Barnett | CRS† | 125 | Surgery | 6, 12 | SF-36 | Before treatment: decreased<br>After treatment: improved | IIb | [56] |
| Gliklich and Metson | CRS† | 108 | Surgery | 12 | SF-36 | Before treatment: decreased<br>After treatment: improved | IIb | [57] |
| Gliklich and Metson | CRS† | 158 | Not defined‡ | N/A | SF-36 | Decreased levels | III | [53] |

†Studies including patients with and without polyposis.

‡Studies containing both treated and non-treated patients.

CRS: Chronic rhinosinusitis; CRSwNP: Chronic rhinosinusitis with nasal polyps; EQ-5D: EuroQol 5D; GBI: Glasgow Benefit Inventory; MPQ: McGill Pain Questionnaire; QoL: Quality of life; SF-12/-36: Short form-12/-36 health survey.

heart failure, angina or back pain. The one exception encountered was in the physical functioning domain [57–60]. Nevertheless, improvement on HRQoL can reach normal values with optimal treatment [58]. Similar results have been shown to be reliable with the generally available questionnaires, by Van Agthoven *et al.* [60]; for example, when investigating HRQoL variations of CRS patients (who did not react to standard treatment) after filgrastim administration. In this case, EuroQoL, SF-36 and MPQ were used, with the result that HRQoL scores for the active-treatment group suggested an improvement compared with placebo, although this not statistically significant. Additionally, the CRS HRQoL scores were all lower than population normative scores and those in a group of patients with CRS undergoing sinus surgery. Videler *et al.* took results from 23 patients who were subjected to radical surgery for refractory CRS [61]. HRQoL and pain were assessed using MPQ before surgery, and after 1 and 2 years of surgery. Surgery evidenced improvement in pain and in the other domains.

Alobid *et al.* found that patients with CRSwNP had impaired QoL in all areas according to SF-36 implementation except for physical functioning [13]. No correlation was found between QoL and gender, age, nasal symptoms, polyp size or CT scan. The study showed a significant amelioration on all areas of SF-36, reaching QoL values of the general population after intranasal and oral steroids or surgical treatment followed by intranasal steroids. In another survey, Radenne *et al.* investigated the impact of CRSwNP on QoL and subsequently demonstrated the reliability and high internal validity

of the SF-36 questionnaire [15]. They also found that CRSwNP has a negative effect on HRQoL, more so than perennial allergic rhinitis.

### Specific questionnaires

Several specific questionnaires are discussed below and in Table 3.

#### RSDI & CSS

In a survey comprising 292 individuals and nine different rhinologic diseases, where CRS and allergic rhinitis were the most affected, lower physical RSDI scores were presented, followed by emotional and functional scores [62]. Another cohort of 123 patients, which included aspirin-tolerant and -intolerant individuals with CRS, showed

**Table 3. Specific quality of life questionnaires in acute and chronic rhinosinusitis with and without nasal polyposis.**

| Study | Disease | Patients (n) | Treatment | Duration of treatment | QoL questionnaire | Impact on QoL | Level of evidence | Ref. |
|---|---|---|---|---|---|---|---|---|
| Garbutt *et al.* | ARS | 166 | Antibiotics | 10 days | SNOT-16 | Before treatment: decreased<br>After treatment: improved | Ib | [51] |
| Hopkins *et al.* | CRS | 3128 | Surgery | 5 years | SNOT-22 | Before treatment: decreased<br>After treatment: improved | IIb | [66] |
| Bachert and Meltzer | ARS | 340 | Local steroids + antibiotics | 15 days | SNOT-20 | Before treatment: decreased<br>After treatment: improved | Ib | [49] |
| Wallwork *et al.* | CRS[†] | 64 | Roxithromycin | 3 months | SNOT-20 | Before treatment: decreased<br>After treatment: improved | Ib | [67] |
| Friedman *et al.* | CRS | 42 | Nasal irrigation | 1.4 weeks | RQLQ | Before treatment: decreased<br>After treatment: improved only Dead sea salt solution group | Ib | [73] |
| Hissaria *et al.* | CRSwNP | 40 | Oral steroids | 2 weeks | RSOM-31 | Before treatment: decreased<br>After treatment: improved | Ib | [72] |
| Ebbens *et al.* | CRS[†] | 116 | Amphotericin nasal lavage | 13 weeks | RSOM-31 | Before treatment: decreased<br>After treatment: did not improve | Ib[‡] | [71] |
| Javer and Genoway | CRS[†] | 95 | Surgery | 6, 12, 36 months | RSOM-31 | Before treatment: decreased<br>After treatment: improved | Ib | [70] |
| Atlas *et al.* | CRS | 50 | Surgery | 3 months | RhinoQoL | Before treatment: decreased<br>After treatment: improved | IIb | [44] |

[†]Studies including patients with and without nasal polyposis.

[‡]Study with negative outcome.

[§]Studies containing both treated and non-treated patients.

ARS: Acute rhinosinusitis; CRS: Chronic rhinosinusitis; CRSwNP: Chronic rhinosinusitis with polyps; CSS: Chronic sinusitis survey; QoL: Quality of life; RQLQ: Rhinoconjunctivitis QoL questionnaire; RhinoQoL: Rhinosinusitis QoL questionnaire; RSDI: Rhinosinusitis disability index; RSOM-31: Rhinosinusitis outcome measure 31; SN-5: Sinonasal 5 survey; SNOT-16/-20/-22: Sinonasal outcome test-16/-20/-22; SOQ: Sinusitis outcomes questionnaire.

**Table 3. Specific quality of life questionnaires in acute and chronic rhinosinusitis with and without nasal polyposis (Cont.).**

| Study | Disease | Patients (n) | Treatment | Duration of treatment | QoL questionnaire | Impact on QoL | Level of evidence | Ref. |
|---|---|---|---|---|---|---|---|---|
| Briggs *et al.* | CRS† | 82 | Surgery | Average of 52 months | SNOT-16 | Before treatment: decreased<br>After treatment: smoking is associated with worst outcomes | IIb | [69] |
| Nathan *et al.* | CRS | 114 | Immunotherapy + antibiotics | 12 months | SOQ | Before treatment: decreased<br>After treatment: improved | IIb | [46] |
| Ragab *et al.* | CRS† | 90 | Local steroids vs surgery | 6, 12 months | SNOT-20 | Before treatment: decreased<br>After treatment: improved | Ib | [68] |
| Kay and Rosenfeld | CRS | 85 | Not defined§ | N/A | SN-5 | Decreased levels | IIb | [45] |
| Piccirillo *et al.* | CRS† | 102 | Local steroids | 6, 12 months | SNOT-20 | Before treatment: decreased<br>After treatment: improved | Ib | [41] |
| Birch *et al.* | CRS† | 53 | Not defined§ | N/A | RSDI | Decreased levels | III | [63] |
| Senior *et al.* | CRS† | 292 | Not defined§ | N/A | RSDI, CSS | Greatest level of disability | III | [61] |
| Anderson *et al.* | CRS† | 47 | Local steroids vs surgery | 6, 12 weeks | SNOT-16 | Before treatment: decreased<br>After treatment: improved | IIb | [42] |
| Robinson *et al.* | CRS† | 123 | Surgery | 18 months | RSDI, CSS | Before treatment: decreased<br>After treatment: improved | III | [36] |
| Gliklich and Metson | CRS† | 104 | Surgery | 6 months | CSS | Before treatment: decreased<br>After treatment: improved | IIb | [38] |

†Studies including patients with and without nasal polyposis.
‡Study with negative outcome.
§Studies containing both treated and non-treated patients.
ARS: Acute rhinosinusitis; CRS: Chronic rhinosinusitis; CRSwNP: Chronic rhinosinusitis with polyps; CSS: Chronic sinusitis survey; QoL: Quality of life; RQLQ: Rhinoconjunctivitis QoL questionnaire; RhinoQoL: Rhinosinusitis QoL questionnaire; RSDI: Rhinosinusitis disability index; RSOM-31: Rhinosinusitis outcome measure 31; SN-5: Sinonasal 5 survey; SNOT-16/-20/-22: Sinonasal outcome test-16/-20/-22; SOQ: Sinusitis outcomes questionnaire.

an improvement on HRQoL (using RSDI and CSS) measures after endoscopic sinus surgery [63]. Birch *et al.* demonstrated no association between physical findings and the symptoms rated on RSDI [64]. While in another survey, a significant correlation between total QoL score and self-estimated symptom score was shown [65]. In addition, several studies have shown that CRSwNP tends to report better HRQoL scores, as measured by CSS and other questionnaires, than those with CRSsNP, despite the presentation of worse CT and endoscopy scores [66].

### SNOT

To determine the SNOT-22 score in a normal population, 116 participants were selected from a local hospital and tennis club. SNOT score ranged from 0 to 50, with a mean score of 9.3 (95% CI: 7.5–11.1). The modal score was 0 and the median score 7 (95% CI: 5–8) [67]. A study of 5-year outcomes for a large cohort of 3128 patients in the UK investigated the effectiveness of extensive surgery as a treatment for NP. The mean SNOT-22 score for all patients was 28.2 (SD: 22.4)

at 5 years after surgery. This was remarkably similar to the results observed at 3 (25.5), 12 (27.7), and 36 (27.7) months, and represented a 14-point improvement over the baseline score. Polyp patients reported better SNOT-22 scores at 5 years (26.2; ± 21.6) than patients with CRS alone (33.3 ± 23.7) [67].

Although SNOT-20 is a good describer of sensitivity to clinical change, it is not as complete as SNOT-22. In patients with CRS, a significant improvement in SNOT-20 results was found by Wallwork *et al.* after 3 months of macrolide therapy [68].

Ragab *et al.* randomly contrast both surgical and medical treatment of CRS by employing PROMs [69]. The authors administrated SNOT-20 on three occasions: before initiating the selected treatment, after 6 months, and at 1 year. Surgical and medical treatments were shown to be effective in improving HRQoL.

The robustness of some of facets of SNOT-16 has been demonstrated, particularly its outstanding discriminant validity. This stems from enabling potential correlations between patients' self-rated overall health and discomfort to be examined.

In a survey with 82 patients suffering CRS, Briggs *et al.* looked for endoscopic sinus surgery outcomes in the smoking population for comparison with non-smoking population [70]. Based on SNOT-16, they found that smoking population did not improve to the same degree as non-smoking population. They demonstrated that smoking significantly worsens outcomes after surgery.

### RSOM

Javer *et al.* found that RSOM revealed best QoL limitations in subjects with CRS in the domains of nasal manifestations and sleep deprivation [71]. Endoscopic sinus surgery statistically improved these HRQoL limitations. Ebbens *et al.* randomly compared with placebo the results of intranasal application of amphotericin B in patients affected with CRSsNP and CRSwNP [72]. The researchers did not identify statistical differences after 13 weeks of treatment. RSOM showed similar outcomes in placebo and amphotericin B groups.

Hissaria *et al.* used RSOM to compare the effectiveness of short-term prednisolone therapy of subjects with CRSwNP against a placebo [73]. Both groups showed improvement. However, the prednisolone group demonstrated better improvement than placebo with statistical significance. Nevertheless, within the prednisolone group, only the six specific parameters relative to nasal manifestations demonstrated significant improvement.

### RQLQ

Although RQLQ is a QoL questionnaire developed and validated for allergic rhinitis, some surveys, such as that presented by Friedman *et al.*, report on the inappropriate use of this instrument for the evaluation of CRS [74]. In this study, a greater beneficial effect of Dead Sea salt solution (hypertonic solution by composition) over saline isotonic nasal irrigation was found. RQLQ scores and symptoms were similar in both clusters before treatment and improved after treatment. However, the patients who received Dead Sea salt solution referred to much more relief than the other group, and only this group showed improvement in RQLQ scores.

## Conclusion

Generic and specific questionnaires have been used to assess the impact of ARS, CRSsNP and CRSwNP on QoL. These measurement instruments are as useful in clinical evaluation as they are in clinical trials. Where validated, these questionnaires show that rhinosinusitis impairs QoL and thereafter improves QoL when appropriate medical or surgical treatment is administered [75,76,77]. On the basis of this review of existing questionnaires used in clinical trials concerning rhinosinusitis, there are two adequate levels of discriminant validity: the RSOM and Rhinosinusitis QoL survey, as also reported by van Oene *et al.* [27].

## Future perspective

QoL survey instruments have clarified that rhinosinusitis affects HRQoL to a considerable extent. The questionnaires involved have not only been useful during clinical trials, but also clinical practice. Although many questionnaires have been developed to evaluate QoL in clinical trials for rhinosinusitis, only two indicate adequate levels of discriminant validity. These are the RSOM and Rhinosinusitis QoL survey. With further advances in the physiopathology and treatments of ARS and CRS, it is expected that the questionnaires in current use will be modified (e.g., generic illness questionnaires for CRS), or new ones be created (i.e., specific questionnaires for ARS) as per EPOS guidelines.

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## Executive summary

- Rhinosinusitis is a highly prevalent and poorly understood disease that can significantly affect health-related quality of life (QoL), and it should therefore be assessed with QoL scales.
- Validity, reliability and responsiveness are the characteristics that enable health-related QoL questionnaires to be effective.
- EuroQol 5D, McGill Pain Questionnaire, Short Form-36 Health Survey and Short Form-12 Health Survey are among the most widely used generic questionnaires in clinical trials for chronic rhinosinusitis (CRS).
- Rhinosinusitis Disability Index, Chronic Sinusitis Survey Score, Sinonasal Outcome Test-20, -16 and -22 are among the most widely used specific questionnaires in clinical trials.
- Although validated for CRS only, Short form-36, Sinonasal Outcome Test-20, -16, and -22 have also been used in acute rhinosinusitis.
- In accordance to the research needs and search strategies provided by the latest European Position Paper on Rhinosinusitis and Nasal Polyps guidelines, a priority is now to develop a validated QoL questionnaire specific to acute rhinosinusitis. In this regard, it could be helpful to identify whether the relative frequency of different symptoms in acute rhinosinusitis predicts different behaviors in response to different therapies.
- The development of tools in the context of clinical trials to shed light on CRS in children with chronic nasal complaints is also an urgent issue.
- Social functioning is more impaired in CRS than in other severe illnesses such as chronic heart failure, angina or back pain.
- Health-related QoL can recover to normal values given optimal medical and/or surgical treatment.

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## Website


101 Short Form-36 Health Survey. www.sf-36.org