EPOS2020/EUFOREA expert opinion on defining disease states and therapeutic goals in CRSwNP

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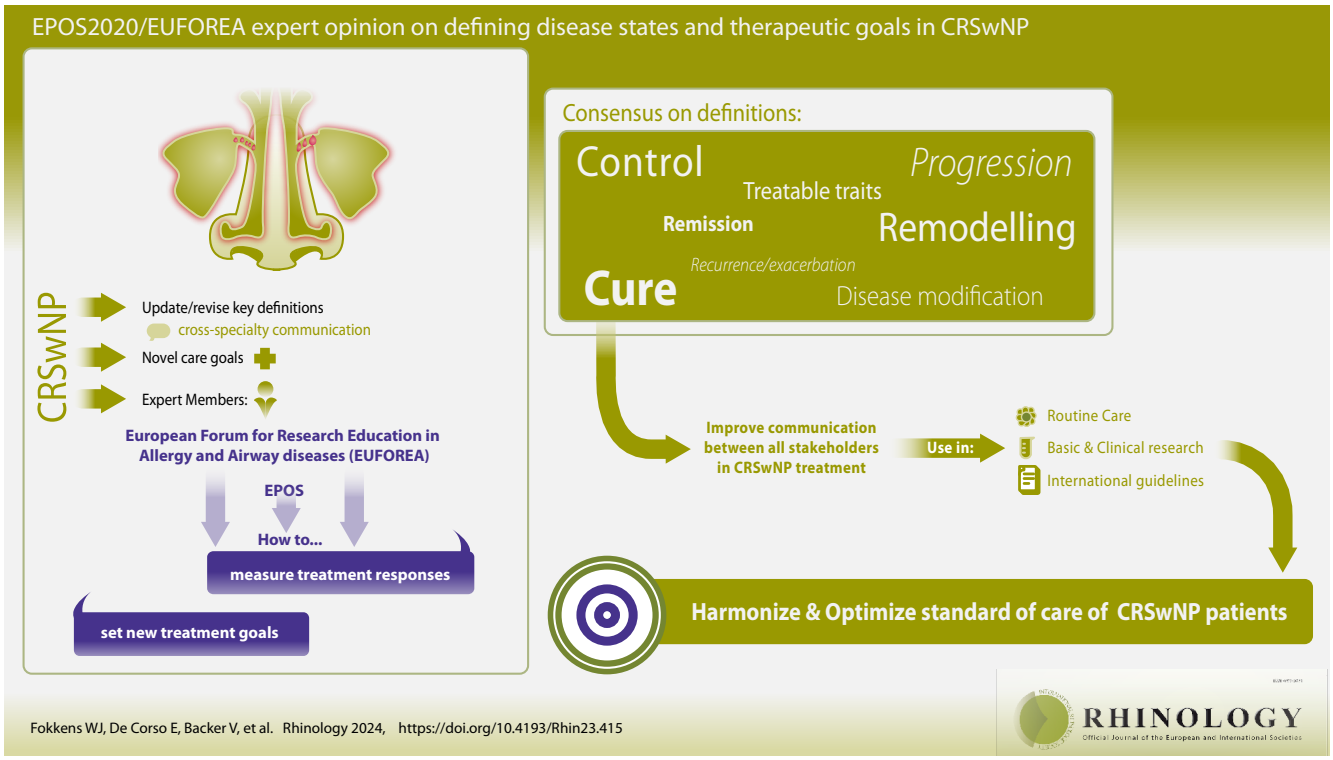
Abstract

Severe chronic rhinosinusitis with nasal polyps (CRSwNP), a form of diffuse bilateral (usually type 2) CRS, is a debilitating disease with a significant impact on quality of life (QoL). With novel knowledge and treatment options becoming available, there is a growing need to update or revise key definitions to enable communication across different specialties dealing with CRS, and to agree on novel goals of care in CRSwNP. The European Forum for Research and Education in Allergy and Airway diseases (EUFOREA) and EPOS expert members discussed how to measure treatment responses and set new treatment goals for CRSwNP.

In this paper a consensus on a list of definitions related to CRSwNP is provided: control, remission, cure, recurrence/exacerbation, treatable traits, remodeling, progression, and disease modification. By providing these definitions, the involved experts hope to improve communication between all stakeholders involved in CRSwNP treatment for use in routine care, basic and clinical research and international guidelines aimed to harmonize and optimize standard of care of patients with CRSwNP in the future.

Key words: chronic rhinosinusitis with nasal polyps, quality of life, definitions, treatment, remission, control, diffuse bilateral (type 2) CRS, eosinophilic CRS

Graphical abstract



Introduction

Chronic rhinosinusitis with nasal polyps (CRSwNP) is present in 1-2% of the European population [1]. The terminology 'CRSwNP' is only describing a phenotype and thus slightly outdated and we now rather speak of diffuse bilateral (usually type 2) CRS, that can or cannot have polyps [1]. However, because the term CRSwNP is still used in treatment evaluation studies, we decided in this paper to pragmatically use that term, because data on diffuse bilateral (usually type 2) CRS are still limited [1]. For future research, using endotype driven nomenclature would be desirable.

With novel knowledge and treatment options becoming available and several more in development for CRSwNP, there is an opportunity to reconsider current treatment goals and update current definitions of CRSwNP and related issues of control, remission and cure. Such definitions will facilitate communication between clinicians and patients regarding therapeutic options and treatment goals reported in international guidelines and decision making in daily clinical practice [2-5].

The European Position paper on Rhinosinusitis and Nasal Polyps, EPOS, is a long-standing initiative of the European Rhinologic Society (ERS) in creating guidance on the management of patients with CRS. The latest version, EPOS2020, advised on many definitions, including one on control [1]. The European Forum for Research and Education in Allergy and Airway disease (EUFOREA) is an international not-for-profit organization with a mission of reducing the burden of chronic respiratory diseases by implementing optimal care [4, 6, 7]. Optimal care implies a correct diagnosis and timely treatment, leading to improvement in quality of life (QoL) of individual patients and cost-savings for society. ENT specialists, pulmonologist, allergologists, and paediatricians working in leading EU and US research institutes are part of the EUFOREA expert panels and have joined forces with patients of the Patient Advisory Board to optimize the therapeutic strategy for chronic respiratory diseases.

The aim of the consensus meeting of the expert panel members of EPOS2020 and EUFOREA in Brussels on June 28, 2023, was to update current concepts surrounding the goals of treatment for CRSwNP and incorporate recent evidence. We included the following in the discussion topics: control, remission, cure, recurrence/exacerbation, treatable traits, remodelling, progression, and disease modification.

Methodology

The active participation of internationally renowned specialists in ENT, pulmonology, allergology, and immunology helped to find an agreement after a full day of discussion. At the Brussels meeting, concepts and therapeutic goals for CRSwNP were discussed point by point until agreement was reached by those authors present. A draft of the document was written, with two subsequent rounds of review by a larger group of experts also listed as co-authors. After review, the points of disagreement were discussed and addressed in two virtual web-based meetings involving all the co-authors in August and September 2023. During the web meeting, the changes made to the concepts and proposed algorithms were discussed and refined until agreement was reached. For definitions where agreement could not be reached by completion of the final virtual meeting, a vote was undertaken. Any definition with an 80% approval was included in the paper. If at least 80% agreement could not be achieved, no definition was included in the paper. In October 2023, a new draft was circulated for one more round of review and final approval by all the authors.

Defining treatment goals in CRSwNP: control, remission, and cure

Control often serves as the goal of treatment in chronic diseases, including CRSwNP, in which a cure is currently rare. However, with the advent of new therapeutic treatments such as biologics with potential disease-modifying effects, there is a need to redefine treatment goals for CRSwNP [3]. Recently, a group of EPOS2020 experts chaired by A. Sedaghat and C. Hopkins participated in a Delphi process on defining control in CRS and to determine which factors should be evaluated when assessing control [8]. Based on this Delphi process the current expert panel first discussed several key definitions for CRSwNP: being uncontrolled, controlled, in remission, or cured.

In the EPOS2020 Delphi process the criteria for the assessment of CRS control that reached full consensus included: patient-reported CRS control, overall symptom severity, severity of nasal obstruction and the use of CRS-related oral corticosteroids (OCS) within the last 6 months (Table 1). The expert board of this paper, based on the factors proposed in the above-mentioned paper for assessing control in CRS in general [9], now proposed for CONTROL in CRSwNP, "**patient reported control**" and the absence of clinically relevant sinonasal **symptoms** of active disease, defined by overall symptom severity, nasal obstruction and loss of **smell**)". CONTROL can be achieved with or without **ongoing / past treatment** (Table 1).

For research purposes, symptoms are not considered clinically relevant/bothersome when a patient scores a VAS ≤ 5 cm for a particular symptom, as a previous study showed that a VAS score of 5 cm for overall symptom severity best distinguished between patients whose CRS symptoms affected their QoL [10].

An important discussion in the group related to smell. Although in CRSsNP, smell seems to be less important, for CRSwNP smell is a crucial symptom and very sensitive to treatment. For this reason, it is included in the definition of control in CRSwNP. It was decided to exclude smell loss obviously caused by reasons other than CRSwNP (e.g., viral, posttraumatic or neurodegenerative cause) but to include anosmia caused by CRSwNP or by the surgery performed for CRSwNP, considering that it may be

Table 1. Criteria for for the assesment of control in CRS and CRSwNP.

EPOS2020 Delphi criteria for the assessment of CRS control	EPOS2020/EUFOREA expert opinion on defining disease states and therapeutic goals in CRSwNP
CRSwNP and CRSsNP	CRSwNP
Delphi process	Expert opinion (for methodology see this paper)
Assesment of - patient-reported CRS control - overall symptom severity, - severity of nasal obstruction - the use of CRS-related oral corticosteroids (OCS) within the last 6 months	Assessment of - patient-reported CRS control - clinically relevant sinonasal symptoms of active disease - overall symptom severity (for research VAS ≤ 5 cm), - nasal obstruction (for research VAS ≤ 5 cm), - loss of smell (for research VAS ≤ 5 cm)
The use of CRS-related oral corticosteroids (OCS) is part of the assessment of control	CONTROL can be achieved with or without ongoing / past treatment.

too challenging to determine if the anosmia is due to surgery or the pathology itself. We realize that this definition results in the impossibility of achieving control in patients with persistent anosmia due to previous surgery.

A second discussion was the cut-off value of the VAS and/or SNOT-22 to define control. Two recent papers evaluated the relationship between control of disease and symptom SEVERITY measured with VAS or SNOT-22. Philips et al. in a group mainly consisting of CRSsNP patients (220 of 309 CRS patients) studied the translation of individual symptom VAS scores to what patients considered to be burdensome using an explicit, descriptive dichotomous anchor scale for symptom burden [11]. In this study, a general determination was made that individual symptom VAS scores of >3.5 cm were maximally predictive of patients' explicit descriptions of their symptoms as burdensome. No separate evaluation was performed for CRSwNP alone [11].

For the specific symptoms considered relevant for control in patients with CRSwNP, a VAS cut-off point was determined as >4.2 cm, (90.1% sensitivity, 87.5% specificity) for burdensome nasal obstruction and a VAS cut-off of >3.7 cm (93.3% sensitivity, 87.6% specificity) for burdensome smell loss. In a group of CRS patients in which more than half were patients with CRSwNP (85/157) studied by Dietz de Loos et al. a cut-off point of >5 cm in the VAS for 'nasal obstruction' (86% sensitivity, specificity 93%) was found to identify patients scoring ≥3 (at least moderate symptom burden) on the nasal blockage/congestion SNOT-22 item [12]. For reduced smell, a cut-off point of >5 in the VAS was found (77% sensitivity, specificity 94%) to identify patients scoring ≥3 in the smell loss item of the SNOT-22 [12]. They did not evaluate overall symptoms.

As far as we know there are no papers evaluating control in patients with CRSwNP alone. For this reason, we cannot presently advise on the exact cut-off for **patient reported control** for research purposes. At this time, the best option is probably to ask the patients whether their individual symptoms are controlled or burdensome with a binary answer (yes/no), as originally described in the 2012 EPOS CRS control assessment recommendations [13].

Uncontrolled CRSwNP was subsequently defined as "**patient-reported lack of control** and the presence of clinically relevant sinonasal **symptoms** of active disease (defined as overall symptom severity, nasal obstruction and smell)".

If control is achieved, no further escalation of therapy is indicated to achieve remission, though current therapy may need to be continued. As long as there is no remission, there is an indication for continued medical follow-up with (potential) adjustment of treatment.

Remission in CRSwNP is defined as **sustained** control (as defined earlier) for ≥ 12 months combined with the absence of active disease preferably evaluated by nasal endoscopy. REMISSION can be reached with or without treatment, excluding systemic corticosteroids and surgery (in the last 12 months). In a state of remission, patients do not have exacerbations (see below) and as such do not need systemic corticosteroids and/or salvage surgery for their nasal polyps.

The expert board agreed that for the definition of remission not only patient reported symptoms and control but also physician reported control should be reached; for this reason, the absence of signs of active disease, preferably evaluated by nasal endoscopy, was considered an important goal to achieve. A similar approach was recently suggested by Canadian rhinologists who defined remission as "absence of symptoms and endoscopic markers of CRS [14]. Nasal secretions, oedema, polypoid swelling and frank nasal polyps might all be considered signs of active disease, although more research is needed in this area, in particular to identify specific signs that can predict loss of control. It was discussed that findings of abnormal mucosa at nasal endoscopy often anticipate and predict loss of control although further data are required. Until more research is done on the subject, the time factor and especially correlation with

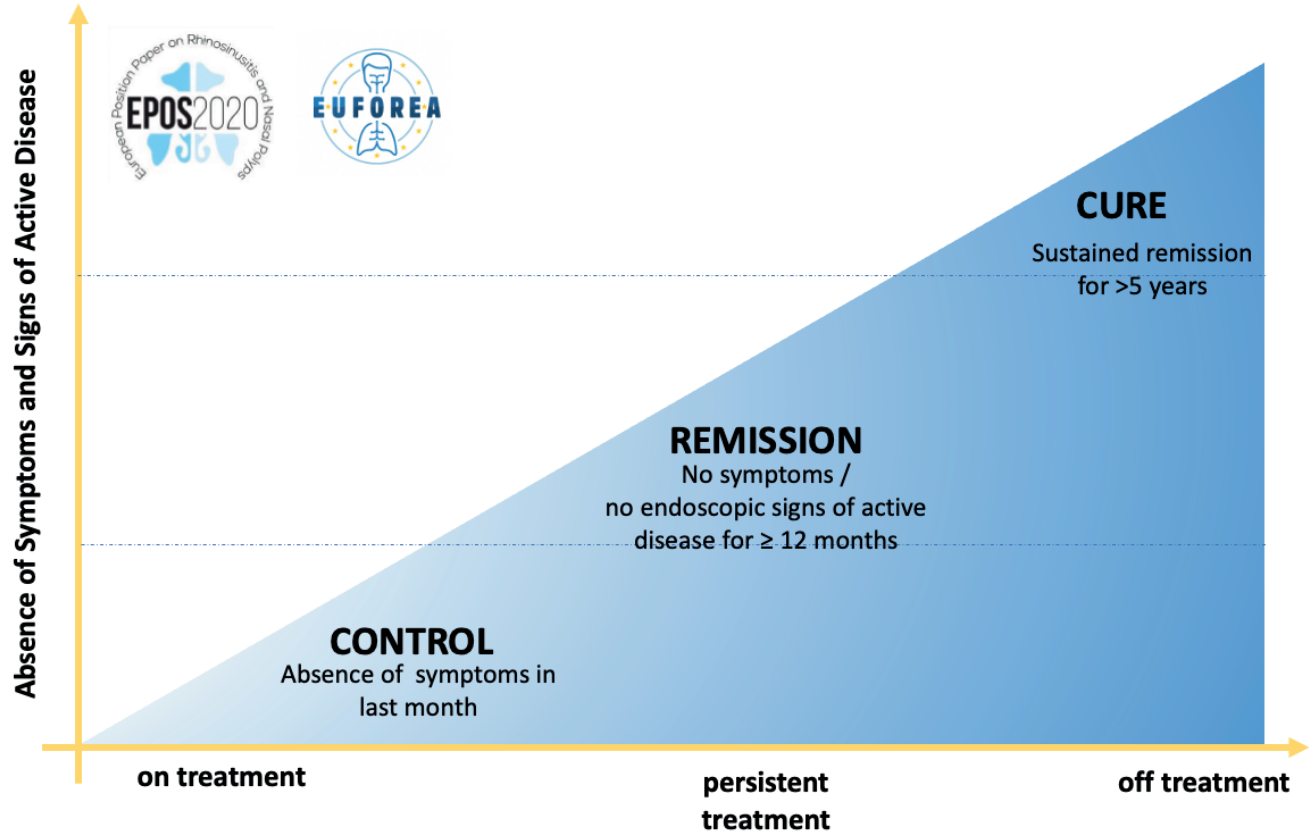


Figure 1. Schematic overview relation between control, remission, and cure.

symptoms are important in determining active disease. For example: nasal polyps can be a sign of active disease. However, the expert panel discussed whether small polyps found in controlled patients, should be considered a sign of active disease and concluded that without symptoms they are probably not a sign of active disease. Further research, including potential identification of specific biomarkers, is needed to discriminate active from non-active nasal polyps.

The expert group felt that performing radiography, even with the low radiation exposure associated with modern (cone-beam) CT scans, in a patient who is controlled should be avoided when possible. The finding of abnormalities without nasal symptomatology is not helpful in the management of the disease.
Lastly, CURE in CRSwNP was defined as sustained remission without treatment for at least 5 years.

As stated above, the treatment goal until now was achieving control [1, 4]. The new treatments targeting the underlying inflammation of CRSwNP and their possible disease modifying effects [3] have encouraged clinicians to aim for more than control in their patients with CRSwNP. Therefore, the expert panel redefined treatment goals for CRSwNP.

The aims of a therapeutic strategy for CRSwNP are to achieve control, then remission and ultimately, to reach a cure (Figure 1). It was discussed that control and, preferably remission should always be considered treatment goals. However, the potential side effects or risks of the medical/surgical treatment should be balanced against the advantages of reaching remission. Ideally, these targets should be discussed with the patient in a shared decision-making process as proposed in the EUFOREA algorithm for CRS [4].
For the time being, disease modifying treatment is not possible and, in most patients, cure is not likely, but it should always remain the ultimate aspiration of those treating CRSwNP.

Recurrence/exacerbation and treatable traits

RECURRENCE is defined as the loss of remission and can occur either on- or off- treatment.
RECURRENCE has mainly been used postoperatively as an indication that the disease has returned. One can argue that this way of considering a disease state is not helpful in a chronic condition.

An acute EXACERBATION in chronic rhinosinusitis (AECRS) is defined as a temporary worsening of symptoms or a loss of control (lasting at least 3 days, and to which a distinct negative impact

Table 2. Treatable traits.

Triggers	allergens, viruses and microbiome imbalance, (intranasal) drugs
Irritants	smoking, vaping, occupational factors, (intranasal) drug abuse, vasoconstrictor misuse, environmental pollution
Co-morbidities:	allergic rhinitis, asthma, nonsteroidal exacerbated respiratory disease (N-ERD), otitis, and obstructive sleep apnoea
Symptomatic anatomical malformations:	nasal valve abnormality and/or septal deviation
Self-management skills	proper rinsing, drop application and spraying techniques, adherence to treatments.
Mental and psychological factors	disease management education

on a patient's QOL or functionality can be attributed [15, 16]. There has not been a definition on the length of an acute exacerbation to differentiate exacerbation from recurrence. We searched the asthma literature but could not find a definition of the maximal length of an exacerbation [17, 18]. There was not unanimous agreement on the length but a suggestion of 6 weeks maximum was accepted. However, data are missing.

Typically, when patients have a recurrence or an exacerbation, a step-up approach is used, and rescue treatment is often given. However, the expert board recognizes the need to consider treatable traits, before switching treatments. The current step up-step down approach is not optimal in the long- term and can lead to excessive use of rescue treatments [19-21].

TREATABLE TRAITS (TTs) are co-existing conditions and hence, therapeutic targets that can be identified by the patient's phenotypes and/or endotypes; TTs are often overlooked in CRSwNP [22]. Targeting TTs is a relatively new strategy to improve patient-centred care, with individual assessment of a set of treatable conditions or factors resulting in an individualized treatment programme based on these traits [19-21, 23]. A typical TT fulfils three criteria: identifiable/measurable, clinically relevant, and treatable [24]. TT strategy has already been implemented in other airway diseases such as COPD and asthma [24, 25] with improvements in both QoL and response to biologics [24, 25].

TREATABLE TRAITS in patients with CRSwNP include triggers, irritants, co-morbidities, symptomatic anatomical malformations, self-management skills, mental and psychological factors, and some laboratory abnormalities (Table 2).

By defining, identifying, and addressing these TTs, we aim to improve outcomes of care, including the reduction in OCS use or sinus surgery needed [22].

Therapeutic response

Several attempts have been made in the past decade within the EPOS2020 and EUFOREA expert panels to define therapeutic response especially in the context of treatment with biologics [1, 7, 26, 27].

In most consensus documents, a therapeutic response using the following 5 criteria has been proposed:

- Reduced nasal polyp size.
- Reduced need for systemic corticosteroids/ reduced need for ESS.
- Improved QoL/quality of life.
- Improved sense of smell.
- Reduced impact of comorbidities.

Over time, the evaluation time has increased from 4 and 12 months to 6 and 12 months and the number of criteria to be met for a certain level of response varies. The 2021 paper [27] presents a comprehensive attempt to define numerical criteria for the management of CRSwNP. Current insights have highlighted several areas of improvement. One area of concern was the criteria used at six months, which were considered too lenient in defining patients who responded well to treatment, whereas at 12 months treatment criteria were rather too restrictive.
The DUPIREAL study [28] compared these criteria with patients' VAS-score after treatment with dupilumab for 12 months. This analysis showed that 34.1% (221/648) patients did not have an adequate response to dupilumab according to the 2021 criteria, although, according to the median VAS of 1.6 cm, patients were satisfied by their treatment and had very low symptom burden.
Another point for improvement of the 2021 criteria was that the re-evaluation of the disease in this treatment algorithm was not sufficiently highlighted. In the beginning of 2023 EUFOREA updated the indications and evaluations of biologics for CRSwNP based on the 2022 consensus meeting [7]. Although several key points were addressed, no cut-off values were defined in the updated algorithm.
As these cut-off values are not always easy to implement in routine clinical practice, the expert board acknowledges the need to define "clinical" and "research" criteria (Figure 2).

Firstly, the expert board finetuned the cut-off points for clinical

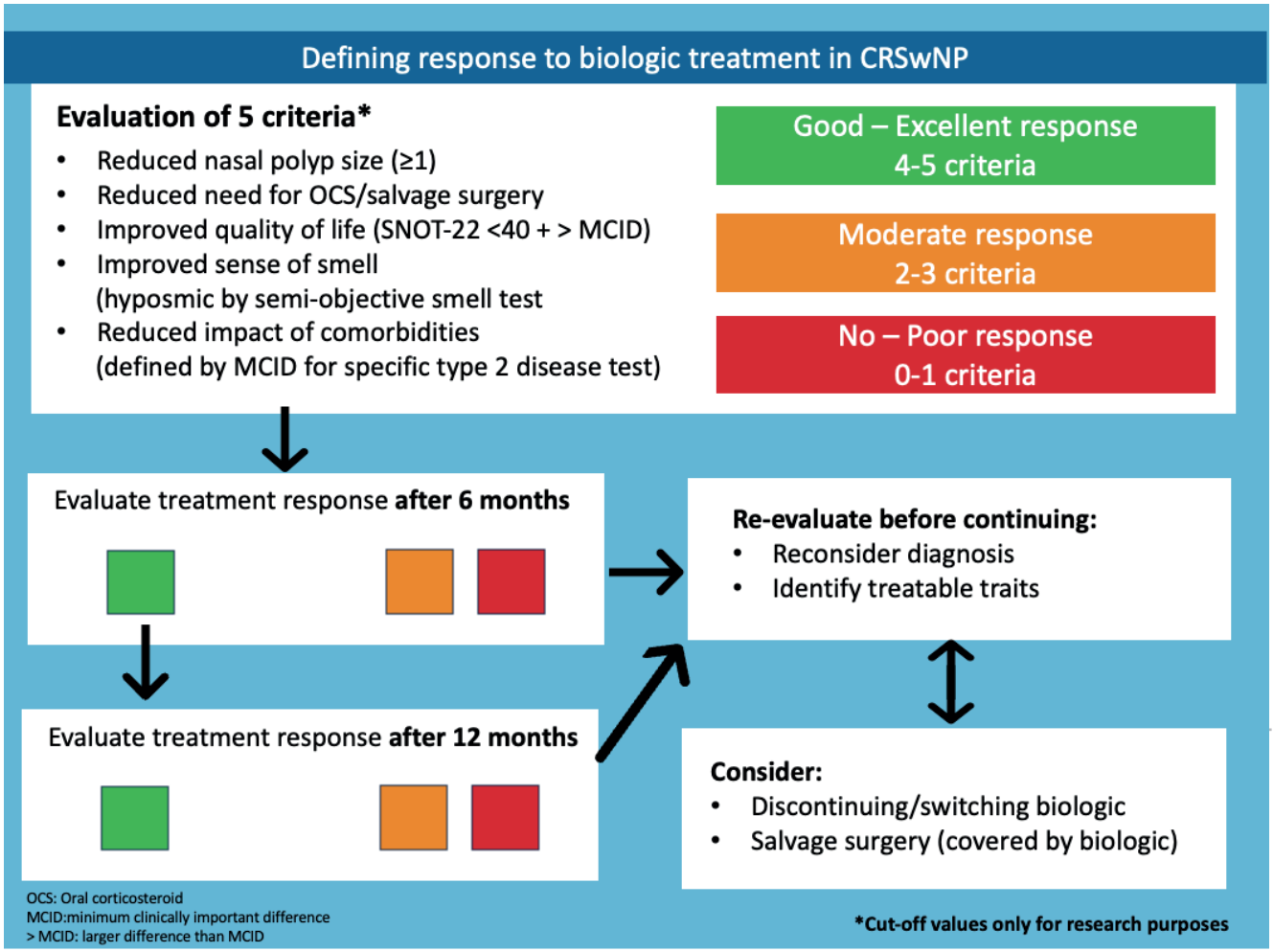


Figure 2. EUFOREA/EPOS criteria on biologic treatment in CRSwNP 2023 for clinical practice and with cut-off values for research purposes.

response in general as no-poor response (0-1 criteria); moderate response (2-3 criteria); good-excellent response (4-5 criteria.
If patients have a good-excellent response, they can continue their biologic. However, if patients have no, a poor or only a moderate response, the expert board advises to re-evaluate before continuing treatment [4], and should consist of a re-evaluation of the diagnosis and identification of TTs. After this, the attending physician can decide whether to discontinue the biologic, switch or do concomitant salvage surgery (under biologic cover) [29, 30].

Secondly, the cut-off points for the research purposes were discussed.
For the first criterion several parameters were proposed: a 50 % reduction in nasal polyp size or a reduction in nasal polyp score of at least 1. An argument in favour of the use of percentages is that, it seems to be easier to go from a polyp score of eight to four than from two to zero with the total nasal polyp score-scoring system, because patients with polyps medial to the middle turbinate tend to score higher. Moreover, if patients at baseline only have polyps present in the frontal sinus, it is difficult to reduce nasal polyp size during the course of treatment using the total nasal polyp score, although clinically the nasal polyps do shrink [31].
However, the implementation of percentages in the clinic will mean that a new grading method for nasal polyps has to be implemented, possibly using endoscopic imaging to enable a computer to determine the total size of the polyps. Currently, this is not feasible and the expert board, therefore, advises using a total nasal polyp score reduction of one or more as the cut-off point and using the rules as defined in the EAACI position paper on endoscopic scoring of nasal polyposis [31]. However, further research into optimizing the nasal polyp grading is necessary [31-33].

The second evaluation criterion is based on the need for rescue treatment. This is defined as no need for oral corticosteroids or salvage surgery specifically for CRSwNP.
The third criterion is improved QoL. 9Two options for a cut-off value were put forward: the minimal clinically important difference (MCID) of 9 (surgical) [34] -12 (medical) [35] or the need for the SNOT-22 <40 because this is the cut-off value for uncontrol-

Table 3. Key definitions on CRSwNP agreed upon by EPOS/EUFOREA expert panel members.

Key definitions in CRSwNP	
Controlled CRSwNP	"Patient reported control" with the absence of clinically relevant sinonasal symptoms of active disease (defined as overall symptom severity, nasal obstruction and smell)". CONTROL can be with or without ongoing / past treatment.
Uncontrolled CRSwNP	"Patient reported lack of control" and the presence of clinically relevant sinonasal symptoms of active disease (defined as overall symptom severity, nasal obstruction and smell)".
Remission	REMISSION in CRSwNP is defined as sustained CONTROL (as defined earlier) for ≥ 12 months combined with the absence of signs of active disease evaluated by nasal endoscopy. REMISSION can be reached with or without treatment (not including systemic steroids and/or sinonasal surgery in the last 12 months).
Disease cure	Sustained remission without treatment for at least 5 years.
Treatable traits	Co-existing conditions and hence, therapeutic targets which can be identified by patient phenotypes and/or endotypes.
Remodelling	The persistent structural cell/tissue changes that manifest clinically. It results from host and environmental factors that may initiate and sustain the cascade of pro-inflammatory responses, related to duration of the disease and long-term uncontrolled inflammation, that drive sinonasal mucosal remodelling and nasal polyp formation.
Disease modification	A treatment or intervention that affect the underlying pathophysiology of the disease and has a beneficial outcome on the course of the disease or slows down the progress of the disease.
Primary prevention	Reducing the incidence of disease by reducing exposure to risk factors or triggers.
Secondary prevention	Early detection of the disease to return a patient to full recovery and preventing persistent disease.
Tertiary prevention	Reduction of the impact of ongoing chronic rhinosinusitis and its complications to maximize quality of life as much as possible.

led CRSwNP [11, 12].

The EUFOREA board acknowledges that in clinical practice and in the real-world data of biologics, the SNOT-22 score tends to drop more than 12 points fairly quickly without the patients being controlled, because of a high baseline SNOT-22 score [36-38]. Therefore, the EUFOREA expert panel considered that an overall SNOT-22 score under 40 fulfilled the improved quality of life criterion, but in situations with lower SNOT-22 scores, also the choice for MICD can be made.

The fourth criterion relates to the sense of smell. Although a smell test is the preferred method to evaluate loss of smell, the expert board acknowledges that it is not always feasible to do a smell test in observational trials with minimal funding and that it is not always routinely done in clinical practice. Also, not all smell tests are validated for the different relevant languages/countries. In that case VAS scoring of smell loss can be performed by the patient [39, 40].

However, for research it is **highly recommended** to use a semi-objective smell test that is validated in the country where the study is performed. When smell testing has been performed, the patient should have a clinically meaningful improvement in the sense of smell. However, for most semi-objective smell tests these data are not available [41]. For that reason, at present, the expert panel was not able to advise more than at least improvement from anosmia to hyposmia.

If a semi-objective smell test is not feasible, a VAS can be performed. However, again the data for clinical meaningful change are missing [42].

The fifth and last criterion is the reduced impact of type 2 comorbidities such as asthma. More insight into different type 2 comorbidities is being colled and more type 2 diseases are being identified and linked to CRSwNP. The expert board suggests using a validated test for the specific type 2 comorbidity and use the MCID for that specific test as an appropriate cut-off value [43, 44].

Remodelling, progression, and disease modification in CRSwNP

REMODELLING refers to the persistent structural cell/tissue changes that manifest clinically. It results from host and environmental factors that may initiate and sustain the cascade of pro-inflammatory responses, related to the duration of the disease and long-term uncontrolled inflammation, which drive sinonasal mucosal remodelling and nasal polyp formation [45-47].

Remodelling in CRSwNP can refer to a combination of the following:

1) changes in epithelial structure (hyperplasia, metaplasia, or shedding);
2) angiogenesis, increased vascular permeability, and oedema;
3) extracellular matrix deposition, degradation and accumulation of plasma proteins;
4) granulocyte influx and fibroblast activation.

However, these microscopic remodelling changes may be macroscopically identified by the presence of mucosal oedema, nasal polyps, pseudocysts, or fibrotic tissue. Remodelling is not only seen in the sinonasal mucosa but also extends to the underlying bone [48-50].

Amongst the expert panel, there was a significant discussion on whether one could define PROGRESSION OF DISEASE in CRSwNP. We started with what has been observed in asthma. Asthma symptoms and signs result from chronic airway inflammation and remodelling. Different inflammatory patterns including the type 2 profile, may lead to persistent inflammation and remodelling which promotes persistent disease [51]. Progression of the disease is mainly correlated with a decline in lung function, which is especially prominent in late-onset asthma. In severe chronic diseases it will manifest as loss of reversibility and fixed airflow obstruction. Furthermore, severe exacerbations of asthma are associated with progression of asthma and a more rapid decline in lung function [52, 53]. In a comparable way in CRSwNP, different patterns of inflammation including type 2 inflammation, lead to remodelling of the sinonasal mucosa. As in asthma chronic inflammation and remodelling are closely interconnected in CRS and associated with a progressive decline in nasal function and, in particular, limiting nasal flow and olfactory function. Similar to asthma, exacerbations in CRSwNP increase the inflammatory load, facilitating the decline in nasal function with worsening of symptoms and requiring rescue treatments. Finally, the progression of the disease in CRSwNP may be defined as a progressive decline of nasal functions, in particular of nasal flow and olfactory function. For that reason, the natural history of the disease may progress from a mild-moderate condition to a severe state. It should be noted that, unfortunately, in many cases the early stages of the disease are frequently unrecognized, and patients are diagnosed only when they already have significant limitation of nasal functions. There is a lack of data on the natural course of CRSwNP and insufficient evidence on the relationship between exacerbations and/or treatment and progression of disease in CRSwNP [54, 55].

DISEASE MODIFICATION, in general, is defined as treatments or interventions that affect the underlying pathophysiology of the disease and have a beneficial outcome on the course of the disease or slow down the progress of the disease [56]. DISEASE MODIFICATION in respiratory disease has mainly been discussed for the use of allergen specific immunotherapy [57, 58].
From a regulatory point of view, a drug can be considered as disease modifying if it fulfils two conditions:

- Reduces the progression of the disease measured by an assessment tool.
- The results are linked to a significant effect on validated biomarkers.

Disease modifying treatments are different from symptomatic treatments as they are able to address the pathogenesis of a disease, preventing progression or leading to a long-term reduction in symptoms even after the dis-continuation of the treatment. At present, there is no cure for CRS and medical treatments typically involve therapies that control symptoms, without modifying the underlying disease. On the other hand, endoscopic sinus surgery could be seen as a disease modifying treatment as evidence has demonstrated that it slows down progression of the disease [59]. Biologics are also suggested to be disease modifying, although more research is necessary [60, 61].
In the absence of more data on the natural course of chronic rhinosinusitis, disease modification may be advocated when a prolonged REMISSION is observed. It can be either on- or off treatment.

Prevention

There are three types of PREVENTION: primary, secondary, and tertiary prevention that rely on recognition of the aetiology and triggers, early recognition of symptoms and a correct diagnosis [62].
Primary prevention in CRSwNP focuses on reducing the disease incidence by reducing exposure to risk factors or triggers. Primary prevention in CRSwNP is difficult to achieve given the fact that many genetic and environmental factors contribute to the development of CRSwNP. Several factors, such as tobacco smoke and occupational toxins, have been proposed that could be avoided to reduce the prevalence of CRSwNP, although in practice these avoidance strategies are very difficult to implement [1, 62].
Secondary prevention focuses on early disease detection to return a patient to full health and preventing persistent or extended disease. In the context of CRSwNP this relates to appropriate management of the disease and to disease modification thereby preventing excessive remodelling [45]. Patients receiving sinus surgery within 12 months of their diagnosis had significantly less sinus-related postoperative health care needs and seemed to have less comorbid asthma compared to patients treated after more than 5 years of disease [59]. Biologics are also presumed to have a potential disease modifying effect, however more research is necessary to confirm these claims [3, 63].
Tertiary prevention focuses on the reduction of the impact of ongoing chronic rhinosinusitis and its complications in order to maximize quality of life as much as possible. In CRSwNP this primarily relates to disease control. This can be achieved by the appropriate therapy according to the guidelines [1, 4] and by the prevention of exacerbations and/or unnecessary treatment with impact on smell, nasal and body function. The EUFOREA expert board acknowledges the need for prevention by giving more attention to the different treatable traits as discussed above [45, 62, 64].

Unmet needs in defining aspects of CRSwNP

Increasing insights into the underlying mechanisms and innovations in the treatment armamentarium for CRSwNP in recent years have led to a growing need to define targets for CRSwNP treatment [60]. Future real-world data on the aetiology, pathop-

hysiology and natural course of the disease, including comorbidities, in individual patients are important and sorely needed. The expert group felt they were most hampered by the current lack of data. A typical example is the lack of data on progression and disease modification of CRSwNP and this paper calls for intensified research on the natural course of the disease and the possibilities to intervene. Also, some basic concepts are not well-defined. For example, we need a further discussion on the definition of disease severity versus symptom severity versus control.

Conclusion

A group of EPOS/EUFOREA experts on CRSwNP met to propose definitions of control, remission, and disease progression in CRSwNP, and to re-evaluate current treatment goals. This report on definitions in CRSwNP proposes several relevant definitions to describe levels of control of disease, remission, exacerbation, and treatment evaluation. The aim of treatment is to achieve control using minimal treatment, and (optimally) remission and (aspirationally) cure together with awareness of side effects. In addition, several unmet needs have been identified.

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Authorship contribution

Most of the authors particiapted in the consensus meeting in June 2023 in Brussels. After the meeting a draft was written (WF, EdC, PWH). All authors participated in two subsequent rounds of review and two virtual webbased meetings in August and Septem-ber 2023. All authors approved the final version.

Conflict of interest

Wytske Fokkens - The department of Otorhinolaryngology of the Amsterdam University Medical centre, location AMC received grants for research in Rhinology from: ALK, Allergy Therapeutics, Chordate, Novartis, EU, GSK, MYLAN, Sanofi-Aventis, and Zon-MW. Wytske Fokkens received consultation and/or speaker fees from Dianosic, GSK, Novartis and Sanofi-Aventis/ Regeneron and is chair of EPOS and board member of EUFOREA. Eugenio de Corso: received fee for consultation, speaker activity, advisory board by Sanofi, Regeneron, GSK, Novartis and Astrazeneca. Vibeke Backer has received unrestricted grants from Sanofi, GSK, ALK Abello, Chiesi, Birk, MSD, AZ, TEVA, and Novartis, as well as participated as Speaker and chair or board member in numerous advisory boards both nationally as well as internationally. I have also received grant after application to support several research studies. Manuel Bernal-Sprekelsen: Speaker honorarium for GSK Spain, Olympus Europe, Sanofi Spain, Viatris Spain. Travel grant Univ. of Essen, Germany and Univ. of Ghent, Belgium. Editor-in-Chief Eur. Arch. ORL-HNS. Leif Bjermer: In the past three years, LB received speakers fee or attended ad board for the following companies, AstraZeneca, Acucort, Birk pharma, GlaxoSmithKlein and Sanofi Genzyme. Adam Chaker reports grants, speaker honoraria, consultancy or advisory fees and/or research support and other all via Technical University of Munich from Allergopharma, ALK Abello, Bencard / Allergen Therapeutics, GSK, Hippo Dx, Novartis, LETI, Roche, Zeller, Sanofi Genzyme/Regeneron, European Institute of Technology, AstraZeneca, Immunotek, all outside the submitted work; In addition, Dr. Chaker has a patent "A ratio of immune cells as prognostic indicator of therapeutic success in allergen-specific immunotherapy": 17 177 681.8 licensed to none, and a patent pending. Zuzana Diamant: In the past 3 years, ZD received speaker or consultant honoraria or served on advisory boards at: Antabio, Foresee Pharmaceuticals, GlaxoSmithKline, Hippo-Dx, QPS-Netherlands, Sanofi-Genzyme-Regeneron, all outside the submitted work. QPS-Netherlands received European grant from ERA4TB and Foresee Pharmaceuticals. She serves as associate editor for Allergy and Respiratory Medicine and acts as Chair of the Asthma Expert Panel at EUFOREA. Philippe Gevaert has participated in advisory boards and received speaker fees from ALK-Abelló, Argenx, AstraZeneca, Genentech, GSK, Novartis, Regeneron, Roche, Sanofi Genzyme, and Stallergenes-Greer. Joseph K Han: Research consultant for Sanofi Regeneron, GlaxoSmithKline, AstraZeneca, Genetech, Novartis. Claire Hopkins: Advisory Board, GSK, Dianosic and Sanofi, Speaker's bureau, Mylan, Olympus. Valerie Hox: consulting fees from GSK, ALK, Astra-Zeneca, Sanofi. Ludger Klimek has received research grants from Allergy Therapeutics/Bencard, Great Britain/Germany; ALK-Abelló, Denmark; Allergopharma, Germany; ASIT Biotech, Belgium; AstraZeneca, Sweden, Bionorica, Germany; Biomay, Austria, Boehringer Ingelheim, Germany, Circassia, USA; Stallergenes, France; Cytos, Switzerland; Curalogic, Denmark; HAL, Netherlands; Hartington, Spain; Lofarma, Italy; Viatris/Mylan, USA; Novartis, Switzerland, Leti, Spain; ROXALL, Germany; GlaxoSmithKline (GSK), Great Britain; Sanofi, France and/or has served on the speaker's bureau or was consulting for the above mentioned pharmaceutical companies. LK is the current President of German Society of Allergology AeDA, Vice-President of the European Academy for Allergy and Clinical Immunology (EAACI), Vice-President of German Academy for Allergy and Environmental Medicine and Editor-in-Chief of AllergoJournal and AllergoJournal International. Valerie Lund: received fee for consultation, advisory board and lecturing from Abbott, Alcimed, EUFOREA, GSK, Novartis, Sanofi Regeneron, GSK; editorial work for Elsevier. Stella Lee: AstraZeneca, Genentech, GSK, Lyra Therapeutics, OptiNose, Sanofi Regeneron. Amber Luong serves as a consultant for Lyra Therapeutics (Watertown, MA, USA), Medtronic (Dublin, IE), NeuroENT Medical (Galway, IE), Sanofi (Paris, France), and Stryker (Kalamazoo, MI, USA). AUL serves on the scientific advisory board for

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