Optimizing Endpoints for CRSwNP Biologic Trials: Regulatory, HTA, and Patient-Centered Evidence Requirements

Poster # HTA69

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BACKGROUND & OBJECTIVE

- CRSwNP is a chronic inflammatory disease with recurrent nasal obstruction/discharge, loss of smell, and facial pressure.
- Burden extends beyond polyp size and includes sleep disturbance/fatigue, steroid exposure, surgery risk, and reduced health-related quality of life. [1,2]

Objective: to define a patient-centered endpoint strategy for Phase III CRSwNP biologic trials that can address regulatory expectations, HTA requirements, and patient-prioritized outcomes.

Treatment goals should extend beyond polyp shrinkage to symptom relief, lower steroid burden, fewer surgeries, and better health-related quality of life. [3]

METHODS: TARGETED LANDSCAPE ASSESSMENT

Evidence review and synthesis to identify measures meaningful to regulators, HTA reviewers, and patients, while assessing usefulness for indirect treatment comparison and economic modeling.

1. **Phase III Biologic Trial Review** — FDA + ClinicalTrials.gov Populations, countries, and endpoint timing
2. **HTA Value Assessment** — Clinical and economic metrics used to judge product value
3. **Guideline Review [4,5]** — FDA, EPOS, ARS, DELPHI panels, and expert statements
4. **Biomedical Literature Review** — PubMed, Embase, PsycINFO (2015-2025)
5. **PRO and QOL Literature Review** — ISPOR and ISOQOL PRO / QOL literature
6. **SME Consultation** — Global respiratory PRO leaders and EPOS contributors

Focus domains: symptoms, disease-specific PROs, utilities, olfaction, disease control, treatment experience, and resource use.

KEY TAKEAWAYS

Across regulatory, HTA, and patient perspectives, the literature converged on four recurring messages:

- **NPS + NCS** remain the core efficacy backbone in pivotal CRSwNP trials. [3,6]
- **SNOT-22** is the leading disease-specific PROM; EQ-5D remains important for assessment of utility decrements. [7]
- **Smell** is highly salient to patients, but the most practical approach for pivotal trials is patient-reported smell severity. [3,8,9]
- Disease-control measures and aligned schedules strengthen HTA value assessment and comparative-evidence use.

RECOMMENDED STAKEHOLDER-ALIGNED ENDPOINT BATTERY

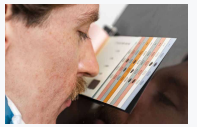
SNOT-22 improves sensitivity to CRSwNP symptom change; EQ-5D remains important for utilities and cross-disease value assessment. [7]

Domain	Suggested measure(s)	Why include it
Objective disease burden	NPS (co-primary); endoscopy or imaging supportive	Core regulatory evidence of structural disease change [3,6]
Core symptom control	NCS diary / verbal rating scale	Captures the most commonly prioritized symptoms in registration trials [3,10]
Disease-specific HRQOL	SNOT-22 total score plus domains	Sensitive to symptom change and widely recognized by guidelines and HTA reviewers [7] but not formally qualified by the FDA or EMA
Health utility	EQ-5D	Needed for utilities and cross-disease comparisons in cost-effectiveness analysis [7]
Olfaction	Patient-reported smell severity; objective smell test supportive or exploratory	Addresses one of the most salient patient symptoms while remaining pragmatic [3,8]
Disease control	OCS use, surgery, exacerbation or progression markers	Reflects meaningful control beyond symptom scores alone that could inform further comparative effectiveness or indirect comparison [4,5]
Heterogeneity / comorbidity	ACQ in asthma; biomarker and comorbidity subgroups	Addresses material burden and treatment response variability across subgroups [11]
Treatment experience + payer inputs	TSQM, dosing burden, and healthcare resource use	Supports patient-centered differentiation and HTA readiness [2]

OLFACTION ENDPOINT SELECTION

Patient-reported smell loss

☑ Low burden and easy to repeat [10]
☑ Regulatory-aligned and captures perceived improvement [3,10]



Objective smell tests (UPSIT / Sniffin' Sticks)

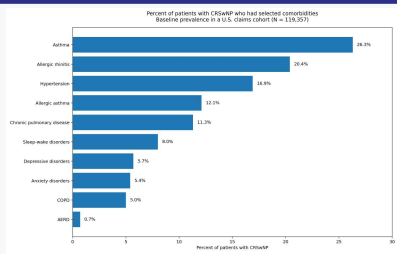
☑ Standardized supportive evidence [9]
- Requires materials, training, and consistent administration
- Influenced by culture, age, and prior olfactory experience
- The FDA does not recommend UPSIT. [3]
- UPSIT score has been previously found to correlate with patient-reported smell loss either weakly or not at all. [7]

Pragmatic recommendation: use patient-reported smell severity as a key secondary endpoint as it is core burden of disease; reserve objective smell testing for supportive or exploratory use when feasible. [1,4]

SUBGROUPS & SCHEDULING

SUBGROUPS

- Pre-specify biomarker subgroups and high-burden comorbidities such as asthma, OSA, migraine, depression, and anxiety. [11]
- Confirm linguistic validation and operational feasibility for multinational studies.
- Pediatric and adolescent evidence remains limited and may require additional qualitative work.



Recommended Assessment Schedule to Support Future Evidence Use:

Daily / weekly	Planned visits	Landmark visits
NCS and smell-severity diary [3,10]	SNOT-22, ACQ or TSQM as relevant [7]	EQ-5D, OCS, surgery, HRU, imaging [7,2]

TRIAL PATTERN & SCHEDULING IMPLICATIONS

Nearly universal [3,6]	Common [5,7,8]	Variable [7]
• NPS + NCS (co-primary)	• SNOT-22 • Smell endpoint(s) • ACQ in asthma	• EQ-5D • PGI-S / PGI-C • HRU / TSQM

Heterogeneous endpoint mixes and schedules can complicate indirect treatment comparison and economic-model inputs.

A practical scheduling structure:

Symptom diary
Frequent capture of NCS and smell severity

↓

Study-visit PROs
SNOT-22 at planned intervals to show trajectory of change

↓

Landmark evidence
EQ-5D, OCS, surgery, HRU, and imaging at decision-relevant time points

REMAINING GAPS

- No single instrument fully captures symptoms, disease control, and treatment experience in CRSwNP. [7, 8]
- SNOT-22 is valuable, but interpretation can be affected by comorbidities. It is not officially endorsed by regulators although used widely in clinical practice.
- Smell assessment remains heterogeneous across trials and geographies. [7]
- Utilities and resource use are not consistently collected despite payer relevance. [7, 2]

This review identified a practical, stakeholder-aligned endpoint and scheduling framework for Phase III CRSwNP trials, but ongoing heterogeneity in olfaction measures and inconsistent collection of utilities, HRU, OCS use, and surgery outcomes still limit cross-trial comparison and downstream HTA use. [7]

CONCLUSIONS

- A stakeholder-aligned CRSwNP strategy should combine symptom, HRQOL, utility, olfaction, disease-control, treatment-experience, and resource-use measures.
- This broader battery improves interpretation of clinical benefit, strengthens HTA readiness, and better reflects what matters to patients. [8, 2]
- Prospective planning of subgroups and schedules improves the future usefulness of Phase III data. [2]
- Capturing systemic corticosteroid burden and initial and revision surgery, including associated complications, can improve interpretation of disease control and long-term treatment burden. [6,2]
- Prospective assessment of healthcare resource utilization can strengthen HTA readiness and future economic modeling.

Key message: Meaningful CRSwNP trials should measure more than polyp shrinkage alone. [8, 9]

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Abbreviations: ACQ, Asthma Control Questionnaire; ARS, American Rhinologic Society; CRSwNP, chronic rhinosinusitis with nasal polyps; EQ-5D, EuroQOL 5-Dimension; EPOS, European Position Paper on Rhinosinusitis and Nasal Polyps; FDA, U.S. Food and Drug Administration; HRQOL, health-related quality of life; HRU, healthcare resource utilization; HTA, health technology assessment; ISPOR, International Society for Pharmacoeconomics and Outcomes Research; ISOQOL, International Society for Quality of Life Research; NCS, nasal congestion score; NPS, nasal polyp score; OCS, oral corticosteroid; OSA, obstructive sleep apnea; PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity; PRO, patient-reported outcome; PROM, patient-reported outcome measure; QOL, quality of life; SNOT-22, 22-item Sino-Nasal Outcome Test; SME, subject matter expert; TSQM, Treatment Satisfaction Questionnaire for Medication; UPSIT, University of Pennsylvania Smell Identification Test.

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