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Special Article

Chronic Rhinosinusitis Outcome Registry (CHRINOSOR): Establishment of an International Outcome Registry Driven by mHealth Technology

Sven F. Seys, PhD[a,b], Peter W. Hellings, MD, PhD[b,c,d], Isam Alobid, MD, PhD[e], Vibeke Backer, MD, PhD[f], Emilie Bequignon, MD, PhD[g], Christian von Buchwald, MD, DMSc[f], Carlo Cavaliere, MD, PhD[h], André Coste, MD, PhD[g], Lauren Deneyer, PhD[a], Zuzana Diamant, MD, PhD, FERS[b,i,j,k], Julia Eckl-Dorna, MD, PhD[l], Wytske J. Fokkens, MD, PhD[d], Simon Gane, MPhil, FRCS[m], Philippe Gevaert, MD, PhD[n], Christiane Holbaek-Haase, MSN[f], Clemens Holzmeister, MD[o], Claire Hopkins, MD, PhD[p], Valérie Hox, MD, PhD[q], Caroline Huart, MD, PhD[q], Roger Jankowski, MD, PhD[r], Mark Jorissen, MD, PhD[c,s], Anette Kjeldsen, MD, PhD[t], Lisa Knipps, MD[u], Bibi Lange, MD, PhD[t], Rik van der Lans, MD, PhD[d], Anu Laulajainen-Hongisto, MD, PhD[v], Kenneth Larsen, MD[t], David T. Liu, MD[l], Valerie Lund, MD, MS, FRCS, FRCSEd[m], Gert Mariën, MSc[a], Simonetta Masieri, MD, PhD[w], Geoffrey Mortuaire, MD, PhD[x], Joaquim Mullol, MD, PhD[y], Sietze Reitsma, MD, PhD[d], Philippe Rombaux, MD, PhD[q], Sven Schneider, MD[l], Andreas Steinsvik, MD, PhD[z], Peter-Valentin Tomazic, MD, PhD[o], Sanna K. Toppila-Salmi, MD, PhD[aa], Laura Van Gerven, MD, PhD[b,c,s], Thibaut Van Zele, MD, PhD[n], Paula Virkkula, MD, PhD[v], Martin Wagenmann, MD[u], and Claus Bachert, MD, PhD[n,bb] *Leuven, Ghent, Brussels, Belgium; Amsterdam, Groningen, The Netherlands; Barcelona, Catalonia, Spain; Copenhagen, Odense, Denmark; Créteil, Nancy, Lille, France; Rome, Italy; Lund, Stockholm, Sweden; Prague, Czech Republic; Vienna, Graz, Austria; London, United Kingdom; Dusseldorf, Germany; Helsinki, Finland; and Lorenskog, Norway*

BACKGROUND: Real-world evidence (RWE) is a valuable instrument to better understand the patient journey and effectiveness of therapies. RWE on the prevalence of uncontrolled chronic rhinosinusitis (CRS) and CRS natural course of disease across Europe is scarce. In addition, there is limited RWE that enables comparison of the effectiveness of marketed therapies including topical or systemic corticosteroids, sinus surgery, or biologics.

OBJECTIVE: To establish an international CHRonic rhINOSinusitis Outcome Registry (CHRINOSOR) based on real-world data collection enabled by mobile health technology.

METHODOLOGY: A digital platform, Galenus Health, supporting patients and physicians in the management of chronic respiratory diseases, is used to collect data on patient profile, disease history, patient outcomes, and a set of relevant clinical outcomes. Adult patients with a diagnosis of CRS are eligible for inclusion.

RESULTS: A collaborative scientific network of 17 university ear-nose-throat (ENT) clinics from 10 European countries has been established with the aim to collect real-world data in a longitudinal and standardized manner. The Galenus Health digital platform is currently being implemented in these ENT clinics taking into account legal, privacy, and data security aspects. Up to 300 patients have already been included.

CONCLUSIONS: CHRINOSOR is a collaborative effort that aims at improving our understanding of CRS, its comorbidities, and the effectiveness of its treatments. Ultimately, these insights will guide us as scientific community to develop future care pathways informed by RWE. **(J Allergy Clin Immunol Pract 2023;11:431-8)**

Key words: *Chronic rhinosinusitis; Nasal polyps; Biologic therapy; Real-world evidence; Mobile health technology*

[a]Research Department, Galenus Health, Belgium
[b]Allergy and Clinical Immunology Research Group, Department of Microbiology, Immunology and Transplantation, KU Leuven, Leuven, Belgium
[c]Department of Otorhinolaryngology-Head and Neck Surgery, University Hospitals Leuven, Leuven, Belgium
[d]Department of Otorhinolaryngology, Amsterdam University Medical Centres, Academic Medical Center, Amsterdam, the Netherlands
[e]Rhinology and Skull Base Surgery Unit, Otorhinolaryngology Department, Hospital Clinic, IDIBAPS, Ciberes, Barcelona, Spain
[f]Department of Otorhinolaryngology, Head and Neck Surgery and Audiology, Rigshospitalet, Copenhagen, Denmark
[g]Service d'ORL et de chirurgie cervico-faciale, Centre Hospitalier Intercommunal de Créteil, Créteil, France
[h]Department of Sense Organs, Sapienza University, Rome, Italy
[i]Department of Respiratory Medicine and Allergology, Institute for Clinical Science, Skane University Hospital, Lund University, Lund, Sweden
[j]Department of Respiratory Medicine, First Faculty of Medicine, Charles University and Thomayer Hospital, Prague, Czech Republic
[k]Department of Clin Pharm and Pharmacol, University Groningen, Univ Med Ctr Groningen, Groningen, the Netherlands
[l]Department of Otorhinolaryngology, Head and Neck Surgery, Vienna General Hospital (AKH), Medical University of Vienna, Vienna, Austria
[m]Department of Rhinology, Royal National Ear, Nose, Throat and Eastman Dental Hospital, UCLH, London, United Kingdom
[n]Upper Airways Research Laboratory, Department of Otorhinolaryngology, Ghent University, Ghent, Belgium
[o]Department of General ORL, Head and Neck Surgery, Medical University of Graz, Graz, Austria
[p]ENT Department, Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom
[q]Service d'Otorhinolaryngologie, Cliniques Universitaires Saint-Luc, Brussels, Belgium

Abbreviations used
CHRINOSOR- CHRonic rhINOSinusitis Outcome Registry
CRS- Chronic rhinosinusitis
CRSsNP- CRS without nasal polyps
CRSwNP- CRS with nasal polyps
ENT- Ear-nose-throat
ESS- Endoscopic sinus surgery
GDPR- General Data Protection Regulation
NPS- Nasal polyp score
RCT- Randomized controlled trials
RWE- Real-world evidence
SNOT-22- Sinonasal Outcome Test-22

Chronic rhinosinusitis (CRS) is a chronic inflammatory condition that affects 5% to 12% of the worldwide population according to epidemiological studies.[1-4] When diagnosis is made based on both symptoms and clinical evaluation via computed tomography scan or nasal endoscopy, prevalence estimates range from 1.2% to 6.8%.[5-8] Numbers on nasal polyp disease are scarce but were found to affect close to 2% of the population with differences in gender, age, and asthma status.[9-11] Central in CRS treatment are saline douching, intranasal corticosteroids, and sinus surgery.[4] A recent study in patients with CRS with nasal polyps (CRSwNP) showed that endoscopic sinus surgery (ESS) and appropriate medical treatment in combination are more effective compared with appropriate medical treatment alone.[12] Despite appropriate medical and surgical treatment of patients with CRS, 40% of patients remain uncontrolled based on a cross-sectional analysis in a tertiary referral setting regardless of their nasal polyp status.[13] Further characterization of patients with uncontrolled disease in the real-world setting globally is, therefore, needed to better understand the root causes and predictors of uncontrolled disease.

Limited information is currently available about the natural course of disease in patients with CRS and how medical or

[r]ENT Department, Hospital of Nancy, Brabois-ILM, University Lorraine, Nancy, France
[s]Laboratory of Experimental Otorhinolaryngology, Department of Neurosciences, KU Leuven, Leuven, Belgium
[t]Department of Otorhinolaryngology, Odense University Hospital, Odense, Denmark
[u]Department of Otorhinolaryngology, Universitätsklinikum Düsseldorf, Dusseldorf, Germany
[v]Department of Otorhinolaryngology-Head and Neck Surgery, Helsinki University Hospital and University of Helsinki, Helsinki, Finland
[w]Department of Oral and Maxillofacial Sciences, Sapienza University, Rome, Italy
[x]Otorhinolaryngology-Head and Neck Department, Huriez Hospital, Centre Hospitalier Universitaire (CHU) Lille, Lille, France
[y]Rhinology Unit and Smell Clinic, ENT Department, Hospital Clinic, IDIBAPS, CIBERES, Barcelona, Catalonia, Spain
[z]Department of Otorhinolaryngology, Akershus University Hospital, Lorenskog, Norway
[aa]Skin and Allergy Hospital, Helsinki University Hospital and University of Helsinki, Helsinki, Finland
[bb]Division of ENT Diseases, Department of Clinical Science, Intervention and Technology, Karolinska Institutet, Stockholm, Sweden

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Corresponding author: Sven F. Seys, PhD, Galenus Health, Thonissenlaan 21/B1, 3500 Hasselt, Belgium. E-mail: sven.seys@galenus.health.
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surgical therapies alter the course of disease.[14] Long-term revision rates of ESS in tertiary centers analyzing both patients with CRSwNP and those with CRS in general vary from 15% to 35% underlining the chronic nature of the disease.[15-18] The time from initial diagnosis to ESS has been shown to impact outcomes after ESS with reduced improvement in Sinonasal Outcome Test-22 (SNOT-22) scores in patients with CRS with delayed ESS.[19] Combining information on the patient journey with patient and clinical outcomes is needed to improve our understanding on the course of disease and eventually also improve patient outcomes.

Recently, biologics have been added as a treatment option for uncontrolled, severe CRSwNP.[20,21] These biologics are directed against the broader spectrum of type 2 (T2) inflammatory pathways involving IL-4, IL-5, IL-13, and IgE.[22] Phase III clinical trials showed efficacy in terms of reduction in nasal polyp score (NPS), quality of life, and symptom severity for dupilumab, omalizumab, and mepolizumab.[23-25] Benralizumab showed improved NPS and nasal blockage compared with placebo.[26] In the absence of head-to-head trials in CRSwNP, dupilumab has shown the largest numerical improvement on most of the outcomes, which was confirmed in 2 recent meta-analyses as well as an indirect treatment comparison study.[27-29] Such analyses however do not take into account differences in patient populations such as disease severity or the presence of comorbidities. Both omalizumab and dupilumab showed improvements in NPS, nasal congestion score, and SNOT-22, independent of blood eosinophil levels[30,31] and comorbid status (dupilumab only).[32,33] Analysis of patients treated with mepolizumab showed reduced NPS and nasal obstruction irrespective of the presence of comorbid asthma or nonsteroidal anti-inflammatory drug–exacerbated respiratory disease.[34] First real-life data have confirmed the beneficial effects of dupilumab for patients with CRSwNP.[35] Nevertheless, the range of clinical response to biologics is variable among patients. In-depth analysis of clinical parameters and biological markers will be required to better target the right biologics for the right patient. Again, in this respect, real-world data will be essential to increase our knowledge in this area.

Real-world evidence (RWE) has been recognized as a separate pillar supporting efficacy and safety data obtained during randomized controlled trials (RCT).[36] RWE and RCT are thereby complementary, and they each have their advantages and disadvantages. One of the major strengths of RWE lies in its high external validity ensuring generalizability toward the patient population seen in clinical practice.[37] On the contrary, data quality may be more difficult to ensure in an RWE setting as compared with RCT. Factors that hinder acquisition of high-quality real-world data relate to completeness of data, accuracy of data, and standardization of data input.

Given the recent developments in the treatment of CRS, including CRSwNP and CRS without nasal polyps (CRSsNP), a consortium of leading scientific experts and Galenus Health, who provide the digital technology and research support, partnered to establish an international CHRonic rhINOSinusitis Outcome Registry (CHRINOSOR). This registry combines patient-reported outcome measures and clinical variables collected from the medical health records of the patient. As such relevant data along the entire patient journey are captured. This provides a higher resolution of data for analysis. In addition, the comorbidity aspect has been addressed also allowing patients with asthma or hay fever to report their symptoms.

AIMS AND RESEARCH QUESTIONS

In CHRINOSOR we aim to collect and study real-world data on an international level to investigate the burden of uncontrolled disease in patients with CRS (including CRSwNP and CRSsNP), the impact on health-related quality of life and socioeconomic impact as well as the effect of disease severity and comorbid disease on these outcome parameters. Such analysis will include the identification of patient subgroups with different CRS phenotypes, CRS severity and control, the pattern of major symptoms, need for step-up treatment, evaluation of the number of revision surgeries, time to revision surgery in these subgroups, evaluation of the frequency and the burden of oral corticosteroid use, and evaluation of the impact of CRS on asthma patient outcomes.

Secondly, it is of considerable interest to identify the proportion of patients with CRSwNP eligible for type 2–directed biologic therapy to evaluate the effectiveness of these therapies and to identify markers of treatment response. Criteria for patient selection and evaluation of treatment response will be evaluated in the real-life setting.[4,20,21]

Lastly, several other research objectives have been identified for evaluation:

- To investigate direct and indirect costs of patients with CRS for society: health-economic analysis.
- To monitor whether patients with CRSwNP treated with biologics are protected from common cold episodes, symptom worsening during pollen season, or symptoms induced by perennial allergens.
- To evaluate the progression of symptoms and quality of life after initiation of pharmacotherapy or ESS.
- To evaluate factors influencing medication and app compliance, behavior of different subject groups, and data to support adherence.

Other investigators or stakeholders with an interest in CRS who would like to submit additional research questions are encouraged to get in contact with the corresponding author.

METHODOLOGY

A consortium of currently 17 tertiary referral centers across Europe has been established to recruit adult patients with a diagnosis of CRS (Figure 1). To reflect the real-life CRS population as much as possible, the number of exclusion criteria are limited. Thus patients with chronic inflammation associated with neoplasia and those with unilateral disease will be excluded.

Patients with CRS who consent to take part in the registry will be invited to use a CE-marked mobile application (app), called Galenus Health, for the management of their disease. The app has been translated in local language for the patients with validation by the local medical experts involved. An overview of the functional setup of the Galenus Health digital platform is outlined in Figure 2. In brief, patients use the app to track their sinonasal symptoms (and lung symptoms for comorbid asthma patients), medication use, and care pathway events via the health diary. A health profile is

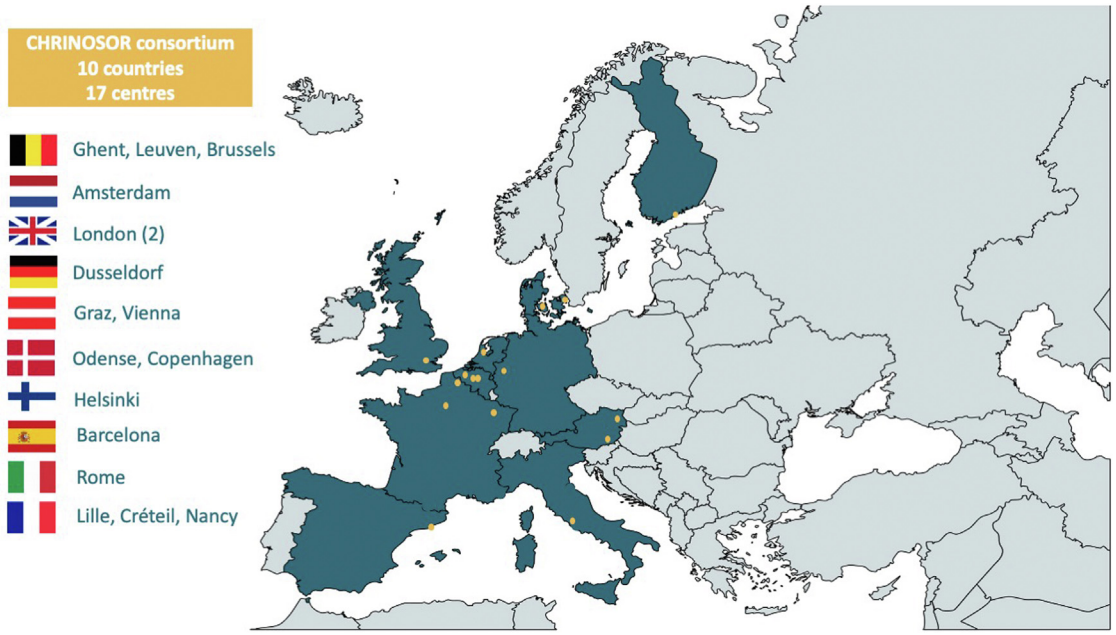

FIGURE 1. The European CHRINOSOR consortium. A consortium of 17 tertiary referral rhinology centers has been established from 12 European countries. *CHRINOSOR*, CHronic RhINOSinusitis Outcome Registry.

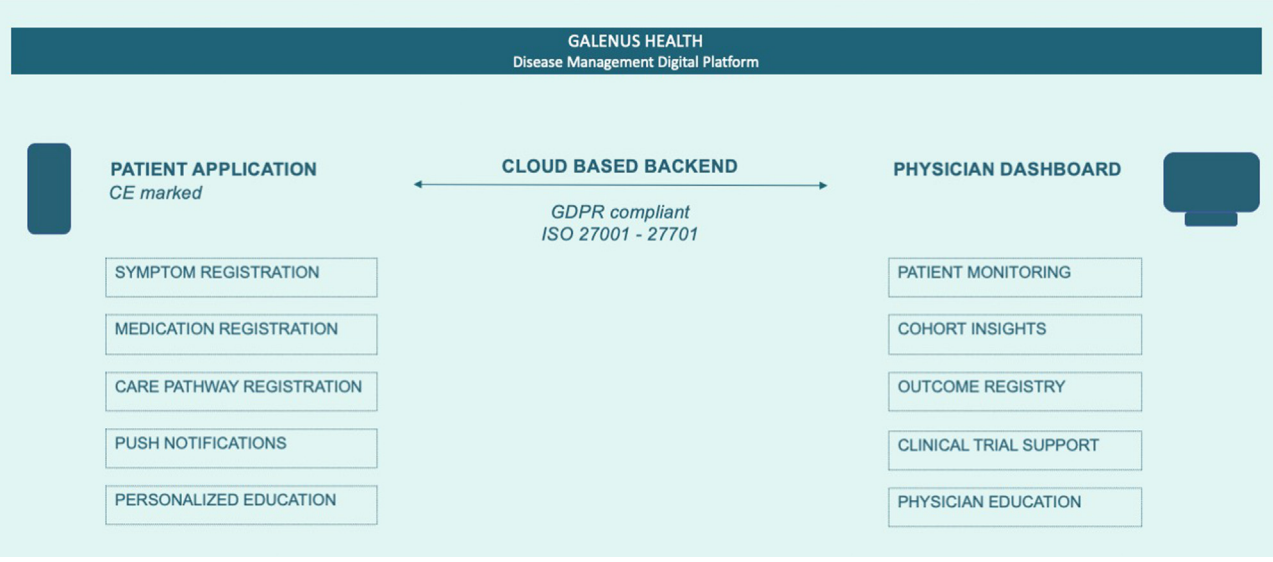

FIGURE 2. Functional setup of the Galenus Health digital platform. The digital platform consists of a CE-marked app for patients and a web-based dashboard for health care providers. The app will be used by patients to track their symptoms, medication use, and care pathway events. The online dashboard will be used by physicians in the context of this registry to validate disease diagnosis and to enter additional clinical outcome variables. Both are connected via a GDPR compliant and secured cloud-based backend based in Europe. *GDPR*, General Data Protection Regulation.

completed by the patient only once to obtain information on demographics, disease history, and comorbidities.

A standard set of outcome measures have been defined by the panel of medical experts (Figure 3). A majority of variables are being collected by the patients through the mobile patient app, whereas a selected set of relevant clinical variables are being added to the registry through the web-based dashboard for physicians. The complete list of questions in the health diary and health profile is

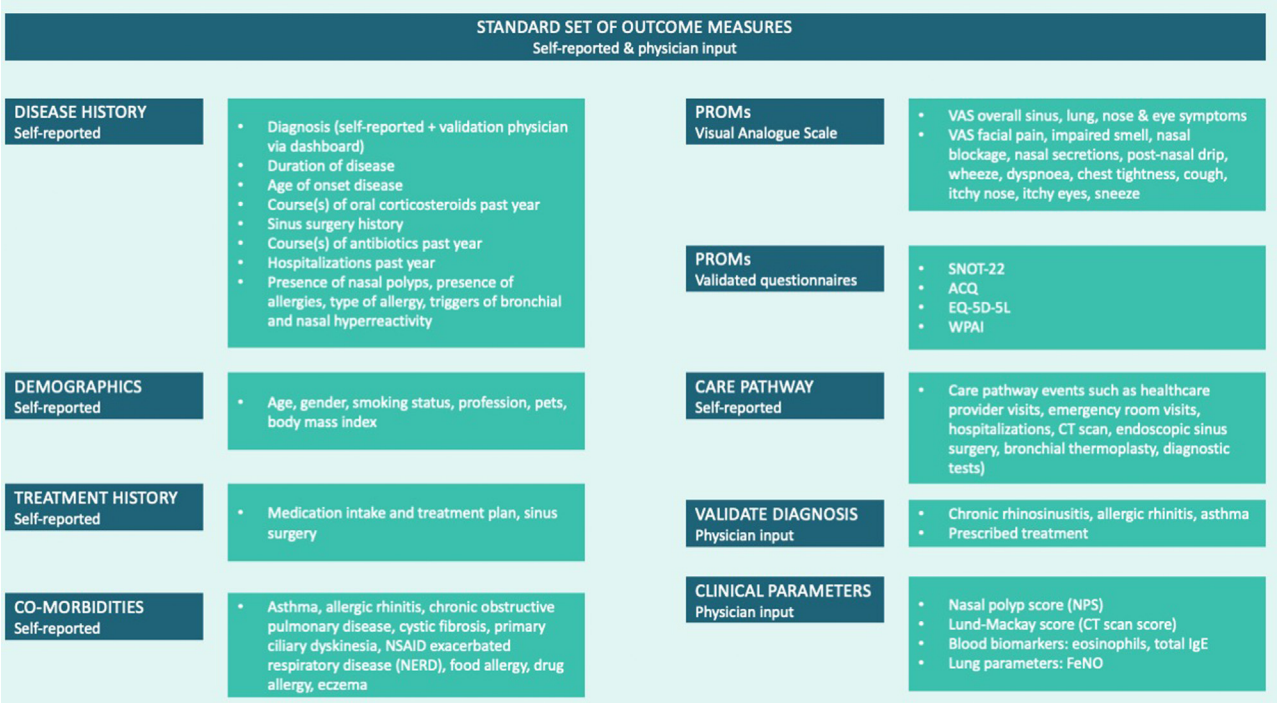

FIGURE 3. Standard set of outcome variables. A standard set of patient-related outcome variables and relevant clinical outcomes have been defined by the expert panel. *ACQ*, Asthma Control Questionnaire; *CT*, computed tomography; *EQ-5D-5L*, EuroQol 5-Dimension 5-Level; *NSAID*, nonsteroidal anti-inflammatory drug; *PROM*, patient-reported outcome measure; *SNOT-22*, Sinonasal Outcome Test-22; *VAS*, visual analog scale; *WPAI*, work performance and activity impairment.

available in Tables E1 and E2 of this article's Online Repository at www.jaci-inpractice.org, respectively. The study conduct is outlined in Figure 4. To maximize data completeness, notifications are sent to the patients via the app on a weekly basis to fill in the health diary and on a monthly basis to complete the validated questionnaires including SNOT-22,[38] Asthma Control Questionnaire-6,[39] Euro-Qol 5-Dimension 5-Level,[40] and Work Performance and Activity Impairment.[41]

GOVERNANCE

A steering committee has been established to oversee the overall research process of CHRINOSOR. The steering committee consists of the principal investigators of each of the centers and the research lead of Galenus Health. The steering committee defines and prioritizes the relevant research questions to be addressed, defines the approach for statistical analysis, interprets the results, and prepares the scientific publication.

LEGAL

Implementation of an mHealth-driven outcome registry is a challenging undertaking. Evidently, several legal requirements related to data management had to be fulfilled including identifying legal basis of data processing, data security, data privacy, and data access.

Ethics committee

CHRINOSOR is a prospective observational study for which ethics approval was obtained in each country at the local institutional review board(s). Given its prospective nature, in most countries, the study is classified as a clinical study, with exception to the Netherlands, Denmark, and the United Kingdom. No additional clinical or laboratory tests are being performed in the context of the study. The study has been registered at clinicaltrials.gov (NCT04670172).

Consent

Patients are prospectively enrolled in the registry upon written informed consent. In case a patient was using the app before, these data will also be included in the registry. Clinical variables collected from the patient's medical health records are included in the registry up to 5 years before inclusion in the registry and during participation in the registry. In countries where CHRINOSOR is not classified as a clinical study, research consent is managed through the app. In this context, an additional information document is provided to the patient in compliance with General Data Protection Regulation (GDPR).

Data privacy and security

Data are coded or pseudonymized in the CHRINOSOR research database with storage in Europe on GDPR compliant and ISO 27001-27701 secured backend and servers. Patients are also able to register in the app with anonymous credentials provided by the hospital department.

Data access

Investigators participating in CHRINOSOR get access to the pseudonymized research database of patients of their ENT clinic via the web-based dashboard. As such, they are in control of this

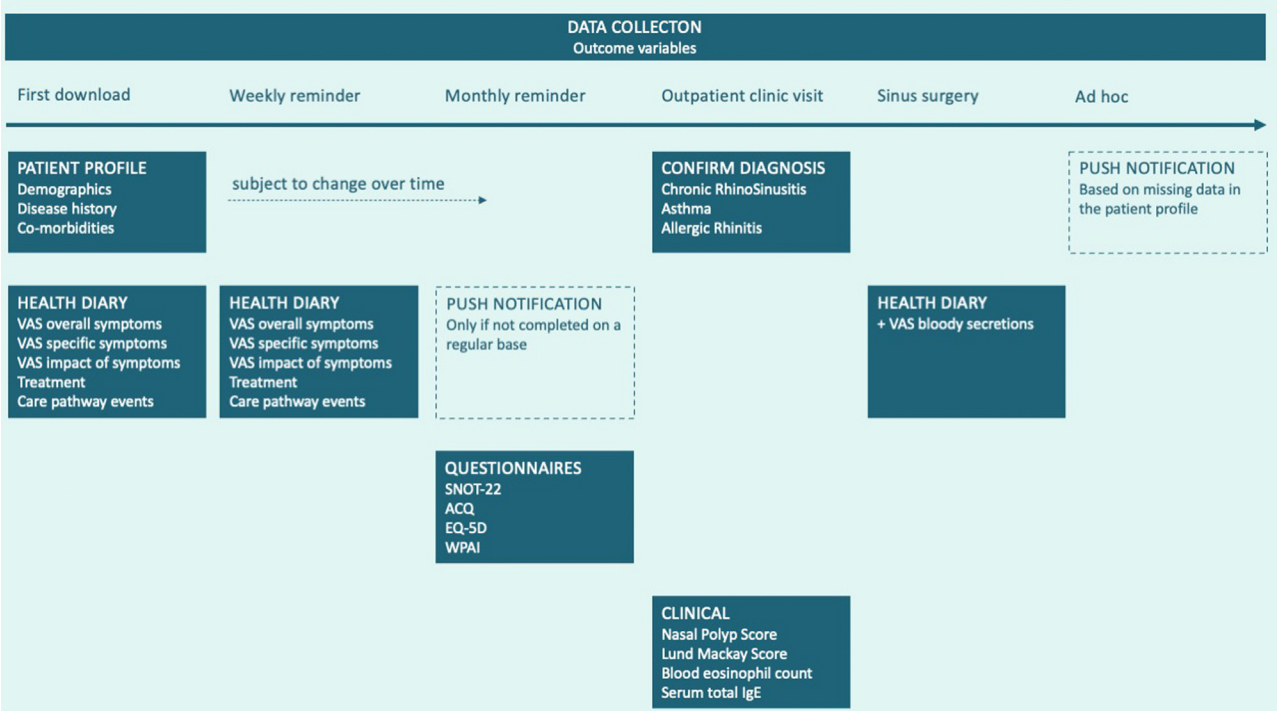

FIGURE 4. Study conduct. On first encounter with the app, the patient will select which symptoms are bothersome (sinus, lung, nose, and eye). On the basis of this selection, the patient will receive the relevant VAS questions in the health diary. After registration in the app, the patient completes the health diary and the health profile. The patient will receive a weekly notification to complete the health diary. The additional validated questionnaires, such as SNOT-22, EQ-5D-5L, WPAI, and ACQ, will be available for the patient to complete on a monthly base. At the time of the outpatient clinic visit with the health care provider, the physician will be asked to confirm the diagnosis of the patient as well as to enter a series of clinical parameters that are collected routinely for follow-up of the patient. No additional clinical or laboratory tests will be requested in the context of the outcome registry. *ACQ*, Asthma Control Questionnaire; *EQ-5D-5L*, EuroQol-5-Dimension-5-Level; *SNOT-22*, Sinonasal Outcome Test-22; *VAS*, visual analog scale; *WPAI*, work performance and activity impairment.

set of data for local scientific research purposes for which additional approval of their institutional review board is required.

STRENGTHS AND LIMITATIONS

It has been demonstrated in the past that digital health technology may be a valuable tool to collect real-life data of patients with chronic respiratory conditions such as CRS[42,43] or allergic rhinitis.[44,45] The biggest challenge of such technologies remains retention of patients over a prolonged period in time. Previous data of mySinusitisCoach demonstrated that patients with CRS use the app on a weekly basis over a period of several months.[43] These data also showed that patient retention in the app is linked with the disease control status of the patient. Recent unpublished data obtained in CHRINOSOR show that the type of therapy and associated follow-up period in the hospital also contribute to differences in patient retention.

Another challenge became obvious during the process of establishing the CHRINOSOR project. We realized that the interpretation and implementation of applicable regulations was not uniform across the participating centers in the different countries. This slowed down the process and led to a re-evaluation of the initially set targets. Also, during the initiation of the clinical study, we realized that the adoption of the mHealth technology in the clinical setting varies among the different countries, which is an interesting observation worthwhile to investigate further.

The major strength of CHRINOSOR lies in the ability to collect data on a large scale from many countries in a standardized manner. As such, the power to demonstrate the effectiveness of therapies increases. It also allows comparative analysis of any kind of parameter between countries. Moreover, data collected through the app will be of higher resolution compared with registries that are purely based on data from electronic health records. As compared with the mySinusitisCoach project, several improvements have been implemented, including the prospective study design, the validation of disease diagnosis in the hospital setting, the use of a real-time data viewer for the physician, and the addition of clinical variable collection through the online dashboard.

The limitations of the study are linked to potential confounders of the patient recruitment approach such as selection bias of patients recruited at tertiary centers or patient-related factors linked to the use of the app such as age, level of education, and willingness or ability to use an app.

LOOKING TO THE FUTURE

As of July 2022, up to 300 patients have been included. It is the ambition of the CHRINOSOR consortium to collect real-world data from thousands of patients with CRS in the upcoming years. In each country, up to 3 centers of excellence will be selected to take part in the registry. A stepwise geographical growth toward other European countries as well as overseas growth in North America, Asia-Pacific, and Middle Eastern countries is being evaluated.

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ONLINE REPOSITORY

TABLE E1. Health diary

CRS Patient	Asthma patient	Rhinitis patient
	Overall symptoms	
How much are your overall sinus symptoms bothering you today?	How much are your overall lung symptoms bothering you today?	How much are your overall nose and eye symptoms bothering you today?
	Disease specific symptoms	
How much is facial pain or pressure (in the forehead, head or eyes) bothering you today?	How much is shortness of breath bothering you today?	How much is nasal blockage bothering you today?
How much is decreased sense of smell bothering you today?	How much is chest tightness bothering you today?	How much is runny nose bothering you today?
How much is nasal blockage bothering you today?	How much is wheezing bothering you today?	How much are red or itchy eyes bothering you today?
How much is runny nose bothering you today?	How much is coughing bothering you today?	How much is itchy nose bothering you today?
How much are nasal secretions dripping into the throat bothering you today?		
	Impact symptoms	
How much are your airway symptoms affecting your daily activities today?		
How much did your airway symptoms affect your sleep quality last night?		
I went to school today? (Y/N); If yes: how much are your airway symptoms affecting your performance at school?		
I went to work today? (Y/N); If yes: how much are your airway symptoms affecting your performance at work?		
	Treatment	
I performed nasal douching with salt water today? (Y/N)		
I took medication to treat my airway disease today? (Y/N) Add medication		
	Care pathway events	
I visited a health care provider or hospital since my last entry? (Y/N) Add event		

CRS, Chronic rhinosinusitis.

TABLE E2. Health profile

Disease
Did a physician diagnose you with asthma? (Y/N); if yes: "my asthma" module
Did a physician diagnose you with allergic rhinitis or hay fever? (Y/N); if yes: "my rhinitis" module
Did a physician diagnose you with chronic sinusitis? (Y/N); if yes: "my chronic sinusitis" module
Do you suffer from any other chronic lung condition? (Y/N); if yes:
• Do you suffer from COPD or chronic bronchitis?
• Do you suffer from cystic fibrosis?
• Do you suffer from primary ciliary dyskinesia?
Did any physician diagnose you with hypersensitivity to NSAIDs (such as aspirin or ibuprofen)?
Personal information
Body length (in cm)
Body weight (in kg)
Profession
Do you have any pets? (Y/N); if yes:
• What kind of pets (free entry)
Smoking status
Did you ever smoke? (Y/N); if yes:
• Have you quit smoking? (Y/N)
• ; if yes:
• How many cigarettes a day did you smoke in the past?
• How many years did you smoke in the past?
• ; if no:
• How many cigarettes a day are you still smoking?
• For how many years have you been smoking?
Allergy
Did a physician diagnose you with any type of allergy? (Y/N); if yes:
• Respiratory allergy? (Y/N); if yes:
• House dust mite allergy
• Tree pollen allergy
• Grass pollen allergy
• Cat allergy
• Dog allergy
• Other allergies
• Food allergy?
• Drug allergy?
• Eczema?
My chronic sinusitis
When did you experience sinus symptoms for the first time?
Did you ear-nose-throat surgeon diagnose you with nasal polyps?
Did you have sinus surgery before? Y/N; if yes: add dates
How many times did you require a course of tablets with steroids (such as prednisone or Medrol) for chronic sinusitis during the past year?
How many times did you require a course of antibiotics for chronic sinusitis during the past year?
My asthma
When did you experience lung symptoms for the first time?
Do you suffer from lung symptoms all year long?
What provokes your lung symptoms? (allergy, change in T°, change in humidity, emotions or stress, cigarette smoke, strong smells, exercise)
How many times did you require a course of tablets with steroids (such as prednisone or Medrol) for asthma during the past year?
How many times did you require a course of antibiotics for asthma during the past year?
How many times were you hospitalized because of an asthma attack in the past year?
My rhinitis
When did you experience nose and/or eye symptoms for the first time?
Do you suffer from nose and/or eye symptoms all year long?
What provokes your nose and/or eye symptoms? (allergy, change in T°, change in humidity, emotions or stress, cigarette smoke, strong smells, exercise)

COPD, Chronic obstructive pulmonary disease; *NSAIDs*, nonsteroidal anti-inflammatory drugs.