Project Plan

Chronic Urticaria Registry (CURE)

An investigator-initiated, observational, multicenter disease registry, driven by the academic and scientific interests of its participants

List of abbreviations and definitions of terms

CSU – chronic spontaneous urticaria
CIndU – chronic inducible urticaria
CU – chronic urticaria (= CSU + CindU)
CURE – the chronic urticaria registry
eCRF - electronic case report form
FDA – food and drug administration
HRQoL – health-related quality of life
IQR – Interquartile range
ISC – international steering committee
LAR - legally authorized representative
SD - standard deviation
CTO – clinical trial office
UV – urticarial vasculitis

Synopsis

Title	A project to establish and run a disease registry for patients suffering from chronic urticaria and urticarial vasculitis
Acronym	CURE (Chronic Urticaria Registry)
Coordinating Societies	CURE is a project driven by the Urticaria Network UNEV gGmbH Schönhauser Allee 163 10435 Berlin, Germany
Countries of registry project	Argentina, Bulgaria, Brazil, Canada, China, Colombia, Croatia, Denmark, Ecuador, France, Germany, Greece, India, Iran, Ireland, Italy, Japan, Kazakhstan, Mexico, North Macedonia, Netherlands, Poland, Portugal, Russia, Saudi Arabia, Slovenia, South Africa, Spain, Thailand, Turkey, United Arab Emirates The extension to additional countries is part of the project.
International Steering Committee	Ana M Giménez-Arnau, Spain Clive Grattan, United Kingdom Daria Fomina, Russia Emek Kocatürk Göncü, Turkey / Germany Jonathan Peter, South Africa Karsten Weller, Germany Mojca Bizjak, Slovenia Pavel Kolkhir, Germany Riccardo Asero, Italy Simon Francis Thomsen, Denmark Former steering committee member: Marcus Maurer, Germany
Endorsing societies	Urticaria Task Forces of Global Allergy and Asthma European Network, European Academy of Dermatology and Venerology (EADV), and World Allergy Organization (WAO)
Registry coordinators	Karsten Weller Pavel Kolkhir Institute of Allergology

	Charité – Universitätsmedizin Berlin Hindenburgdamm 30, 12203 Berlin, Germany
Background	Epidemiology, duration, course, response to treatment and underlying causes of chronic urticaria and urticarial vasculitis are ill defined. A disease registry is an appropriate tool to assess these features.
Aim	The aim of this project is to establish and to run a global registry for all patients with chronic urticaria and urticarial vasculitis and to improve the data in the above mentioned areas and, therefore, to enhance the understanding of the diseases and their subtypes.
Focus of registry	Chronic spontaneous urticaria, chronic inducible urticaria, urticarial vasculitis
Inclusion and exclusion criteria	All patients with chronic spontaneous and inducible urticaria or both can be enrolled / recorded in the registry, if a written, dated and signed informed consent is available. Since 2024, also patients with urticarial vasculitis can be enrolled / recorded in the registry, if a written, dated and signed informed consent is available.
Registry Design	The chronic urticaria registry (CURE) is a prospective, international, multicenter, observational (non-interventional) disease registry to better characterize the epidemiology, duration, course, response to treatment and underlying causes of chronic urticaria and urticarial vasculitis. Data collected during normal routine patient visits and assessments of the management of chronic urticaria and urticarial vasculitis are requested by the CURE registry. Participating physicians are encouraged to enter comprehensive baseline data upon enrollment of the patient and to perform follow-up assessments and update the patient data in the registry on an ongoing basis (every 6 months). Patients will be followed in the registry for as long as the physician and patient deem appropriate. Participation in CURE and data submission is voluntary (at the discretion of the physician and the patient). The treating physicians determine independently upon all patient care and management. Management and care of patients are not affected by participation in CURE.
Core variables / Items / Areas of Focus	• Demographic data • Duration of disease • Course of the disease • Symptom pattern • Underlying causes • Triggering factors • Comorbidities • Diagnostic results (e.g. laboratory values and biopsy results) • Treatment • Treatment response

	• Disease activity • Disease control • Quality of life impairment • Direct health care costs • Absence from work/school
Mile stones	1) Establishment of an international steering commitee (ISC) including representatives from Italy, France, Spain, Germany and UK (initial CURE core countries) - completed 2) Definition of core variables - completed 3) Generation of data abstraction forms for basic and follow up entries - completed 4) Programming of the CURE eCRF and database - completed 5) Submission of proposals for regulatory approval of the coordinating center in Germany (Dept. of Dermatology and Allergy, now Institute of Allergology, Charité - Universitätsmedizin Berlin) and other participating centers – completed 2014 Enrollment of first patient and launch of CURE in Germany, Spain, France, Italy and UK – completed with exception of the UK 6) Recruitment of partners / supporters – constantly ongoing 7) Expansion to a global registry (Rest of Europe, USA, Canada, Brazil, India, China, Japan, etc.) – constantly ongoing 8) Re-Submission for regulatory approval of the coordinating center in Germany (Institute of Allergology, Charité - Universitätsmedizin Berlin) and other participating centers – constantly ongoing 9) Update of CURE variables – constantly ongoing 10) Digitization of data capture from patients and physicians – ongoing
Registry duration	The duration of the registry is determined by its purpose. Patients will be followed in the registry until the registry's objective has been fulfilled or the initiator, UNEV gGmbH, decides to close or terminate it.
Sample size	The registry has no predefined sample size.
Framework	1) Investigator-initiated registry coordinated by non for profit organization Urticaria Network (UNEV) 2) Academia-driven 3) Open for cooperation with stakeholders (industry, patient organizations, payers, health authorities)
Key features	• Web-based • Basic data (Physician module) – entered once • Follow up data (Physician module) – around every 6 months
Data entry	• Open to all urticaria and urticarial vasculitis treating physicians / centers

	• Open to all chronic urticaria and urticaria vasculitis patients
Statistical analyses	The statistical analyses of the registry data is performed in regular intervals. For qualitative parameters, descriptive statistics such as the population size and the percentage of available data for each class of the parameter is presented. Quantitative parameters are summarized by presenting, for example, the population, the mean, standard deviation (SD), median, IQR, minimum and maximum values. Statistics may be presented, if sample size permits, for cohorts of interest. Due to the observational nature of the registry, all analyses can be considered exploratory. The CURE data may also be analyzed together with data from other, comparable research projects, such as the Chronic Angioedema Registry (CARE).
Analysis Populations	All patients in CURE are intended to be included in the analyses. Patients with missing data will not be excluded from the patient analysis population but will be included to the extent that evaluable data are present. However, some patients with missing values might be excluded from specific analyses.
Funding	• Partnerships • Grants • Donations
Electronic Access Terms and Conditions	Fulfilment of regulatory standards.

Introduction

Chronic Urticaria

Chronic urticaria is one of the most common skin diseases. It is characterized by the recurrent appearance of short-lasting, itchy wheals, angioedema, or both for at least 6 weeks. Chronic urticaria is subdivided into chronic spontaneous urticaria (CSU) and chronic inducible urticarias (CIndUs), such as symptomatic dermographism, cold urticaria and cholinergic urticaria. Epidemiological studies were able to demonstrate a point prevalence of 0.5-1% for CSU. For the CIndUs a lifetime prevalence was shown to be up to 10% for the total population, when mild courses are considered.

Publications of the past years have demonstrated that many patients with chronic urticaria experience a major impairment of their health-related quality of life (HRQoL). In addition, it has been found

Urticarial vasculitis

Urticarial vasculitis (UV) is a rare form skin disorder characterized by recurrent, long-lasting, itchy wheals and angioedema, often accompanied by vasculitis of small vessels. This condition is distinct from chronic spontaneous urticaria (CSU) and chronic inducible urticarias (CIndUs).

Epidemiological studies on urticarial vasculitis are limited, but it is estimated to affect a small percentage of urticaria patients. Like chronic urticaria, many patients with urticarial vasculitis experience a significant impairment of their health-related quality of life (HRQoL). It has been observed that a considerable proportion of these patients suffer from the disease for many years, which can severely impact their quality of life and daily functioning

Despite the known burden of urticarial vasculitis and some retrospectively

that a considerable proportion of patients suffer for years from the disorder.
Despite the high frequency of chronic urticaria and the availability of some retrospectively assessed data on the course of the disease, the epidemiology, duration of disease, course of disease, underlying causes, treatment responses and medical expenses are still insufficiently investigated. A registry is an appropriate tool to assess these features in the real-life setting.
For this reason, this registry project was initiated in 2014 as the first medical registry for chronic urticaria, the Chronic Urticaria Registry (CURE).

assessed data on its course, the epidemiology, disease duration, disease course, underlying causes, treatment responses, and medical expenses are still insufficiently investigated. A registry is an appropriate tool to assess these features in a real-life setting.
For this reason, the first medical registry for chronic urticaria, the Chronic Urticaria Registry (CURE), has included urticarial vasculitis as an additional diagnosis in the registry in 2024.

Registry aim and areas of interest

The aim of this project is to establish and to run a global registry for all patients with chronic urticaria, i.e. CSU, CIndU and UV. The registry collects real life data with the objective to improve the knowledge on CU and UV, among others regarding its epidemiology (e. g. frequency, duration, course of disease), underlying causes, comorbidities, trigger factors, treatment and treatment response, costs and impact of disease as well as to globally improve the understanding of chronic urticaria and its subforms as well as UV. The results of the registry are intended to be published in scientific journals and should help to improve the medical care for affected and future patients.

Registry design and plan

1. Registry Design and procedure

CURE is an international, multicenter, observational (non-interventional) disease registry for all patients with CSU, CIndU and UV.

Participation in CURE is voluntary (at the discretion of the physician and the patient). Prerequisite for adding a patient to CURE is that the patient is informed thoroughly about the aims and nature of the registry with the patient information form and that a dated and signed written informed consent is available.

Is an informed consent available, baseline data of interest will be captured with the eCRF system secuTrial*, such as data on the onset and course of disease, suspected causes, trigger factors, family history, comorbidities, medication, diagnostic measures (and their results), treatments (including their efficacy and tolerability). After this baseline entry, follow up entries should be done every 6 months. The course of the patient's disease can be documented in and followed by the registry as long as the treating physician considers this as making sense and as long as the patients not disagree to this follow up.

Data collection is facilitated by standardized baseline and follow up paper or electronic (RedCap** – Research Electronic Data Capture) questionnaires for patients and treating physicians. REDCap is a secure, web-based application designed for data collection and

management in research. Patients may also be given the opportunity to document their disease activity daily via the Chronic Urticaria Self Evaluation App (CRUSE).

This registry study will not affect the management and treatment of the patients in any way. It is a pure observational (non-interventional) study. Accordingly, patients will not be treated differently with regard to the usual medical routine when participating in the CURE registry. Only the entry of patient data into the registry is different from the usual medical routine in these patients.

No personal data such as name, initials, date of birth, address, are recorded in CURE. The entered data are pseudonymized so that only the treating physician knows which patient belongs to which registry record. The treating physicians are asked to put a note in the original patient chart, documenting that the patient is in the registry.

Data submission is voluntary. Participating physicians are encouraged to enter comprehensive baseline data upon given informed consent by the patients and to perform follow-up entries (around every 6 months).

All relevant CURE data will be entered into the CURE eCRF*. The data captured in CURE may require adjustments/changes from time to time (e.g., if new diagnostic approaches or treatments become available). These adjustments/changes will be decided and approved by the ISC of CURE. For details on the ISC, please see the CURE ISC Charter.

The basis for the later data processing and analyses of the registry data will solely be the data available in the CURE data bank. Every entering physician/center has access to their own entered data. Data entered will be used for analytical purposes. There is no predefined sample size. Should a data check by the data management of CURE reveal that there is critical data missing or implausible or contradictory data present in individual data sets, the participating physicians/centers are asked to review and complete/correct the entered data.

CURE should gather data from chronic urticaria and urticarial vasculitis patients from treating physicians from all over the world. It is part of the CURE project to extend CURE globally.

The CURE data may also be analyzed scientifically together with data from other, comparable research projects, such as the Chronic Angioedema Registry (CARE), if the ISC of CURE approves this.

The CURE database was developed and is maintained by the Clinical Trial Office (CTO) of the Clinical Study Center of the Charité – Universitätsmedizin Berlin, Invalidenstr. 97 / Am Platz vor dem Neuen Tor 4, 10115 Berlin (former KKS (Koordinationszentrum für Klinische Studien) Charité). The CTO is responsible for the eCRF system, i. e. programming, hosting, login administration, data storage and data preparation for analyses).

*The name of the eCRF system is secuTrial, an FDA/GCP compliant software. The CURE eCRF is protected by a secure login. In the future, it is intended to replace secuTrial by REDCap.

**REDCap is widely used across the globe by academic, nonprofit, and government organizations to facilitate high-quality data collection for research and operational purposes.

2. Important Steps of the Establishment of CURE

In a first step, an ISC for CURE was convened. The main tasks of the ISC are to develop the specific topics and items/questions of the registry, to decide on specific data analyses of CURE data and to supervise the latter as well as to decide on adjustments/updates of the registry content.

In a second step, the actual web-based registry was programmed. To this end, a CURE medical data abstraction form was implemented in a well-established eCRF program (secuTrial) with audit trail, the backbone of CURE.

In a third step, the registry was first activated for the entering center at the Dept. of Dermatology and Allergy (now Institute of Allergology), Charité – Universitätsmedizin Berlin, after approval of the responsible ethics committee and the data protection officer was available. Since then, the number of participating centers and physicians is constantly expanded in Germany and world-wide.

In a fourth step, the registry enables a fully digital patient and physician data entry, i.e., patients and physicians may enter CURE relevant data into REDCap, which will be transferred to/joined with the secuTrial data bank. The aim is to enable a more time efficient data capture and a higher data quality and completeness. In the future, it is intended to migrate CURE to REDCap completely.

Registry Population

CURE is open to all urticaria-treating physicians/centers and all CSU, CIndU and UV patients. It is the intention to follow as many patients as possible in CURE. There is no predefined sample size as this is an observational registry. There is also no limit with regard to the age or gender of patients. No selection of patients is intended since it is the aim to collect unbiased data from the real-life clinical setting.

1. Inclusion and Exclusion Criteria

All patients with CSU, CIndU and UV can be enrolled/recorded in the registry, if a written, dated and signed informed consent is available.

The data for CURE should be collected from the real-life management situation in clinical practice (observational approach). As children and adolescents (minors) can also be affected by CSU, CIndU or UV, it makes sense to not exclude these patient groups from participation. Given that the patient concerned should not be of legal age or if there is a guardianship in place, an information of the patients concerned as well as of the parents or guardians will be performed. Before including patient data into the registry, a dated and signed written informed consent of the person concerned or the parent / guardian (i.e. the LAR) must be available.

Patients depending on the entering physician/center or the coordinating societies are not eligible for the registry.

2. Foreseeable risks and disadvantages linked to a registry participation

Study participation is not linked to any risk or disadvantage for the patients. The same applies to a refusal of participation.

3. Benefits for participants and future affected individuals

There is no direct benefit for patients taking part in CURE. For future affected individuals (group benefit) new insights into CSU, CIndU and UV, their course, causes, comorbidities, treatment response and impact can, however, be expected from the results of CURE. This will help to improve the understanding of the diseases and may also serve to improve the future care for affected individuals.

Conditions that lead to a withdrawal from / termination of CURE

A patient may withdraw from the registry at any time for any reason without prejudice to their future medical and clinical care by the treating physician.

Conditions that lead to a withdrawal from/termination of the registry are:

- withdrawal of the dated and signed written informed consent
- termination of the patients participation by the treating physician
- termination of the registry

In case a patient withdraws their informed consent, no further data on their case will be entered into the registry. In addition, the patient can object to further processing of their data and request deletion of their data.

Patient insurance

There is no patient insurance for this registry, because no interventions are linked to this registry.

Honorarium for patients

Patients will not receive any honorarium for taking part/being entered in this registry. Patient participation does not go along with any extra time or extra costs for the patient, the registry just documents what is performed during routine medical care.

Administrative Considerations

1. Participating Physicians / Centers

The participating physician/center should ensure that all persons assisting with CURE are adequately informed about the project and the project plan.

2. Institutional Review Board or Independent Ethics Committee Approval and Other Governing Regulatory Bodies

If IRB/IEC and/or other governing regulatory body's approval is required for CURE, the participating physician/center must obtain written and dated approval/favorable opinion from the IRB/IEC and/or other governing regulatory bodies, including approval of written patient information and informed consent forms, before entering patients in CURE. When required, status reports must be submitted to the IRB/IEC and/or other governing regulatory bodies.

It is the CURE physician's responsibility to communicate with their local IRB/IEC to ensure accurate and timely information is provided at all phases during the registry. In particular, the appropriate approvals must be in place prior to patient entry into CURE.

3. Ethical Conduct of the Registry

This registry will be compliant with relevant global and local regulations and best practices, such as the International Conference on Harmonization Good Clinical Practice (ICH GCP) guidelines (ICH E6).

4. Patient Information, Consent and Assent

It is the CURE physician's responsibility to provide each patient with full and adequate information regarding the objectives and procedures of CURE prior to including patients in the registry. Before enrolling in CURE, each patient, patient's parent(s), or patient's LAR must consent to participate after the nature, scope, and possible consequences of the registry have been explained in a form understandable to them. A patient information form that includes information about the registry will be given to the patient, patient's parent(s), or patient's LAR. After reading this patient information, the patient, patient's parent(s), or patient's LAR must give consent in writing on the informed consent form of CURE. The patient's consent must be confirmed at the time of consent by the personally dated signature of the patient, patient's parent(s) or patient's LAR. If the patient, patient's parent(s), or patient's LAR is unable to read, oral presentation and explanation of the written informed consent form and patient information form to be supplied to the patient must take place in the presence of an impartial witness. Consent must be confirmed at the time of consent orally and by the personally dated signature of the patient, or by a local legally recognized alternative (e.g., the patient's thumbprint or mark) or by the personally dated signature of the patient's parent(s) or the patient's LAR. The witness and the person conducting the informed consent and patient information discussions must also sign and personally date the informed consent document. A copy of the signed and dated consent document must be given to the patient, patient's parent(s), or patient's LAR. The original signed and dated consent document will be retained by the CURE physician.

5. Project Plan Adherence

The CURE physician/center must adhere to the CURE project plan as defined in this document. The physician is responsible for enrolling only those patients who have met the eligibility criteria.

6. Premature Closure of the Registry

If conditions arise during the course of the registry which indicate that CURE should be halted due to an unacceptable patient risk, CURE may be terminated after appropriate consultation between the coordinating societies and the participating physician(s)/center(s). Conditions that may warrant termination of the registry or site include, but are not limited to:

- Failure of the participating physician/center to comply with pertinent global regulations
- Submission of knowingly false information from the registry site to the registry
- the insufficient adherence by the participating physician/center to project requirements

7. Retention of Data

The participating physician/center must agree to retain all records, all original signed informed consent forms and any original source data relating to CURE for the relevant minimum of 10 years to comply with their local and international regulations.

8. Publication and Disclosure Policy

It is intended to publish CURE data results in peer-reviewed scientific journals. The data from CURE is intended to be analyzed in regular intervals, e.g. twice yearly. The ISC will discuss and decide on possible CURE publications (for details see CURE ISC Charter). The scientific neutrality of publications arising from CURE cannot be restricted in any way.

Funding of the registry

CURE is partially financed by UNEV gGmbH, Schönhauser Allee 163, 10435 Berlin, Germany, a non-profit organization and wholly-owned subsidiary of the Urticaria Network e. V., which holds all shares in UNEV gGmbH. The UNEV gGmbH is dedicated to promoting research on urticaria disorders and improving patient care.

CURE received a starting grant from the European Academy of Dermatology and Venereology (EADV), headquartered at Via S. Balestra 22B, CH-6900 Lugano, Switzerland.

CURE is or has been supported by Novartis, Sanofi-Aventis, Noucor (formerly known as Uriach) and MOXIE GmbH.

The acquisition of financial support from further sources is intended in order to cover the costs associated with CURE.