Project Plan

CURE: Chronic Urticaria Registry

CURE is an investigator-initiated, observational, multicenter, open-ended disease registry study, driven by the academic and scientific interests of its participants.

Project Title: CURE: Chronic Urticaria Registry

Project Plan Version and Date: Version 1.1, 21. JUL. 2016

Project Type: Disease Registry

Indication: Chronic Urticaria

Countries of registry project: Core countries: Germany, France, Italy, United Kingdom, Spain. The extension to additional countries is part of the project

Study Design: International, investigator-initiated, observational (non-interventional), multi-center, open-ended disease registry

Coordinating society: CURE is a project driven by the Urticaria Network e.V.

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SYNOPSIS

Title	A project to establish and run a disease registry for patients suffering from chronic urticaria
Acronym	**CURE (Chronic Urticaria Registry)**
Coordinating Societies	CURE is a project driven by the Urticaria Network e.V. Urticaria Network e.V. (UNEV) Charitéplatz 1 D-10117 Berlin, Germany Representative: Prof. Dr. Marcus Maurer
International Steering Committee	Marcus Maurer (Berlin, Germany) – Chair Ana Gimenez-Arnau (Barcelona, Spain) – Co-Chair National representatives of Italy (Riccardo Asero), France (Pascale Mathelier-Fusade), UK (Clive Grattan) Karsten Weller (Berlin, Germany) – Principal Coordinator
Endorsing societies	Urticaria Task Forces of Global Allergy and Asthma European Network (GA²LEN), European Academy of Allergy and Clinical Immunology (EAACI), European Academy of Dermatology and Venerology (EADV), and World Allergy Organization (WAO)
Registry coordinator	PD Dr. med. Karsten Weller Allergie-Centrum-Charité Department of Dermatology and Allergy Charité – Universitätsmedizin Berlin Charitéplatz 1, D-10117 Berlin
Background	Epidemiology, duration, course, response to treatment and underlying causes of chronic urticaria are ill defined. While a registry would be an appropriate tool to assess these features, this is, as of yet, not available.
Aim	The aim of this project is to establish and to run a global registry for all patients with chronic urticaria.
Focus of registry	Chronic spontaneous and inducible urticaria
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.
Registry Design	The chronic urticaria registry (CURE) is a prospective, international, multicenter, observational (non-interventional), open-ended disease registry to better characterize the epidemiology, duration, course, response to treatment and underlying causes of chronic urticaria. Data collected during normal routine patient visits and assessments for the management of chronic urticaria 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 (around every 6 months). Patients may also be given the opportunity to participate in reporting PRO data related to their chronic urticaria. 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). All patient care and management is determined by the treating physician. Management and care of patients are not affected by participation in CURE.
Core variables / Items / Areas of Focus	• Demographic data • Duration of the disease • Course of the disease • Frequency of angioedema • Underlying causes • Comorbidites • Triggering factors • 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 Committee (ISC) including representatives from Italy, France, Spain, Germany and UK (core countries) 2) Definition of core variables 3) Generation of data abstraction forms for basic and follow up entries 4) Recruitment of partners / supporters 5) Programming of the CURE eCRF and database 6) Submission of proposals for regulatory approval of the coordinating center in Germany (Dept. of Dermatology and Allergy, Charité - Universitätsmedizin Berlin) and other participating centers 7) Enrolment of first patient and launch of CURE in Germany, Spain, France, Italy and UK 8) Expansion to a global registry (Rest of Europe, USA, Canada, Brazil, India, China, Japan, etc.)
Registry duration	The duration of the registry is open-ended.
Sample size	The registry has no predefined sample size.
Framework	• Investigator-initiated registry coordinated by non for profit organization Urticaria Network e.V. (UNEV) • Academia-driven (GA²LEN, EAACI and EADV Task Forces for Chronic Urticaria) • Cooperation with stakeholders (industry, patient organizations, payers, health authorities)
Key features	• Web-based • Basic data (Physician module) – entered once (30 minutes) • Follow up data (Physician module) – intended every 6 months (15 minutes) • Patient module may be additionally developed during the project
Data entry	• Open to all urticaria-treating physicians / centers • Open to all chronic urticaria patients
Data analyses	The statistical analyses of the registry data will be 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 will be presented. Quantitative parameters will be summarized by presenting, for example, the population, the mean, standard deviation (SD), median, 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 will be considered exploratory.
Funding	• Partnerships • Grants • Donations

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

CSU – chronic spontaneous urticaria
CIndU – chronic inducible urticaria
CURE – the chronic urticaria registry
eCRF - electronic case report form
FDA – food and drug administration
HRQoL – health-related quality of life
ISC – international steering committee
LAR - legally authorized representative
SD - standard deviation

1 INTRODUCTION

Chronic urticaria is one of the most common skin diseases. It is characterized by the recurrent appearance of short-lasting, itching 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 that a considerable proportion of patients suffers 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. While a registry would be an appropriate tool to assess these features, this was, until recently, not available.

For this reason, this registry project was first initiated in 2014 as the first medical registry for chronic urticaria, the Chronic Urticaria Registry (CURE). CURE is an investigator-initiated, open-ended registry, driven by the academic and scientific interests of its participants. CURE is observational (non-interventional) and collects real life data on all types of chronic urticaria patients, suffering from CSU, CIndUs, or both.

The aim of this registry project is to improve the data for chronic urticaria in the areas mentioned above and, therefore, to improve the understanding of the disease and its subtypes.

2 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 and CIndU. The registry will collect real life data with the objective to improve the knowledge on chronic urticaria, among others regarding its epidemiology (e.g. frequency, duration, course of disease), underlying causes, comorbities, trigger factors, treatment response, costs and impact of disease as well as to globally improve the understanding of chronic urticaria and its subforms. The results of the registry will be published and should help to improve the medical care for future patients.

Core variables of this registry are:

- Demographic data
- Duration of the disease
- Course of the disease
- Frequency of angioedema
- Underlying causes
- Comorbidites
- Triggering factors
- Treatment response

- Disease activity
- Disease control
- Quality of life impairment
- Direct health care costs
- Absence from work/school

3 REGISTRY DESIGN AND PLAN

3.1 Registry Design and Procedures

CURE is an international, multicenter, observational (non-interventional), open-ended disease registry for all patients with chronic urticaria.

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, data on the patient's medical history will be documented during a basic registry entry performed by the participating physician(s)/center(s) in the CURE eCRF, such as onset of the chronic urticaria, comorbidities, medication, suspected causes, diagnostic measures (and their results), treatments (including their efficacy and tolerability). After this basic entry, follow up entries will be done participating physician(s)/center(s) around every 6 months, recording additional data on the disease, among others on the course and on additional diagnostic and therapeutic procedures. Patients may also be given the opportunity to participate in reporting PRO data related to their chronic urticaria later during the project course. 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.

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 the registry. The entered data will be pseudonymized so that only the entering physician knows which actual patient belongs to which registry record. The recording 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 enrollment of the patient and to perform follow-up assessments and update the patient data in the registry on an ongoing basis (around every 6 months).

All relevant CURE data will be abstracted from the patient charts and entered into the CURE eCRF. The name of the eCRF system is secuTrial, a FDA/GCP compliant software. The CURE

eCRF is protected by a secure login. The data abstracted from the patient record may be adjusted/changed over time (in case these changes are decided and approved by the International Steering Committee (ISC) of CURE). For details on the ISC, please see 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 eCRF. Every entering physician/center has access to his own entered data. Data entered will be used for analytical purposes. There is no predefined sample size.

CURE should gather data from chronic urticaria patients from all over Germany, Spain, France, Italy and the UK (core countries). However, it is part of the CURE project to also extend CURE to additional countries, including North America and Asia.

3.2 Important Steps of the Establishment of CURE

In a first step, an International Steering Committee (ISC) for CURE was convened. The main tasks of the ISC are to develop the specific 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. For details on the ISC and its role in CURE see CURE ISC Charter.

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 with audit trail, the backbone of the CURE.

In a third step, the registry was first activated for the entering center at the Dept. of Dermatology and Allergy, Charité – Universitätsmedizin Berlin, after approval of the responsible ethics committee and the data protection officer was available.

Ongoing steps consists of the involvement and activation of additional entering centers and entering physicians into CURE. Moreover, a patient module may be set up in the future in order to obtain direct input from the affected patients, mainly based on already well-established patient reported outcome (PRO) tools.

3.3 Registry Framework

CURE is an investigator-initiated registry coordinated by non for profit organization Urticaria Network e.V. (UNEV) and the Department of Dermatology and Allergy, Charité – Universitätsmedizin Berlin. It is academia-driven (supported by GA²LEN, EAACI and EADV Task Forces for Chronic Urticaria) and cooperates with stakeholders (industry, patient organizations, payers, health authorities).

3.4 Registry Duration

The duration of the registry is open-ended. Patients will be followed in the registry for as long as the physician or patient deems appropriate.

4 REGISTRY POPULATION

CURE is open to all urticaria-treating physicians/centers and all chronic urticaria patients. It is the intention to follow as many chronic urticaria 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.

4.1 Inclusion and Exclusion Criteria

All patients with chronic spontaneous urticarira, chronic inducible urticaria, or both 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 chronic urticaria, 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 legal authorized representative - LAR) must be available.

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

4.2 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.

4.3 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 chronic urticaria, its 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 disease and may also serve to improve the future care for chronic urticaria affected individuals.

5 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

6 DATA ENTRY AND PROCESSING

All data relevant to the registry, will be entered pseudonymized into the registry (no personal data such as name, initials, date of birth, address are recorded in the registry), stored in the registry data bank, electronically processed, and later analyzed. Since all data in will be pseudonymized, it will not be possible to identify patients solely by the registry data. Only the

treating physician and his employees will be able to link the individual patient to its pseudonymized registry data, but these are not allowed to transfer this confidential information to anyone. The recording physicians are asked to put a note in the original patient chart, documenting that the patient is in the registry.

Data entry and submission is voluntary. Participating physicians are, however, 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 (around every 6 months).

All relevant CURE data will be abstracted from the patient charts and entered into the CURE eCRF. The data abstracted from the patient record may be adjusted/changed over time (in case these changes are decided and approved by the ISC of CURE). The basis for the later data processing and analyses of the registry data will solely be the data available in the CURE eCRF. Every entering physician/center has access to his own entered data. Data entered will be used for analytical purposes. There is no predefined sample size. The CURE database was developed and is maintained by the KKS Charité (Koordinationszentrum für Klinische Studien der Charité (KKS Charité), Charité - Universitätsmedizin Berlin, Augustenburger Platz 1, 13353 Berlin, Germany). The KKS Charité as well as the coordinating societies designees are responsible for registry data management activities.

In case a patient withdrew his informed consent, no further data on his case will be entered into the registry. In addition, the patient can disagree to a further processing of his data and require a deletion of his/her data.

7 PATIENT INSURANCE

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

8 HONORARIUM FOR PATIENTS

Patients will not receive any honorarium for taking part 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.

9 QUALITY CONTROL AND ASSURANCE

All relevant CURE data will be abstracted from the patient charts and entered into the CURE eCRF which can be accessed via the internet, allowing for remote data entry at hospital/physician centers. The name of the eCRF system is secuTrial, a FDA/GCP compliant software containing an audit trial. The CURE eCRF is protected by a secure login. The data abstracted from the patient record may be adjusted/changed over time (in case these changes are decided and approved by the International Steering Committee of CURE). Responsible for the eCRF system (programming, hosting, login administration, data storage, data preparation for analyses) is the

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The CURE database was developed and is maintained by the KKS Charité (Koordinationszentrum für Klinische Studien der Charité (KKS Charité), Charité - Universitätsmedizin Berlin, Augustenburger Platz 1, 13353 Berlin, Germany). The KKS Charité as well as the coordinating societies designees are responsible for registry data management activities. Queries will be periodically raised by the data managers. Data entries as well as changes made to data will be tracked by the audit trail of the eCRF system.

Patient confidentiality will be protected. No personalized data, such as name, initials, date of birth, address are recorded in the registry. All data relevant to the registry, will be entered pseudonymized. For more details see also section 6.

10 PLANNED STATISTICAL METHODS

10.1 General Considerations

It is neither intended to have a time limit of the registry, nor a limit regarding the number of enrolled persons.

10.2 Statistical Analyses

Statistical analyses of the registry data will be 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 will be presented. Quantitative parameters will be summarized by presenting, for example, the population, the mean, standard deviation (SD), median, 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 will be considered exploratory.

10.3 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.

11 ADMINISTRATIVE CONSIDERATIONS

11.1 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.

11.2 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.

11.3 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 Harmonisation Good Clinical Practice (ICH GCP) guidelines (ICH E6).

11.4 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 the inclusion of patients in the registry. Before enrolling into 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 him/her. 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.

11.5 Patient Confidentiality

No personal data such as name, initials, date of birth, address, are recorded in the registry. The entered data will be pseudonymized. Since all data in CURE are pseudonymized, it is not possible to identify patients solely by the registry data. Only the treating physician and his employees are able to link the individual patient to its pseudonymized registry data, but these are not allowed to transfer this confidential information to anyone.

11.6 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.

11.7 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

11.8 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 years to comply with their local and international regulations.

11.9 Public Posting of Registry Information

The present registry is posted on the www.clinicaltrials.gov website.

11.10 Publication and Disclosure Policy

It is intended to publish CURE data results in peer-reviewed scientific journals. The data from CURE is planned to be analyzed twice yearly. The International Steering Committee (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.

12 FUNDING OF THE REGISTRY

CURE is partially financed by: the Urticaria Network e.V. (UNEV), Charitéplatz 1, 10117 Berlin, Germany, a non-profit organization aiming to promote research on urticaria (hives), and to improve patient care as well as by the European Academy of Dermatology and Venereology

(EADV), via S. Balestra 22B, CH-6900 Lugano, Switzerland. The acquisition of funding from various other sources is planned. This includes companies and other stakeholders. Current

In addition, the registry is non-financially supported by the urticaria task forces of the European Academy of Allergy and Clinical Immunology (EAACI), the World Allergy Organization (WAO) and the Global Allergy and Asthma European Network (GA²LEN).