**Collaboration Agreement**

Project

**Chronic Angioedema Registry (CARE)**

between

Urticaria Network e.V.

Schönhauser Allee 163

10435 Berlin

Germany

hereinafter „UNEV“

and

XXX (Institution/doctor’s office including full address)

hereinafter „medical institution“

UNEV and the Medical Institution are also individually each referred to as the "Party" and collectively also as the "Parties".

**Preamble**

UNEV is a non-profit organization. UNEV aims to support research in the field of urticaria and angioedema and to improve the care for affected patients. To achieve this purpose, UNEV develops and operates, among other things, the Chronic Angioedema Registry (hereinafter „CARE“). This is an international, academic, peer-governed, prospective, open-ended registry for recurrent angioedema.

The Institute of Allergology at Charité – Universitätsmedizin Berlin is specialized on the management of patients with recurrent angioedema.

UNEV and the medical institution aim to collaborate with respect to the operation of the Registry in accordance with the following regulations.

The following agreements are made on cooperation:

**1. Subject of Agreement (CARE)**

1.1 As part of the operation of CARE UNEV collects, analyses and reports quality real world data on all types and forms of recurrent angioedema.

1.2 The medical institution takes part in the CARE project and will perform the required documentation in CARE in accordance with the CARE project plan enclosed as **ANNEX 1**. ANNEX 1 is an integral part of this agreement. This applies as well to amendments to the project plan and, where applicable, more recent versions of the project plan.

1.3 The parties acknowledge that the CARE project is non interventional and observational. No recommendations will be given to the participating medical institutions regarding the management (e.g. regarding the diagnostic procedures and treatment strategies) of patients. The collaboration partners agree that the CARE project does not fulfill the criteria of a clinical trial in the sense of the Pharmaceutical Products Act.

# 2. Conduct of the research; project managers

2.1 The project CARE shall be conducted in strict compliance with all applicable national regulations, Good Pharmacoepidemiology Practice, and all other applicable laws, directives, guidances and professional standards, as well as the terms and conditions of the project plan (Annex 1).

2.2 The medical institution shall, before the project commences, obtain all necessary approvals, e.g. approval by the responsible review board (Ethics Committee) and competent authority for commencement of the project if applicable. Any necessary registrations/approvals are to be made/obtained in good time and be proven to UNEV before the start of the project.

2.3 The medical institution may not start entering data until the responsible review board (Ethics Committee) and competent authority have issued a favourable opinion and have given approval of the project, if applicable.

# 2.4 The medical institution represent that they have the requisite and necessary experience, equipment, facilities and personnel to properly take part in the CARE project. Upon request by UNEV, the medical institution shall provide documentation to support this.

2.5 The medical institution shall appoint a project manager and an investigator.

The project manager is a representative of the medical institution, who is responsible for the orderly performance of the work pursuant to the subject of this agreement.

The investigator is a representative of the medical institution, who is responsible for gathering information from the patients from the medical institution and for data entries in the electronic data capture system.

In some medical institutions, one person may perform the role of the project manager and investigator.

The person appointed as project manager by the medical institution is:

Project manager: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

In the event that the project manager should leave during the term of this agreement or should be relieved of their duties as project manager, an team member equally qualified to conduct the project may be appointed as their successor after UNEV has been notified. If this is not possible or if UNEV has good reasons for not agreeing to the appointed successor, the agreement may be terminated early for good cause.

2.6 The parties shall be in contact at regular intervals to report on the progress of the project and to clarify any issues that have arisen.

**3. Enrolment of Patients**

3.1 For the purposes of this agreement, a patient shall be deemed enrolled in the project if said patient meets all selection and registration criteria set forth in the project plan (ANNEX 1) and the informed consent form and the patient or, when the person is not able to give informed consent, their legal representative has given written consent after being informed of the nature, significance, implications and risks of the project.

3.2 The decision of whether a patient is enrolled in the project is solely made by the medical institution.

**4. Informed Consent**

4.1 The medical institution shall, in accordance with the project plan and the informed consent form, duly provide opportunity for the patient or, when the person is not able to give informed consent, their legal representative, in a prior interview, to understand the objectives, risks and inconveniences of the project, and the conditions under which it is to be conducted as well as information of their right to withdraw from the project at any time.

4.2 The medial institution shall, in accordance with the project plan (ANNEX 1) and the informed consent form, obtain written informed patient consent, or, when the person is not able to give informed consent, that of their legal representative, after being informed of the nature, significance, implications and risks of the project. The consent must meet the requirements of the General Data Protection Regulation (GDPR).

**5. Reporting and Documentation**

5.1 The medical institution agrees to duly complete and submit all requested data via the electronic data capture system, and in compliance with the Electronic Access Terms and Conditions.

5.2 The medical institution shall produce the documentation in a manner that makes it pertinent and useable for the project. In case of any ambiguity in respect to the manner of documentation, the medical institution shall immediately notify UNEV to clarify the issue. The medical institution acknowledges that the documentation as defined supra may be updated and amended from time to time by UNEV.

5.3 The medical institution shall correct incorrect data via the electronic data capture system as soon as the medical institution becomes aware of incorrect data. All corrections will be documented by the “audit trail” of the electronic data capture system.

5.4 The medical institution shall notify UNEV when a patient quits the project. The medical institution shall include in this notification the exact time of termination. In this case, UNEV shall immediately delete the patient data concerned.

5.5 The medical institution will take care that the source records are maintained and stored in a secure manner (in accordance with all applicable laws and regulations).

5.6 UNEV will take care that the project data entered in the electronic data capture system is maintained and stored in a secure manner (in accordance with all applicable laws and regulations).

5.7 UNEV shall ensure that the processing of results and data is consistent with provisions of data protection laws.

5.8 The medical institution hereby agrees to the processing of the investigator’s personal data provided to electronic data capture system by the investigator or obtained from other participating CARE centers. The Investigator has the right to have access to and correct his/her personal data.

5.9 The Investigator has the right to have access to and correct his/her entered data.

5.10 Adverse events and/or laboratory abnormalities identified in the entered data are not followed up by UNEV. The medical institution is in charge to take care of reporting these events in accordance with all applicable laws and regulations, if applicable.

# 6. Data access and use, Work results

# 6.1 The medical institution has unrestricted right to access and to use its own entered data.

# 6.2 All materials, documents and information supplied by UNEV to the medical institution shall be the sole and exclusive property of UNEV.

# 6.3 UNEV owns the CURE dataset and has the right to access, use and publish the entered data. Entered data can only be deleted with the approval of UNEV.

6.4 Work results are all results created during the execution of the work according to this contract, in particular know-how, inventions, industrial property rights, works protected by copyright as well as documentation, reports and documents, also insofar as they are executed by third parties on behalf of a party. The UNEV is exclusively entitled to the work results generated within the framework of the project.

**7. Compensation**

Participation in CARE is free of charge to the medical institution. No financial compensation is paid by UNEV to the medical institution for taking part in the CARE project and for entering patient data into the electronic data capture system.

**8. Analyses and Publication**

# 8.1 Analyses of the CARE dataset can be suggested by all medical institutions who complete the minimum number of required full patient data sets (basic and follow up data) in the electronic data capture system. This number is currently thirty, as defined in the CARE Charter and Statutes, and is subject to annual review by the CARE International Steering Committee.

8.2 Notwithstanding the remaining provisions of this agreement, the medical institution shall have the right to publish, present or otherwise publicly disclose the results of analyses of their data and disseminate information pertaining to institution’s activities conducted under this agreement, including own project data, for own, non-commercial purposes in research and teaching. However, the medical institution shall declare that he/she is a contract partner of UNEV whenever he/she writes or speaks in public about a matter that is the subject of this agreement or any other issue relating to UNEV.

8.3 Disclosure as set forth above may not impair or compromise UNEV’s rights as regards patentable or copyrightable material or confidentiality obligations of the medical institution. UNEV shall have the right to require the medical institution, as applicable, to remove specifically identified confidential information (other than research results) and/or to delay the proposed publication, presentation or other public disclosure for an additional sixty (60) days to enable UNEV to seek patent protection.

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## 8.4 The medical institution agrees that it shall not, without UNEV’s prior written consent, independently publish, publicly disclose, present or discuss any results of or information pertaining to medical institutions and project managers activities conducted under this agreement until such a publication is released.

8.5 In particular the medical institution agrees to submit any proposed CARE publication, presentation or other public disclosure to UNEV for review at least sixty (60) days prior to submitting such proposed publications, presentations or other public disclosures to a publisher or other third party.

**9. Confidentiality**

9.1 The medical institution agrees to hold in confidence all materials, documents and information that UNEV discloses pursuant to this agreement, and all materials, documents and information gathered or developed pursuant to this agreement ("confidential information"). The medical institution will use such confidential information only for the purpose of fulfilling their obligations and exercising their rights hereunder and will not - without the prior written consent of UNEV - disclose it to any third party except for staff and consultants as required by law and with UNEVs knowledge, and the medical institution’s agents and employees who have a need to know such information to perform the project. The medical institution shall ensure in an appropriate manner that the employees, freelancers and subcontractors called in by them in the performance of this contract also observe the aforementioned confidentiality. The obligations of confidentiality hereunder shall survive and continue beyond the termination of this agreement.

9.2 No party hereto will use any other party's name in advertising, promotions, or other commercial materials without that party's prior express written permission, except that UNEV may quote from and/or reference any publications resulting from the project. The medical institution will not originate any publicity, news release or other public announcement, written or verbal, whether to the public, press or otherwise, relating to this agreement, the protocol, the project conducted hereunder, or to any amendment(s) hereto, without the prior express written consent of UNEV, except as required by law.

**10. Liability**

10.1 UNEV shall be liable exclusively for intent and gross negligence. In the event of gross negligence, liability for indirect damage and consequential damage is excluded.

10.2 If a claim is made against UNEV by a third party due to the inaccuracy of the data entered into the CURE by the medical institution, the medical institution is obliged to indemnify UNEV against liability.

**11. Term and Termination**

11.1 This Agreement shall be effective as of the date it is duly signed by the parties and shall continue in effect until completion of all obligations herein or unless earlier terminated pursuant to this section.

11.2 Both parties may terminate this agreement upon thirty days written notice to the end of a month.

11.3 Extraordinary termination is only possible for good cause. Good cause shall be deemed to exist in particular an investigator becomes unable or unwilling to perform his obligations under this agreement. Possible reasons for an extraordinary termination: data fraud, falsification or falsification of data, termination of the investigator's employment within the medical institution without a capable replacement.

**12. Obligations of Personnel**

Where the medical institution employs personnel or any other person to perform obligations under this agreement, they will submit these persons to the terms of this agreement. The medical institution shall in particular ensure that these obligations remain in full force and effect.

**13. Miscellaneous**

13.1 This agreement constitutes the entire agreement between the parties hereto, pertaining to the subject matter hereof and supersedes all prior and contemporaneous agreements, except those contemplated hereunder or not inconsistent herewith.

13.2 This agreement is personal in nature and the medical institution shall not, without the prior express written consent of UNEV, assign or transfer this agreement or any rights or obligations hereunder. UNEV may assign or transfer this agreement to a successor or affiliated organization, provided that in the case of any such assignment, the assignee shall be bound by the terms and obligations provided in this agreement.

13.3 This agreement shall be governed by the law of Germany without regard to conflict of laws principles.

13.4 Any dispute arising from this agreement between the medical institution and UNEV shall be exclusively referred to the jurisdiction of Berlin, Germany.

13.5 The medical institution shall immediately notify UNEV if any obstacle, legal or in fact, arises, or if they become aware of such obstacle, that may affect the conduct of the project at the site. In such a case, the parties will consult with each other and amicably find a way to complete the project, or terminate this agreement.

13.6 This agreement is executed in two copies of which each party, i.e. UNEV and the medical institution, receives one.

# 14. Severability

In the event that individual provisions of this agreement are ineffective, this shall not affect the validity of the remaining provisions. Any such invalid provision shall be replaced by a provision which best reflects what the parties hereto intended or would have intended if they had been aware of the invalidity of the provision. The same shall hold for any omissions in the agreement.

**Urticaria network e.V.**

|  |
| --- |
|  |
| Date |
|  |
| Signature |
| PD. Dr. Frank Siebenhaar, Treasurer |
| Title, Name, Position |

**Medical Institution**

|  |
| --- |
|  |
| Date |
|  |
| Signature |
|  |
| Title, Name, position |

ANNEX 1 – CARE Project Plan

**Project Plan/Protocol**

CARE: Chronic Angioedema Registry

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

**Project Title:** CARE: Chronic Angioedema Registry

**Project Plan Version and Date:** Version 1.0, 02. APR. 2023

**Project Type:** Disease Registry

**Indication:** Chronic Recurrent Angioedema

**Countries of registry project:** All countries with GA2LEN Angioedema Centers of Reference and Excellence (ACAREs). The extension to additional countries is part of the project.

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

**Coordinating societies:** CARE is a project driven by the GA2LEN network of Angioedema Centers of Reference and Excellence (ACAREs) and the Urticaria Network e.V. (UNEV).

UNEV Office
urticaria network e.V.
Schönhauser Allee 163
10435 Berlin, Germany

ACARE Office
c/o DGAKI
Robert-Koch-Platz 7
10115 Berlin, Germany

**SYNOPSIS**

|  |  |
| --- | --- |
| Title  | A project to establish and run a disease registry for patients with chronic recurrent angioedema  |
| Acronym  | **CARE (Chronic Angioedema Registry)**  |
| Coordinating Societies   | CARE is a project driven by the GA2LEN network of Angioedema Centers of Reference and Excellence (ACAREs) and the Urticaria Network e.V.  UNEV Officeurticaria network e.V.Schönhauser Allee 16310435 Berlin, Germany ACARE Officec/o DGAKIRobert-Koch-Platz 710115 Berlin, Germany |
| International Steering Committee  | Aharon Kessel, Haifa, Israel Andrea Zanichelli, Milan, Italy Anete Grumach, Sao Paulo, Brazil Ankur Jindal Chandigarh, India Anthony Castaldo Asli Gelincik, Istanbul, Turkey Clemens Schöffel, AustriaConnie Katelaris, Westmead, AustraliaDanny Cohn, Amsterdam, NetherlandsDaria Fomina, Moscow, RussiaEmel Aygören-Pürsün, Frankfurt, GermanyHenriette Farkas, Budapest, HungaryHenrik Balle Boysen, Horsens, DenmarkHilary Longhurst, Auckland, New ZealandInmaculada Martinez-Saguer, Mörfelden, Germany Karsten Weller, Berlin, GermanyLaurence Bouillet, Grenoble, FranceMarc Riedl, San Diego, USA Marcus Maurer, Berlin, Germany Markus Magerl, Berlin, Germany Mauro Cancian, Padova, ItalyMichihiro Hide, Hiroshima, JapanMoshe Ben-Shoshan, Montreal, CanadaNoemi Bara, Sangeorgiu de Mures, RomaniaPetra Staubach, Mainz, Germany Roman Hakl, Brno, Czech RepublicStefan Cimbollek, Sevilla, Spain Stephen Betschel, Toronto, Canada Tamar Kinanciyan, Vienna, Austria Teresa Caballero, Madrid, Spain Thomas Buttgereit, Berlin, Germany Timothy Craig, Hershey, USAVesna Grivcheva-Panovska, North Macedonia Yu-Xiang Zhi, China |
| CARE Management Team  | Dr. Thomas Buttgereit - Chief Scientific Coordinator PD Dr. med. Karsten Weller - Principal Investigator Annika Gutsche - Chief Statistician Dr. Pavel Kolkhir - CURE liaison officer PD Dr. Frank Siebenhaar - UNEV liaison officer Prof. Dr. Markus Magerl - ACARE liaison officer  Prof. Dr. Marcus Maurer - HAEi liaison officer   |
| Endorsing societies   | TBD |
| Registry coordinator   | Dr. Thomas Buttgereit  Institute of Allergology Charité – Universitätsmedizin Berlin Hindenburgdamm 30, 12203 Berlin  |
| Background  | Epidemiology, duration, comorbidities, impact, course, response to treatment and underlying causes of chronic recurrent angioedema 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 recurrent angioedema.  |
| Focus of registry  | Chronic recurrent angioedema  |
| Inclusion and exclusion  criteria  | All patients with chronic angioedema, ie recurrent angioedema episodes for longer than 6 weeks, can be enrolled/ recorded in the registry, if a written, dated and signed informed consent is available.   |
| Registry Design   | The chronic angioedema registry (CARE) 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 recurrent angioedema.  Data collected during normal routine patient visits and assessments for the management of chronic angioedema are included and analysed in CARE. Participating physicians/sites 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 may also be given the opportunity to participate in reporting PROM data related to their chronic angioedema. Patients will be followed in the registry for as long as the physician and patient deem appropriate.  Participation in CARE 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 CARE.   |
| Core variables / Items / Areas of Focus  | * Demographic data
* Duration of disease
* Course of the disease
* Frequency of angioedema
* Underlying causes
* Comorbidities
* 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 a CARE International Steering Committee (CARE ISC) – ongoing
2. Establishment of a CARE Management Team (CARE MT) and CARE office – ongoing
3. Definition of core variables - ongoing
4. Generation of data reporting forms for baseline and follow up entries  - ongoing
5. Recruitment of partners / supporters - ongoing
6. Programming of the CARE eCRF and database - ongoing
7. Submission for regulatory approval of the coordinating center in Germany (Institute of Allergology, Charité - Universitätsmedizin Berlin) and other participating centers - ongoing
8. Enrolment of first patient and launch of CARE – Q3/4 2023
9. Expansion to a global registry – Q1 2024
10. First publication Q2 2024
 |
| 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) and GA²LEN e.V.
* Academia-driven – ACAREs and other physicians/sites who treat patients with recurrent angioedema
* Endorsed by national and international scientific and medical societies
* Cooperation with stakeholders (industry, patient organizations, payers, health authorities)
 |
| Key features  | * Web-based
* Baseline data (Physician module) – entered once (30 minutes)
* Follow up data (Physician module) – every 6 months (20 minutes)
 |
| Data entry  | * Open to all angioedema-treating physicians / centers
* Open to all chronic angioedema 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.  |
| Electronic Access Terms and Conditions | Fulfilment of regulatory standards* Compliance with 21 CRF Part11, FDA guidelines on electronic records and electronic signatures
* GCP, Good Clinical Practice
* EU GMP Annex 11: Computerised Systems
* Standard requirements for GCP-compliant data management in multinational clinical trial, ECRIN (European Clinical Research Infrastuctures Network)
* German Medicinal Products Act
* GAMP5, Supplier Guide for Validation of Automated Systems in Pharmaceutical Manufacture

Data privacy in secuTrial®* Personal data or data that can identify a patient is not stored on the server. Patients are identified via a pseudonym.
* Only the treating physician is able to re-identify a patient via a data printout.
* Users can only see data that has been collected in their centre, as ensured by a system of differentiated roles and rights.
* The data is encrypted before it is transmitted to the server.
* secuTrial® complies with FDA 21 CFR Part 11 and GDPR.
* secuTrial® fulfils all the necessary requirements for use in clinical trials (Phase II/III) and can be easily validated as a productive system in the respective clinical setting.

This software also supports differing levels of security based on the user credential, as assigned by the study clinical data manager in concert with the study information technology lead. In addition, cloud-security software backs the software. |

**LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS**

AE – angioedema

AE-BK – bradykinin-mediated angioedema

AE-MC – mast cell-mediated angioedema

CSU – chronic spontaneous urticaria

CIndU – chronic inducible urticaria

CARE – the chronic angioedema registry

CURE – the chronic urticaria registry

eCRF – electronic case report form

FDA – food and drug administration

HAE – hereditary angioedema

HRQoL – health-related quality of life

ISC – international steering committee

LAR – legally authorized representative

PROM – patient reported outcome measure

SD – standard deviation

**1 INTRODUCTION**

Angioedema (AE) is the localized deep dermal, subcutaneous or submucosal edema of tissues resulting from the increase in vascular permeability and extravasation of intravascular fluids. Patients with chronic AE experience recurrent swellings for longer than 6 weeks. Chronic AE is classified into different types, which include mast cell-mediated angioedema (AE-MC) and bradykinin-mediated angioedema (AE-BK) and chronic AE of unknown origin. AE can be a sign of anaphylaxis, can be with wheals, or without wheals. AE-MC may occur through an allergic mechanism, specifically a type I hypersensitivity leading to mast cell activation and release of mediators such as histamine and leukotrienes. Chronic AE-MC, with and without wheals, may occur in chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CINDU; except symptomatic dermographism). Chronic forms of AE-MC can also be caused by nonallergic non-IgE-mediated mast cell activation (due to some medications such as NSAIDs etc. and infections, or unidentified causes) or may be immunoglobulin E–mediated, as part of an allergic response. AE-BK occurs due to increased production of bradykinin due to a lack of regulation or overproduction of bradykinin or inhibition of bradykinin degradation. AE-BK subtypes include hereditary angioedema (HAE) and angioedema due to acquired C1 inhibitor deficiency. HAE includes HAE with C1-INH deficiency (type 1 HAE, HAE-1, 85% of HAE cases, HAE with low antigenic and functional C1-INH levels) and HAE due to C1-INH dysfunction (Type 2 HAE, HAE-2, 10% of HAE cases, characterized by normal or elevated antigenic but low functional C1-INH levels), HAE with mutation in the F12 gene (HAE-FXII), HAE with mutation in the angiopoietin-1 gene (HAE-ANGPTI), HAE with mutation in the plasminogen gene (HAE-PLG) and HAE with other or unknown genetic mutations (HAE-UNK).

AE-BK is less common and often more severe than AE-MC. Response to antihistamine or corticosteroid therapy is indicative of a mast-cell mediated process, although not all AE-BK respond to antihistamines, while AE-BK does not respond to antihistamines or corticosteroids nor epinephrine and can be life-threatening. Recommended treatments of AE-BK include C1-INH concentrates, the bradykinin B2-receptor antagonist, icatibant, and kallikrein inhibitors. Knowledge on the discriminating features of these two diseases is critical for the proper management. To assess the disease activity, disease control and, health related quality of life, several patient-reported outcome measures (PROMs) including Angioedema Control Test (AECT), Angioedema Activity Score (AAS), Hereditary Angioedema Activity Score (HAE-AS), Angioedema Quality of Life Questionnaire (AE-QoL) and Hereditary Angioedema Quality of Life Questionnaire (HAE-QoL) have been developed. AAS, AECT and AE-QoL can be used for both AE-MC and AE-BK, and these PROMs have been translated to many languages and used in many clinical studies.

Publications of the past years have demonstrated that many patients with chronic angioedema experience a major impairment of their health-related quality of life (HRQoL). In addition, a considerable proportion of patients experience chronic AE for years or life-long, in HAE.

Despite the high frequency of chronic angioedema and the availability of some retrospectively assessed data on the course of the disease, the epidemiology, comorbidities, 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 2023 as the first medical registry for chronic angioedema, the Chronic Angioedema Registry (CARE). CARE is an investigator-initiated, open-ended registry, driven by the academic and scientific interests of its participants. CARE is observational (non-interventional) and collects real life data on all types of chronic angioedema.

The aim of this registry project is to improve the knowledge of chronic angioedema by collecting and analysing data for chronic angioedema in the areas mentioned above and, therefore, to improve the understanding of the disease and its types and 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 angioedema, i.e. patients with AE-MC, AE-BK, and other types. The registry will collect real life data with the objective to improve the knowledge on chronic angioedema, among others regarding its epidemiology (e.g. frequency, duration, course of disease), underlying causes, comorbidities, trigger factors, treatment response, costs and impact of disease as well as to globally improve the understanding of chronic angioedema and its types and subtypes. The results of the registry will be published and should help to improve the medical care for patients.

Core variables of this registry are:

* Demographic data
* Duration of disease
* Course of the disease
* Frequency of angioedema
* Underlying causes
* Comorbidities
* 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**

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

Participation in CARE is voluntary (at the discretion of the physician and the patient). Prerequisite for adding a patient to CARE 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 provided.

Following informed consent, patient data on the medical history are documented during a baseline registry entry performed by the participating physician(s)/site(s) in the CARE eCRF, such as onset of the chronic angioedema, comorbidities, medication, suspected causes, diagnostic measures (and their results), treatments (including their efficacy and tolerability). After this baseline entry, follow up entries will be done by participating physician(s)/sites(s) 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 PROM data related to their chronic angioedema later during the project course, for example by using an app. 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 participating patients in any way. It is a purely observational (non-interventional) study. Accordingly, patients will not be treated differently with regard to the usual medical routine when participating in the CARE 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 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 included 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 (every 6 months).

All relevant CARE data will be obtained from the patient charts or visits and entered into the CARE eCRF. The name of the eCRF system is secuTrial, a FDA/GCP compliant software. The CARE 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 CARE. Details on the CARE ISC, its structure and responsibilities are detailed in the CARE ISC Charter and Statutes, which are available from the CARE office and website. The basis for the later data processing and analyses of the registry data will solely be the data available in the CARE eCRF. Every entering physician/site has access to their own entered data. Data entered will be used for analytical purposes. There is no predefined sample size.

CARE aims to gather data from chronic angioedema patients from treating physicians from all over the world. It is part of the CARE project to extend CARE globally.

**3.2 Important Steps of the Establishment of CARE**

As a first step, an International Steering Committee (ISC) for CARE and a CARE MT and office are implemented. The main tasks of the ISC are to develop the specific questions of the registry, to decide on specific data analyses of CARE data and to supervise the latter as well as to decide on adjustments/updates of the registry content. Details on the CARE ISC, its structure and responsibilities, as well as details on the CARE MT and office are detailed in the CARE ISC Charter and Statutes, which are available from the CARE office and website.

As a second step, the actual web-based registry is programmed. To this end, a CARE medical data documentation form was developed and implemented in a well-established eCRF program with audit trail (secuTrial), the backbone of CARE.

As a third step, CARE is first activated and pilot tested at the Institute of Allergology, Charité – Universitätsmedizin Berlin, after approval by the responsible ethics committee and data protection officer.

The next steps consist of the involvement of additional entering physicians and sites (global roll out), data analyses and the development of the first publication. A patient module may be set up in the future to obtain direct input from the affected patients, mainly based on already well-established PROMs.

**3.3 Registry Framework**

CARE is an investigator-initiated registry coordinated and operated by non-for-profit organizations, i.e. the Urticaria Network e.V. (UNEV) and the Global Allergy and Asthma European Network (GA²LEN). CARE is open for cooperations with all stakeholders (e.g. medical and scientific societies, industry partners, 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**

CARE is open to all angioedema-treating physicians/sites and all chronic angioedema patients. It is the intention of CARE to obtain data from as many chronic angioedema patients as possible. 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 angioedema, i.e. recurrent swelling attacks for longer than 6 weeks, can be enrolled/recorded in the registry, if a written, dated and signed informed consent is available.

The data for CARE are collected from the real-life management situation in clinical practice (observational approach). As children and adolescents (minors) can also be affected by chronic angioedema, it makes sense to not exclude these patient groups from participation. Before including patient data into the registry, a dated and signed written informed consent by the patient or the parent / legal guardian (i.e. the legal authorized representative - LAR) must be available.

**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 CARE. For future affected individuals (group benefit) new insights into chronic angioedema, its course, causes, comorbidities, treatment response and impact can be expected from the results of CARE. This will help to improve the understanding of the disease and may also serve to improve the future care for patients with chronic angioedema.

**5 CONDITIONS THAT LEAD TO A WITHDRAWAL FROM / TERMINATION OF CARE**

A patient may withdraw from the registry at any time for any reason without implications for 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 patient participation by the treating physician
* termination of the registry

**6 DATA ENTRY AND PROCESSING**

All CARE data are pseudonymized, i.e. 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. As a result, it is not possible to identify patients solely by their registry data. Only the treating physician is able to link individual patients to their pseudonymized registry data, and this information is confidential. 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 (every 6 months).

All relevant CARE data are obtained from the patient charts and/or visits and entered into the CARE 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 CARE). The basis for the later data processing and analyses of the registry data will solely be the data available in the CARE eCRF. Every entering physician/site has access to their own entered data. Data entered will be used for analytical purposes. There is no predefined sample size. The CARE database was developed and is maintained by the Urticaria Network e.V.  .

In case a patient withdraws informed consent, no further data are entered into the registry. In addition, the patient can disagree to further processing of their data and request the deletion of their 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 information obtained during routine medical care.

**9 QUALITY CONTROL AND ASSURANCE**

CARE data are entered into the CARE eCRF, which can be accessed via the internet, allowing for remote data entry. The name of the eCRF system is secuTrial, a FDA/GCP compliant software containing an audit trial. The CARE 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 CARE). Responsible for the eCRF system (programming, hosting, login administration, data storage, data preparation for analyses) is the

Urticaria Network e.V.

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The CARE database was developed and is maintained by the Urticaria Network e.V.  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 are 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 patients.

* 1. **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, or interquartile ranges. 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.

* 1. **Analysis Populations**

All patients entered in CARE 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 may be excluded from specific analyses.

**11 ADMINISTRATIVE CONSIDERATIONS**

**11.1 Participating Physicians / Sites**

Participating physicians/sites should ensure that all persons assisting with CARE 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 regulatory approval is required for CARE, the participating physician/site must obtain written and dated approval/favorable opinion, including approval of written patient information and informed consent forms, before entering patients in CARE. If required, status reports must be submitted to the IRB/IEC and/or other governing regulatory bodies.

It is the responsibility of CARE physicians/sites to communicate with their local IRB/IEC to ensure that 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 CARE.

**11.3 Ethical Conduct of the Registry**

This registry is 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 CARE physician’s responsibility to provide each patient with full and adequate information regarding the objectives and procedures of CARE prior to the inclusion of patients in the registry. Before enrolling into CARE, 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 by use of the informed consent form of CARE. 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 is retained by the CARE 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 CARE are pseudonymized, it is not possible to identify patients solely by the registry data. Only the treating physician can link individual patients to their pseudonymized registry data, and this information is confidential.

**11.6 Project Plan Adherence**

The CARE physician/site must adhere to the CARE 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 CARE should be halted due to an unacceptable patient risk, CARE may be terminated after appropriate consultation between the coordinating societies and the participating physician(s)/site(s). Conditions that may warrant termination of the registry or site include, but are not limited to:

* Failure of the participating physician/site to comply with pertinent global regulations
* Submission of knowingly false information to the registry
* Insufficient adherence by the participating physician/site to project requirements

**11.8 Retention of Data**

The participating physician/site must agree to retain all records, all original signed informed consent forms and any original source data relating to CARE for the relevant minimum of 10 years and 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 CARE data results in peer-reviewed scientific journals. The data from CARE is intended to be analyzed twice yearly. The CARE ISC and the CARE MT will discuss and decide on possible CARE publications (for details see CARE Charter and Statutes). The scientific neutrality of publications arising from CARE cannot be restricted in any way.

**12 FUNDING OF THE REGISTRY**

CARE is partially financed by the Urticaria Network e.V. (UNEV) as well as GA2LEN e.V. and its network of Angioedema Centers of Reference and Excellence (ACARE). The acquisition of funding from various other sources is planned. This includes companies and other stakeholders.