**Participation Agreement**

Project

**Chronic Angioedema Registry (CARE)**

between

UNEV gGmbH

Schönhauser Allee 163

10435 Berlin

Germany

hereinafter „UNEV“

and

Name and address of participating center

Hereinafter „participating centre”

UNEV and the participating centre are also individually each referred to as the "Party" and collectively also as the "Parties".

1. **Definitions**

UNEV: 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 chronic (recurrent) angioedema.

CARE: The Chronic Angioedema Registry (CARE) is a disease registry research project for recurrent angioedema of all presentations/aetiologies. CARE applies modern methodologies and parameters from recent scientific knowledge, and therefore, will equip physicians with information to enhance patient care and guide future therapeutic decisions.

Representative: A physician who treats patients with angioedema and allied disorders (Health Care Professional, “HCP”) and who represents a participating centre.

participating centre: A treatment centre, admitted to the CARE Registry by the CARE Management Team, where the Representative works and where he or she treats patients with chronic angioedema and allied disorders.

Data: Coded (pseudonymized) information of data, according to the UNEV/CARE Protocol, in the CARE Registry on patients with chronic angioedema collected by the participating centre s or in the course of a CARE project.

CARE projects: A project, approved by the CARE Management Team after advice from the International Steering Committee, based on data from the CARE Registry.

The Management Team of CARE: The management Team of CARE which has the power of management of and represents UNEV/CARE.

Controller, Processing, Personal data, Personal data breach, Pseudonymization and Anonymization have the meaning ascribed to them in the GDPR.

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

1.2.1. As part of the operation of CARE UNEV collects, analyses and reports quality real world data on all types and forms of recurrent angioedema. Participating centre agrees to collect data on all eligible patients in accordance with the CARE project plan enclosed as ANNEX 1. Also participating centre will perform the required documentation in CARE. 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 centers regarding the management (e.g. regarding the diagnostic procedures and treatment strategies) of patients. The collaboration partners agree that the CARE project does not fulfil the criteria of a clinical trial in the sense of the Pharmaceutical Products Act.

# 2. Conduct of the research; project managers

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

# 2.2 The participating centre represent that they have the requisite and necessary experience, equipment, facilities and personnel to properly take part in the CARE Registry.

2.3 The participating centre shall appoint a project manager.

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

The person appointed as project manager by the participating centre is:

please enter name of the project manager at participating center

2.4 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. Main Terms and conditions

Herewith parties agree to the following terms and conditions:

3.1 Data will be collected, stored, and used in accordance with the Protocol, applicable data safety and data protection laws including but not limited to the General Data Protection Regulation (GDPR) and local implementation legislation, and any research ethics board (“REB”) instructions if applicable.

3.2 Each Party will process personal data in accordance with the GDPR and any other applicable laws or regulations covering the protection of personal data.

3.3 The Parties are (separate) Controllers within the meaning of Article 4 Nr. 7 GDPR. UNEV is the Controller responsible for the processing (including the transfer) of the Data provided by the participating centre in accordance with the Protocol and the terms of this Agreement. CARE aims to improve the knowledge on recurrent angioedema, by CARE data analyses, interpretation, reporting and publication. Reports containing descriptive information as well as the results of analyses of CARE patient data will be provided for information to CARE ISC members, participating centres and eligible partners at regular intervals. In addition to these regular descriptive data summaries, specific analyses of scientific or clinical interest are conducted and published in an aggregated format. The participating centre remains the Controller with responsibility for all Personal data processed and contained in medical records at the participating centre. The participating centre is the Controller responsible for the processing of Personal data that it processes in accordance with this Agreement and the Protocol for the purpose of providing the Data and including it in the CARE Registry.

3.4 The legal basis for the participation to the CARE Registry and the associated processing of Personal data is the consent of patients (or their legal representatives in accordance with applicable laws). The participating centre will obtain the written informed consent of patients (or their representatives) before providing the Data and inform the patients and their representatives. UNEV shall provide the participating centre with all necessary information that is required by GDPR (especially Article 13 GDPR) so that the patients and their representatives can be fully and transparently informed about the intended use of their Personal data.

3.5 In order to protect the identity of the patients the participating centre shall act as the contact point for patients and will answer requests of patients (or their representatives) to exercise their rights pursuant to Articles 15 to 22 GDPR. UNEV shall assist the participating centre in responding to those requests, in particular, by providing the Centre with the necessary information without undue delay. UNEV shall forward any requests it receives to the participating centre without undue delay.

3.6 Each Party shall implement appropriate measures to ensure appropriate level of security in accordance with Article 32 GDPR in their respective area of responsibility. In particular, UNEV is responsible for ensuring the security of the CARE Registry. UNEV shall enter into appropriate data protection agreements with processors and other entities that are involved in the data processing in the context of the CARE Registry and the CARE projects in order to ensure an appropriate level of data protection.

3.7 In the event of a personal data breach involving the Data, the Parties shall inform each other immediately and support each other in order to fulfil the GDPR requirements within the legal timeframe. The Parties name the following contacts for data protection issues.

For the participating centre: please enter

For UNEV and CARE: datenschutzbeauftragte@urtikaria.net

3.8 The Parties agree to participate in quality control of Data according to the CARE project plan and CARE Charter.

3.9 The Data which are entered in the CARE Registry by the Representative is (pseudonymized) Personal data of patients of the participating centre and no use will be made of them other than for the purpose stated in the Protocol. UNEV shall use appropriate safeguards to prevent any unauthorized use or disclosure of Data and shall report to participating centre, without undue delay, any unauthorized use or disclosure of Data of which it becomes aware as arranged for in the Protocol.

3.10 Use of the Data is limited to representatives, participating centre and UNEV. The Data will be used for scientific research and/or regulatory purposes only. Proposals for specific analyses of CARE data and publications are processed by the CARE office and put forward for consideration by the CARE Management Team. The Management Team may seek advice from the CARE International Steering Committee. In general, data collected in CARE shall be processed in a pseudonymized form exclusively within UNEV.

3.11 The Parties shall acknowledge, in accordance with academic standards, each other’s contribution to the Data in any research publication arising from the CARE Registry.

3.12 Results and data are owned by the Party that generates them. A Party will decide alone on the protection measures to be taken for its own results and initiate them in its own name and its own expense.

3.13 Results generated by the collaborative work of two or more Parties within a CARE project and which cannot be reasonably separated, shall be jointly owned by the Parties involved, according to their intellectual contribution. Such Parties shall negotiate in good faith the sharing of the Results.

3.14 To the extent necessary for the implementation of the project, the contractual Parties shall grant each other non-exclusive, non-transferable, royalty-free rights of use to the results and data, including inventions, for the duration and purposes of the CARE Registry.

Each Party is and shall remain the owner of its intellectual property (protected and unprotected) existing at the time of the conclusion of this Agreement.

3.15 This contract overrules and supersedes all previous contracts between participating centre and UNEV concerning CARE.

3.16 For the purposes of this Agreement, the term "Confidential Information" means any information of whatever type and in whatever form, i.e. by whatever medium, obtained by one Party from the other Party (the "Information Provider") before or during the term of this Agreement and relating in any way to the Registry. This includes in particular documents, drawings, software, know-how, data, technical, financial or personnel information as well as information relating to inventions, discoveries, methods, etc. which are marked "Confidential"/"Secret" or for which confidentiality results from the circumstances.

3.17 Information disclosed orally or visually shall be designated as confidential/secret at the time of disclosure and shall be summarised in an adequate form, marked as "Confidential"/"Secret" and transmitted to the recipient of the information within 30 (thirty) days of such disclosure. The contracting parties agree that such information is also covered by the protection of this contract during the aforementioned 30-day period.

3.18 Publications containing results and data of other contractual partners require the prior written consent of the respective contractual partner concerned (apart from regular reports on the progress of the registry). No contractual partner may unreasonably withhold its consent. Consent shall be granted if university contract partners, in fulfilment of their legal obligation to publish research results, publish only fundamental scientific statements or knowledge which do not constitute business secrets of the respective contract partner concerned. Feedback regarding a publication must be provided within 30 days of the request by the contractual partner asked for approval. If no feedback is received within this period, consent shall be deemed to have been granted. The obligation to obtain consent shall remain in force until two years after the end of the project.

3.19 The participating centre has unrestricted right to access and to use its own entered data. All materials, documents and information supplied by UNEV to the participating centre shall be the sole and exclusive property of UNEV. Entered data can only be deleted with the approval of UNEV.

3.20 External scientific parties may receive excerpts of Data if: (i) the Data is fully anonymized and cleaned of all links to patients, including all links to the participating centres in which patients are treated; and (ii) the Data is only used for research into and registration of the effectiveness and adverse events of medicinal products used by the patients concerned. In the event of a dispute under this Agreement, the Parties shall first meet to attempt to resolve the matter amicably. If an amicable resolution cannot be found, any claim arising under or in connection with this agreement or the legal relationships established by this Agreement instituted against a Party (the “Defending Party”) by another Party shall be brought in the courts of Berlin, Germany.

3.21 If UNEV will cease to exist, the future ownership or cancellation of the CARE Registry has to be determined at the final meeting of the CARE International Steering Committee.

3.22 In no event will any Party’s liability towards the other Party include any indirect damages, including loss of profit, loss of revenue and loss of business opportunities.

**4. Details on Reporting and Documentation**

4.1 The participating centre 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.

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

4.3 The participating centre shall correct incorrect data via the electronic data capture system as soon as the participating centre becomes aware of incorrect data. Data will be transferred at regular periods from REDCap into an electronic case report form program to process and monitor the data. Outlier and diagnostic plots are used to check for plausibility, consistency and integrity.

4.4 The participating centre shall notify UNEV when a patient quits the CARE Registry. The participating centre shall include in this notification the exact time of termination. In this case, UNEV shall immediately delete the patient data concerned.

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

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

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

4.8 The participating centre 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.

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

**5. Details on Analyses and Publication**

# 5.1 Analyses of the CARE dataset can be suggested by all participating centres 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.

5.2 Notwithstanding the remaining provisions of this agreement, the participating centre shall have the right to publish, present or otherwise publicly disclose the results of analyses of their data and disseminate information pertaining to centers’s activities conducted under this agreement, including own project data, for own, non-commercial purposes in research and teaching. However, the participating centre 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.

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## 5.3 The participating centre 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 participating centres and project manager’s activities conducted under this agreement until such a publication is released.

5.4 In particular the participating centre 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.

**6. Details on Confidentiality**

6.1 Both parties agree to hold in confidence all materials, documents and information that each party discloses pursuant to this agreement, and all materials, documents and information gathered or developed pursuant to this agreement ("confidential information"). Both parties 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 the other party - disclose it to any third party except for staff and consultants as required by law and with UNEVs knowledge, and the participating centre’s agents and employees who have a need to know such information to perform the project. Both parties 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.

6.2 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 participating centre 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.

**7. Details on Liability**

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

**8. Term and Termination**

8.1 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.

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

8.3 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 participating centre without a capable replacement.

**9. Obligations of Personnel**

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

**10. Miscellaneous**

10.1 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.

10.2 This agreement is personal in nature and the participating centre 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.

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

10.4 Any dispute arising from this agreement between the participating centre and UNEV shall be exclusively referred to the jurisdiction of Berlin, Germany.

10.6 This agreement is executed in two copies of which each party, i.e. UNEV and the participating centre, receives one.

# 11. 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.

**UNEV gGmbH**

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

**Participating center**

|  |
| --- |
|  |
| 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 1.1, 17.10.2024

**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 and the UNEV gGmbH.

ACARE Office UNEV Office
c/o DGAKI, Robert-Koch-Platz 7 Schönhauser Allee 163

10115 Berlin, Germany 10435 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 UNEV gGmbH  UNEV OfficeUNEV gGmbH 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 Fairfax, USAAsli Gelincik, Istanbul, Turkey Clemens Schöffl, Graz, AustriaConnie Katelaris, Campbelltown, 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 Jie Shen Fok, Melbourne, AustraliaJonathan Bernstein, Cincinnati, USAJonny Peter, South Africa, Cape Town Karsten Weller, Berlin, GermanyLaurence Bouillet, Grenoble, FranceMarc Riedl, San Diego, USA Markus Magerl, Berlin, Germany Mauro, Cancian, Padova, ItalyMichihiro Hide, Hiroshima, JapanMoshe Ben-Shoshan, Montreal, CanadaNoemi Bara, Sangeorgiu de Mures, RomaniaPetra Staubach, Mainz, Germany Philip Li, Hongkong, ChinaRoman Hakl, Brno, Czech RepublicStefan Cimbollek, Sevilla, SpainStephen Betschel, Toronto, CanadaTamar Kinaciyan, Vienna, Austria Teresa Caballero, Madrid, Spain Thomas Buttgereit, Berlin, Germany Timothy Craig, Hershey, USAVesna Grivcheva-Panovska, Skopje, North Macedonia Yu-Xiang Zhi, Beijing, ChinaFormer ISC member: Marcus Maurer, Berlin, Germany |
| CARE Management Team  | Dr. Thomas Buttgereit - Chief Scientific CoordinatorPD Dr. med. Karsten Weller - Principal InvestigatorAnnika Gutsche - Chief StatisticianDr. Pavel Kolkhir - CURE liaison officerPD Dr. Frank Siebenhaar - UNEV liaison officerProf. Dr. Markus Magerl - ACARE liaison officer Former CARE Management Team member: Prof. Dr. Marcus Maurer |
| 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) - completed
2. Establishment of a CARE Management Team (CARE MT) and CARE office - completed
3. Definition of core variables - completed
4. Generation of data reporting forms for baseline and follow up entries - completed
5. Recruitment of partners / supporters - ongoing
6. Programming of the CARE eCRF and database - completed
7. Submission for regulatory approval of the coordinating center in Germany (Institute of Allergology, Charité - Universitätsmedizin Berlin) - completed
8. Enrolment of first patient and launch of CARE: Oct. 2023
9. Expansion to a global registry - ongiong
10. First publication - completed
 |
| 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 UNEV gGmbH (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 UNEV gGmbH (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 UNEV gGmbH  .

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

UNEV gGmbH

Schönhauser Allee 163
10435 Berlin, Germany

The CARE database was developed and is maintained by the UNEV gGmbH    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 UNEV gGmbH  (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.