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 GA^{2}LEN 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 GA^{2}LEN network of Angioedema Centers of Reference and Excellence (ACAREs) and the Urticaria Network e.V. (UNEV).

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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 GA^{2}LEN network of Angioedema Centers of Reference and Excellence (ACAREs) and the Urticaria Network e.V. UNEV Office urticaria network e.V. Schönhauser Allee 163 10435 Berlin, Germany ACARE Office c/o DGAKI Robert-Koch-Platz 7 10115 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, Austria Connie Katelaris, Westmead, Australia Danny Cohn, Amsterdam, Netherlands Daria Fomina, Moscow, Russia Emel Aygören-Pürsün, Frankfurt, Germany Henriette Farkas, Budapest, Hungary Henrik Balle Boysen, Horsens, Denmark Hilary Longhurst, Auckland, New Zealand Inmaculada Martinez-Saguer, Mörfelden, Germany Karsten Weller, Berlin, Germany Laurence Bouillet, Grenoble, France Marc Riedl, San Diego, USA Marcus Maurer, Berlin, Germany Markus Magerl, Berlin, Germany Mauro Cancian, Padova, Italy Michihiro Hide, Hiroshima, Japan Moshe Ben-Shoshan, Montreal, Canada Noemi Bara, Sangeorgiu de Mures, Romania Petra Staubach, Mainz, Germany Roman Hakl, Brno, Czech Republic Stefan Cimbollek, Sevilla, Spain Stephen Betschel, Toronto, Canada Tamar Kinanciyan, Vienna, Austria Teresa Caballero, Madrid, Spain Thomas Buttgereit, Berlin, Germany Timothy Craig, Hershey, USA Vesna 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

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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.

10.2 Statistical Analyses

Statistical analyses of the registry data will be performed in regular intervals. For qualitative parameters, descriptive statistics such as the population size and the percentage of available data for each class of the parameter will be presented. Quantitative parameters will be summarized by presenting, for example, the population, the mean, standard deviation (SD), median, minimum and maximum values, 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.

10.3 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 GA^{2}LEN 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.