Request for advice from the ethics committee on the implementation of a medical-scientific project that does not involve the clinical testing of a drug or medical device

|  |  |
| --- | --- |
| 1. Study title: | Establishment and management of the first  disease registry for recurrent angioedema, the  Chronic Angioedema REgistry (CARE). |
| 2. Ethics committee application number: |  |
| 3. Decisions of other ethics committees on the same matter: | None |
| 4. Subject of the study and its objectives; state of the hypotheses, separated into main and secondary hypotheses, and the clinical parameters (primary and secondary endpoints) against which the hypotheses will be tested: | The planned study is an observational study without invasive investigations.  Angioedema is a swelling of deep dermal or mucosal tissue that arises from a vascular reaction caused by an increase in the permeability of blood vessels. The first occurrence of angioedema is a frightening event for many patients, but some patients suffer from recurrent (chronically recurring) angioedema for several months up to years, significantly affecting their quality of life. Angioedema is divided into mast cell mediated angioedema and bradykinin mediated angioedema, based on the current international WAO / EAACI guideline. The existence of mixed forms and other forms is critically discussed in the specialist literature. In a few cases, the exact cause of recurrent angioedema remains unclear. Mast cell mediated angioedema is the most common cause of recurrent angioedema and results from degranulation of mast cells with associated release of histamine and other vasoactive and pro-inflammatory mediators. Examples of disease patterns with mast cell mediated angioedema are type 1 allergies or acute or chronic urticaria with or without the appearance of wheals. Chronic urticaria is one of the most common dermatologic conditions defined by the occurrence of wheals and / or angioedema over a period of more than 6 weeks. Bradykinin-mediated angioedema occurs much less frequently and is due to an imbalance in the contact system that ultimately leads to increased formation of bradykinin. Bradykinin is a vasoactive peptide and important effector molecule of the contact system. One of the most important mediators of the contact system is the C1-inhibitor (C1ÎNH). In hereditary angioedema (HAE) caused by C1INH deficiency, a rare autosomal dominant inherited disease with mutations in the SERPING gene, C1INH is either insufficiently produced or is dysfunctional, in the occurrence of recurrent angioedema.  In the meantime, further even rarer mutations in genes outside the SERPING gene have been identified in some patients with HAE, which lead to bradykinin-mediated angioedema. For example, in the factor XII gene, kininogen gene, plasminogen gene, angiopoietin gene and HSST gene. Other forms of recurrent angioedema include drug-induced angioedema, e.g., by antihypertensive drugs such as ACE inhibitors.  Clinical studies in recent years have demonstrated impressively that many patients with various forms of recurrent (chronic) angioedema experience a pronounced reduction in their quality of life.  This is not least due to the unpredictability of the occurrence of the sometimes painful swelling attacks in different localizations of the body along with restrictions in everyday life, but also to the fact that it is a potentially life-threatening clinical picture if, for example, there are attacks in the area of the upper respiratory tract.  The epidemiology, the duration, the course of the disease, underlying causes, the response to therapy and the cost of illness of angioedema remain furthermore insufficiently studied even due to the frequency of data and only some few data concerning the progression of different forms of recurrent angioedema.  While the maintenance of a registry would be an appropriate way to investigate these open topics, such a registry is has not yet been established.  For this reason, we are planning to establish the first disease registry for chronic recurrent angioedema, the Chronic Angioedema REgistry (CARE). This registry is initially planned without a time limit, is driven by the academic-scientific interests of the participating doctors treating angioedema patients, and is intended to record patients with all forms of angioedema. The registry represents an observational study that provides data from the real treatment situation in the clinical practice (real life data).  The subject areas of the registry will include, among others:   1. Demographic characteristics of patients, 2. Data on disease progression of different forms of   angioedema,   1. Data on underlying causes, 2. Data on patient comorbidities, 3. Data on treatment response, 4. Data on quality-of-life impairment of and 5. Data on direct and indirect medical costs.   The aim of the study is to improve the data on the different forms of angioedema in the above-mentioned areas, and thus to improve the overall understanding of the disease and its forms. The results from the disease registry will be published and will help to improve the care of future affected patients.  References:   1. Maurer M, Magerl M, Betschel S, Aberer W, Ansotegui IJ, Aygören-Pürsün E, Banerji A, Bara NA, Boccon-Gibod I, Bork K, Bouillet L, Boysen HB, Brodszki N, Busse PJ, Bygum A, Caballero T, Cancian M, Castaldo A, Cohn DM, Csuka D, Farkas H, Gompels M, Gower R, Grumach AS, Guidos-Fogelbach G, Hide M, Kang HR, Kaplan AP, Katelaris C, Kiani-Alikhan S, Lei WT, Lockey R, Longhurst H, Lumry WR, MacGinnitie A, Malbran A, Martinez Saguer I, Matta JJ, Nast A, Nguyen D, Nieto-Martinez SA, Pawankar R, Peter J, Porebski G, Prior N, Reshef A, Riedl M, Ritchie B, Rafique Sheikh F, Smith WB, Spaeth PJ, Stobiecki M, Toubi E, Varga LA, Weller K, Zanichelli A, Zhi Y, Zuraw B, Craig T. The international WAO/EAACI guideline for the management of hereditary angioedema-The 2021 revision and update. Allergy. 2022 Jul;77(7):1961-1990. doi: 10.1111/all.15214. Epub 2022 Feb 3. PMID: 35006617. 2. Zuberbier T, Abdul Latiff AH, Abuzakouk M, Aquilina S, Asero R, Baker D, Ballmer-Weber B, Bangert C, Ben-Shoshan M, Bernstein JA, Bindslev-Jensen C, Brockow K, Brzoza Z, Chong Neto HJ, Church MK, Criado PR, Danilycheva IV, Dressler C, Ensina LF, Fonacier L, Gaskins M, Gáspár K, Gelincik A, Giménez-Arnau A, Godse K, Gonçalo M, Grattan C, Grosber M, Hamelmann E, Hébert J, Hide M, Kaplan A, Kapp A, Kessel A, Kocatürk E, Kulthanan K, Larenas-Linnemann D, Lauerma A, Leslie TA, Magerl M, Makris M, Meshkova RY, Metz M, Micallef D, Mortz CG, Nast A, Oude-Elberink H, Pawankar R, Pigatto PD, Ratti Sisa H, Rojo Gutiérrez MI, Saini SS, Schmid-Grendelmeier P, Sekerel BE, Siebenhaar F, Siiskonen H, Soria A, Staubach-Renz P, Stingeni L, Sussman G, Szegedi A, Thomsen SF, Vadasz Z, Vestergaard C, Wedi B, Zhao Z, Maurer M. The international EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria. Allergy. 2022 Mar;77(3):734-766. doi: 10.1111/all.15090. Epub 2021 Oct 20. PMID: 34536239. |
| 5. Explanation of the significance of the study: | See page 4. |
| 6. Which of the following determinations apply:  a) “Medizinproduktgesetz, § 23b, MPG” (German law: Medical Devices Act according to § 23b MPG - exception of clinical examination),  b) “Strahlenschutzverordnung, § 28a Röv, StrlSchV” (German law: Radiation Protection Regulations § 23 StrlSchV),  c) “Röntgenverordnung, § 28a Röv  (German Law: X-ray Regulations  § 28a RöV),  d) Genetic Diagnostics Act (German  law) and  e) Data protection laws (German  law):   * Exact specification to be complied with by the responsible data protection law (for Charité:   EU Data Protection Regulation (DSGVO / German law), Berlin data protection law (BlnDSG / German law), and if applicable,   * According to the group of participants, additional state data protection laws, data protection laws or “BDSG” (German law). | EU Data Protection Regulation (DSGVO / German law), Berlin Data Protection Act (BlnDSG / German law),if applicable, state data protection laws and / or Federal Data Protection Act (BDSG / German law) as well as local data protection laws and guidelines according to the participating centers. |
| 7. If applicable: designation and characterization of the test products: | Not applicable. |
| 8. Significant results of the pre-clinical tests or reasons for not performing them: | Not applicable. |
| 9. Main content and results of previous studies / applications of the products to be tested in the study: | No comparable previous studies. |
| 10. Description of the planned measures / examination methods and any deviations from possible measures / examinations commonly used in medical practice (what is "routine", what is done differently in the study?):  If validated questionnaires are used for study purposes, please indicate the name of the questionnaires and where they are published (references). Please attach non-validated questionnaires. | This registry study has no influence on the treatment of the included patients. It is purely an observational study. Accordingly, there are no deviations from the usual measures / examinations in medical practice.  Simply entering patient and treatment data into the registry represents a step that deviates from "routine". It is important that no personal data such as surname, first name or date of birth is recorded in the registry.  The entry of patient data in the registry is pseudonymized. Only the entering doctor can link to the entry to the specific patient. The entering doctors are asked to record the fact of registry entry as well as the pseudonym assigned to the patient in their regular patient documentation, i.e., in the corresponding patient file.  Before patient data is entered into the angioedema registry it is required that the patients concerned have been informed in detail about the purpose and content of the registry via patient information leaflet and an existing declaration of consent (written, dated and signed) from the patient.  In total, several entries for the same patient should be made in the angioedema registry during the progression of treatment; a basic entry should be followed by follow-up entries, since the registry should also collect data on the development of the disease over time.  The angioedema registry will collect data from angioedema patients from all over Germany, but in the progression also from patients from other countries and continents such as Brazil, the USA, Hungary, Austria and France (core countries). In a later step, the registry will be extended to other countries, including Asia.  In the following, the most important steps of the registry establishment are presented as an overview:   1. As a first step, an International Steering Committee (ISC) for the CARE Registry will be established. Among other things, the ISC will be responsible for developing the specific questions of the angioedema registry as well as overseeing and deciding on data analysis and updates in the registry. The patient questions will also include established Patient Reported Outcome (PRO) instruments, (e.g., questionnaires on disease-related quality of life, disease control, disease activity, etc.) Part of the ISC will be one representative from each country as well as the coordinating chief auditor of the study. Currently, the following participants are planned for the ISC:   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  The respective ISC members should also each serve as the primary contact for the CARE registry in their country.   1. In a second step, the actual web-based angioedema registry will be programmed. The developed questions for the angioedema registry will be integrated into a common “eCRF-program” (SecuTrial, electronic case report forms) with audit trail, which complies with current data protection criteria and the “GCP” (Good Clinical Practice). Initially, paper questionnaires will be used, which will then be transferred to the “eCRF-program”. In the further progress, a database will be created to record the patients' answers and the subsequent analyses. This will be done using the REDCap-system (Research Electronic Data Capture), a secure web application for building and managing online surveys and databases. REDCap complies with 21 CFR Part 11, FISMA, HIPAA, and GDPR requirements and is specifically designed to support both online and offline data collection for research studies and operations. 2. In a third step, the registry will be activated for the core countries first. From this point on, patient data can be entered into the registry . 3. In a fourth step, the angioedema registry is to be further expanded internationally and expanded to other countries, including Asia and South America.   Analyzes of registry data are planned at 3-monthly intervals. |
| 11. Assessment and weighing of the foreseeable risks and disadvantages of participation in the study against the expected benefits for the study participants and persons who will become ill in the future (benefit-risk assessment). | There are no risks or disadvantages for patients through their entry into the angioedema registry. The same applies to a refusal to be included in the registry. |
| 11 a. Medical benefit to be tested for the study participants (individual benefit for the individual patient) | Not applicable. |
| 11 b. Medical benefit to be tested for persons with the disease in the future (group benefit) | The results of the registry provide new insights, including the demographic characteristics of affected patients, disease progression in the various forms of recurrent angioedema, the underlying causes, the comorbidities of patients, the response to therapy, the impairment of the quality of life of those affected as well as the direct and indirect medical costs to be expected. This will allow a better understanding of the different forms of angioedema and may serve to improve the care of future patients. |
| 11 c. **Risks** and burdens to study participants (list all in detail). | Not applicable. |
| 12. Measures to control risks: | Not applicable. |
| 13. Termination criteria: | Not applicable. |
| 14. Number of persons concerned and their age and gender: | All affected patients with various forms of recurrent angioedema can be entered in the registry, given that a written, dated, signed patient declaration of consent is available. The number of patients that can be included in the registry is not limited. The intention is to consciously record unselected data from clinical reality (real life data). |
| 15. Biometric planning stating statistical methodology, including justification for number of cases:  Indication of the statistician(s):  (If advice is given by the Institute of Biometry of the Charité, a signature must be included.) | Not applicable. There is no time limit for the registry, nor is there a limit on the number of patients participating. |
| 16. Presentation and, if necessary, explanation of the **inclusion and exclusion criteria:** | All affected patients with recurrent swellings can be entered in the registry, given that a written, dated, signed patient declaration of consent is available. |
| 16 a. **Study information** (who provides it verbally and in writing as well as indication of how much time is left between informed consent and consent (written information attach)): | Patients eligible for the registry will be informed about the angioedema registry in writing (with the help of a patient information leaflet) and, if necessary, additionally verbally. A written, dated, signed patient declaration of consent must be present before patient data is entered into the registry.  Participants will be given adequate time to decide if they wish for their entry in the angioedema registry.  See attachment: patient information leaflet. |
| 16 b. **Declaration of consent** (written form as attachment): | See attachment. |
| 16 c. If applicable, **information and consent of the legal representative** (if applicable, also description of the procedure for setting up court-ordered care): | If the patient is not of legal age or if there is a guardianship relevant to the entry in the registry, the person and the legal guardian or guardian will be informed. A written, dated, signed patient declaration of consent must be present from the person and the legal guardian or guardian before patient data is entered into the registry. |
| 17. Measures to recruit study participants (notice board? Newspaper ads? etc.): | Patients at the Institute of Allergy Research at the Charité are primarily recruited from the special consultation for urticaria and the angioedema consultation. In principle, however, a recruitment of all affected patients from the clinical practice (from medical care) is possible. |
| 18. If applicable: **reason for inclusion and demonstration of therapeutic benefit for persons who are minors and / or unable to consent:** | Since data from the real treatment situation in clinical practice should be collected (real life data) and also children may be affected by recurrent angioedema, children and adolescents (minors) should not be excluded. The same applies to patients that cannot agree to participate on their own. |
| 19. Relationship between study participant and doctor of the study (is the doctor of the study also the treating doctor?): | There is a possibility that the doctor, who is contacting and informing the patients about the registry, is at the same time the patient's attending doctor. |
| 20. Statement on the involvement of persons possibly dependent on the sponsor: | Dependent persons are not included in the registry. |
| 21. Measures that allow a determination of whether a study participant is participating in more than one study at the same time or before the expiration of a period specified in the previous study.  Is participation in multiple studies possible? | This is a purely observational study that cannot be influenced by other studies and does not itself influence other studies. Therefore, no explicit measures are planned to determine whether a registry patient is participating in other clinical studies in parallel or is included in the registry before the expiration of a time limit specified in the previous study. |
| 22. If applicable: remuneration or reimbursement of study participants (amount and what will be paid?): | Not applicable. |
| 23. If applicable: plan for continued treatment and medical care of affected persons after the end of the study: | Not applicable. |
| 24. If applicable: insurance of the study participants (confirmation of insurance and insurance conditions, insurer, scope of insurance, duration of insurance): | Not applicable. |
| 25. Documentation Procedures:   * Reference to CRF-forms (case report forms), if applicable, * Specification of data to be recorded, * Handling of samples, * Storage / archiving (incl. time limits) and * Access to data and samples | The creation of the registry questions is part of the project; these cannot be submitted at the time of application. The documentation of the patients shall take place with the help of a common and tested eCRF program. |
| 26. If applicable: description of how the health status of healthy affected persons will be documented: | Not applicable. |
| 27. If applicable: methods to identify, document and report unwanted events (when, by whom and how?): | Not applicable. |
| 28. Procedure to protect the confidentiality of the stored data, documents and, if applicable, samples, description of the pseudonymization or anonymization of the data and samples of study participants **(initials and date of birth as coding scheme are not allowed!)**.   * Description of the separation of medical records, study documentation and assignment of personal data, * Naming of access rights including access to participant identification lists during and after carrying out the study, * Detailed specification of the procedures for transmission, encryption, restriction of processing (blocking) and deletion (including details of the network structure used, if any, and servers used) and * If applicable, access to identifying data for legally authorized auditors (third parties) for the dedicated inspection of the files required for this purpose. | Patient data is entered into the eCRF pseudonymously. Therefore, data attributable to patients cannot be found in the registry documentation.  The basis for subsequent data processing is solely the data entered into the eCRF. Data such as, surname, first name, initials or date of birth, is not recorded.  However, the combination of data concerning age, gender, and duration of illness will make it possible to ensure that patients are not entered into the registry twice. Patients are informed about the entry, evaluation and publication of the data in the patient information leaflet. |
| 29. Declaration of compliance with data protection:   * Assurance that all data of the study participant being collected and stored will be treated confidentially (according to data secrecy and medical confidentiality), * Assurance that the identified data will only be accessible to the study director and / or his authorized employees (authorized by him / her), * Indication of the measures taken to ensure confidentiality, * Measures for data protection transmission of data that cannot be linked to a person by third parties, * Statement on information options, and the possibility of revocation, correction and deletion, * Measures to ensure the rights of the participants and * If transfers to non-EU countries are intended: data protection compliance measures, e.g., existence of an adequacy decision by the EU Commission or explicit consent of study participants to such transfers, are to be adhered to. | The angioedema registry adheres to all legal data protection regulations. |
| 30. Names and addresses of the institutions involved in the study as study center or study laboratory, as well as the director of studies and the study doctors:   * Specification of external service providers with specification of the data access possibility. | Charité - Universitätsmedizin Berlin  Institute of Allergology  Campus Benjamin Franklin  Hindenburgdamm 30  12203 Berlin  Project leader: Dr. med. Thomas Buttgereit  In future, further study centers and / or doctors caring for angioedema patients shall be involved in the registry and enter patient data into the registry. |
| 31. Specification on the suitability of the trial site, in particular on the appropriate resources and facilities available there, as well as on the employees available to conduct the clinical trial and experiences in conducting similar trials: | The Institute of Allergology at the Charité conducts its own clinical studies on a regular basis and beyond this consistently participates in a number of multicenter studies. Thus, extensive experience of conducting clinical trials has been available for many years. The Institute of Allergology also participates in a series of registry studies. Adequate resources, conditions, and employees are available to maintain the angioedema registry. |
| 32. Agreement on access by the auditor / chief auditor / head of clinical trials, to the data and the principles of the publication:   * Publications in a way that they do not lead to a conclusion to the person. | The project manager and those involved in the project have the right to publish the data from the survey and the data evaluation. Decisions on planned publications will be made within the framework of the ISC. The scientific neutrality of the publications resulting from the registry and the data on which they are based on is not subject to any restrictions. |
| 33. Details of funding for the study:  Funding source (name and location) and amount of funding in €:   * If applicable, specification of the cost center for internal service billing of the fee. | The study is partly funded by:  Urticaria Network e.V. (UNEV) Schönhauser Allee 163 10435 Berlin  In addition, fundraising is planned from various other sources. These include the European Academy of Dermatology and Venereology (EADV), the European Academy of Allergy and Clinical Immunology (EAACI), and companies in the pharmaceutical industry.  Due to the nature of the registry, a cost calculation per participant is not useful.  In total, establishing and hosting of the angioedema registry is currently expected to cost around 100,000 euros for the first three years. However, depending on the expansion, success and funding of the registry, these costs may be significantly higher.  There is no reimbursement / remuneration for patients included in the registry. |

Name and signature of the applicant(s):

I hereby assure that the information provided in this application is correct. I believe it is possible to conduct this study in accordance with the protocol and national legislation.

Surname:

First Name:

Service Address:

Position:

Date:

Signature: