CLOUD-R HAE REGISTRY

Version 3.0_ 11.09.2018

TITLE
Registre international sur les angiœdèmes isolés

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External Data Processor	Cloud-R s.r.l Milan, Piazza Giuseppe Grandi, 24 – Italy

Historique des mises à jour du protocole

Version	Date	Raison de la mise à jour
1.0	02.10.2017	Transmission INDS
2.0	03/05/2018	Mise à jour réglementaire et insertion des centres associés
2.1	07.08.2018	Correction concernant la MR-003 des centres associés
3.0	11.09.2018	Correction concernant la MR004 et RGPD

PAGE DE SIGNATURE DU PROTOCOLE

Registre international sur les angiœdèmes isolés

CLOUD-R HAE REGISTRY

Ce protocole a été lu et approuvé.
Les deux parties s'engagent à mener la recherche conformément au protocole et aux dispositions législatives et réglementaires en vigueur qui leur sont applicables..

National Coordonator France

Professeur Laurence Bouillet
CREAK, Médecine Interne
CHUGA

Date:

Data Controller:

CHU Grenoble Alpes
Représenté par :
La Directrice Générale
Mme Monique SORRENTINO

Date:

1. RESUME

<table>
<tr><td colspan="2">Titre</td><td>Registre international sur les angiœdèmes isolés</td></tr>
<tr><td colspan="2">Titre court /acronyme</td><td>Cloud-R HAE Registry</td></tr>
<tr><td rowspan="2">Equipe(s) projet</td><td>Nombre d’équipes associées à l’étude, recherche ou évaluation :</td><td>Hôpital Saint Antoine, APHP : Pr O.Fain
Hôpital Claude-Huriez-CHRU Lille : Pr D.Launay
Hôpital Edouard Herriot, Lyon : Dr S.DebordCHU de Toulouse : Pr L.Sailler
Hôpital Saint Eloi, CHU Montpellier : Dr A.du Than
CHU de Besançon : Dr F.Pelletier
CHU de Nice : Dr PY.Jeandel
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CHU de Rouen : Dr G.Armengol.
CHU de Nancy : Pr R.Jaussaud
CHU Ile de La Réunion : Dr N.Marmion.
CHU de Limoges : Dr Céline MENETREY

16 équipes au total.</td></tr>
<tr><td>Nom, titre et fonction du responsable de l’équipe coordinatrice :</td><td>Professeur Laurence Bouillet
Coordonnatrice nationale du CREAK</td></tr>
<tr><td colspan="2">Contexte de l’étude, recherche ou évaluation</td><td>Les angiœdèmes isolés regroupent différentes pathologies rares qui sont mal connues. A ce jour aucune base de données suffisamment importante n’a pu être créée. Afin de mieux connaitre ces pathologies, il est impératif de réunir tous ces cas au sein d’un registre international afin de mieux identifier les caractéristiques des patients, leurs besoins, et leur réponse thérapeutique.</td></tr>
<tr><td colspan="2">Objectifs principal et secondaire</td><td>Ce registre a pour objectifs de collecter des données cliniques et biologiques
PAS DE COLLECTION BIOLOGIQUE ; le registre collecte juste les résultats des examens biologiques faits en routine.</td></tr>
<tr><td colspan="2">Préciser en quelques lignes la justification d’intérêt public de l’étude, la recherche ou l’évaluation</td><td>Ce registre permettra de cibler et de personnaliser le traitement. Il permettra aussi d’évaluer le rapport bénéfice/risque des traitements.</td></tr>
</table>

Type d'étude (cohorte, rétrospective, cas-témoin…)	Cohorte Registre maladie multicentrique européen
Population concernée (critères d'inclusion et de non inclusion)	Critères d'inclusion : Tout patient ayant un angioedème isolé sans urticaire superficielle associée. Patients ayant un angioedème héréditaire avec ou sans déficit en C1Inhibiteur. Patient majeur ayant donné leur consentement (signature) Patient mineur dont les parents/responsables légaux auront donné leur consentement (signature) Critères d'exclusion : Patient en incapacité de donner son consentement. Urticaire chronique superficielle avec angioedème.
Taille de la population d'étude	Il s'agit d'un registre. Il n'y a pas de nombre limite. En France, on évalue le nombre de patients potentiellement incluables à 1500 environ
Origine des données de santé à caractère personnel (source(s) utilisée(s))	L'origine des données sera le dossier médical du patient. Chaque médecin (de chaque site) sera responsable du recueil des données et de leur ajout dans la base de données. Les données seront accessibles sur le plan national et international uniquement si le médecin qui a rentré les données donne son accord.
Mode de recueil des données à caractère personnel (papier, électronique …) et lieu d'hébergement de la base de données	Les données seront archivées par le nom de l'étude dans les locaux du service de médecine interne (unité CREAK) du CHU de Grenoble Alpes jusqu'à la fin de la période d'utilité pratique (au moins 15 ans). Les données seront recueillies sous eCRF via la société Cloud-R s.r.l.
Circuit des données à caractère personnel et modalités de protection de leur confidentialité	Les personnes ayant un accès direct aux données prendront toutes les précautions nécessaires en vue d'assurer la confidentialité des informations relatives aux recherches, aux personnes qui s'y prêtent et notamment en ce qui concerne leur identité ainsi qu'aux résultats obtenus. Ces personnes, au même titre que les médecins eux-mêmes, sont soumises au secret professionnel. Pendant la recherche ou à son issue, les données recueillies sur les personnes qui s'y prêtent et transmises au Responsable de traitement par les médecins (ou tous autres intervenants spécialisés) seront rendues anonymes. Elles ne doivent en aucun cas faire apparaître en clair les noms des personnes concernées ni leur adresse.

	La codification des sujets sera réalisée en utilisant la première lettre du nom, puis la première lettre du prénom, puis le numéro du site qui inclut. Les documents établissant la correspondance entre le code du sujet et son identité seront conservés par chaque site investigateur.
Principales variables et méthode d'analyse des données	La méthode d'analyse dépendra du nombre de patients inclus et du pourcentage de données disponibles pour chacun d'eux. Les paramètres quantitatifs seront analysés avec : moyenne, médiane, déviation standard… Des analyses de sous-groupes seront réalisées : sous-groupe de patients (enfants, femmes…), sous-groupe de symptômes (attaque laryngée, abdominales…)…. Des analyses de survie seront possibles en fonction des requêtes de chaque investigateur.
Calendrier et organisation de l'étude, recherche ou évaluation	Chaque centre français alimentera le registre en se connectant directement à l'eCRF (accès personnel pour chaque centre associé). Un conseil scientifique national et international se réunira tous les 6 mois pour déterminer les analyses à faire en fonction des problématiques soulevées par les centres associés.

2. INTRODUCTION

Angioedema is a disease characterized by the appearance of self-limiting edema that last 1-5 days and affect the subcutaneous tissue and/or gastrointestinal and oropharyngeal mucosa. In this last location edema can be lethal causing asphyxia, in all other cases full recovery is complete. Attacks can appear as part of the syndrome urticaria angioedema and can be of allergic origin. But there is a group of non-allergic angioedema that occur without hives and can be either hereditary or acquired. These angioedema are identified in some cases on the basis of etiology, in others are identified by the mediator and an overall classification of these forms of angioedema was published in 2014 as a result of a consent conference organized by the proponents of this registry (Cicardi et al. Allergy 2014; 69:602-16). Being these forms of angioedema rare, there are not significative case studies inclusive of a high number of patients. This registry aims to collect in a single place a high number of subjects with recurring angioedema and without urticaria.

3. OBJECTIVES OF THE STUDY

3.1 Primary Objectives

Gather clinical and laboratory data related to the different forms of angioedema and detect the therapy options used to manage this pathology.

4. STUDY DESIGN

International multicenter illness registry

5. SUBJECTS SELECTION AND EXCLUSION

5.1 Inclusion criteria

- Patients with acquired (idiopathic histaminergic, idiopathic non histaminergic, associated to ACE-inhibitor, acquired with C1-inhibitor deficiency) or hereditary angioedema, without urticaria, with or without C1-inhibitor deficiency, diagnosed starting from 1975 by the participant centers.

- For adults able to provide the written informed consent: signature of the informed consent

- For minors: signature of written informed consent by the minor's parents and/or guardian/legal representative. The minor shall in any case receive information related to his understanding capacity and, when possible, shall sign a specific document for the informed consent.

5.2 Exclusion criteria

- Patients non compos mentis
- Patients for whom it is not possible to obtain the informed consent

6. SUBJECTS TREATMENT

6.1 Product under trial

No medicinal product is tested in the study

7. EVALUATIONS

At the inclusion of the patient in the registry, upon acceptance of the informed consent, the patient's personal and demographic data will be collected, together with the clinical and laboratory characteristics for the diagnostic confirmation, the main concomitant diseases and the treatments used during acute events. A patient account via the eCRF will be created to permit patient to download application "Cloud R HAE Carnet de suivi" via an email sent by software. This application permit patient to enter attacks electronically and replace paper diary use actually. Attacks entered by patient will be transferred in the registry after doctor validation in eCRF.

The data source is the medical record of individual patients.
Prospectively further data will be gathered regarding the duration, severity, treatment of acute angioedema events, the presence of drugs in the prophylaxis and comorbidities.

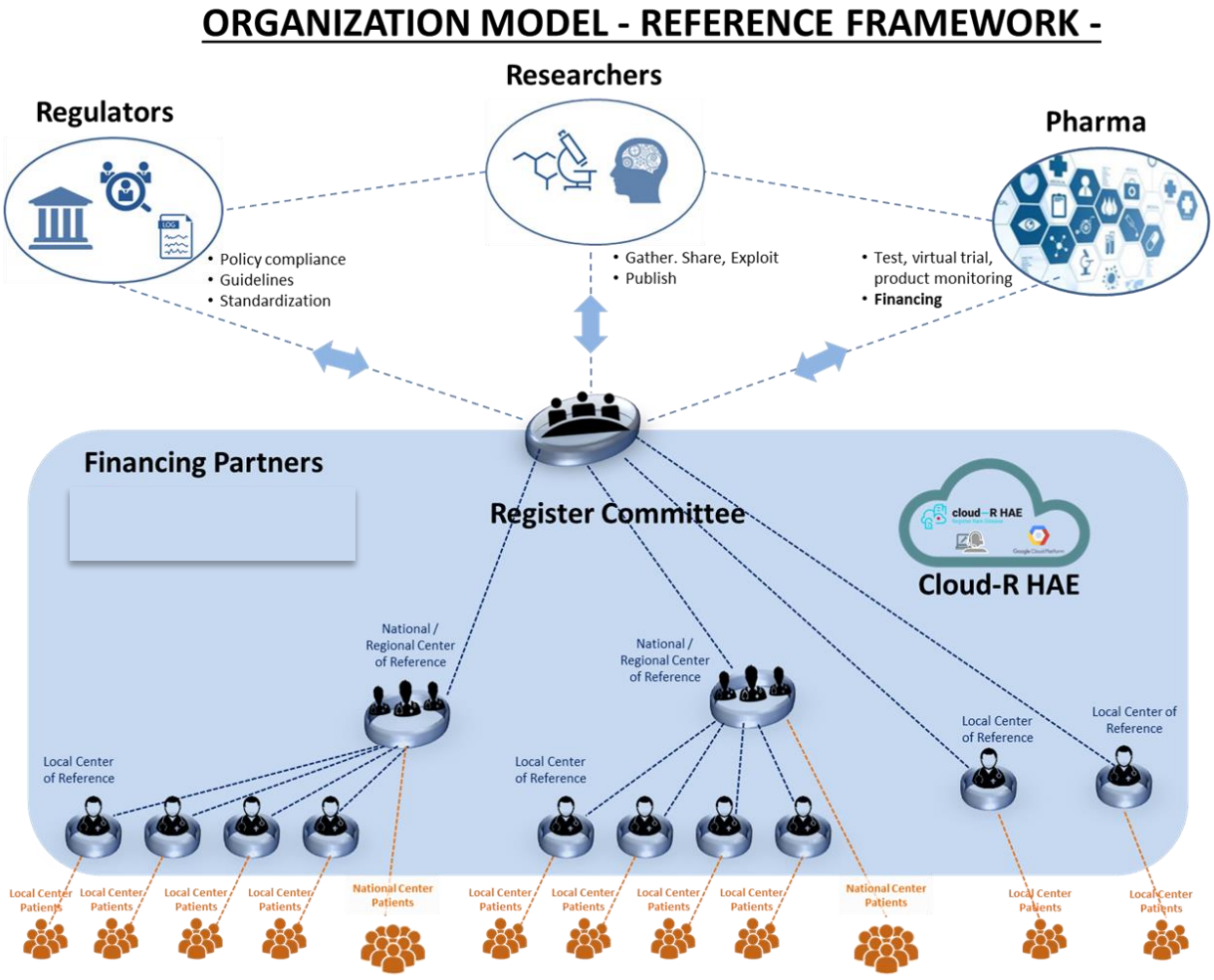
8. FLOWCHART

	Retrospective	Baseline	Prospective
Signature of informed consent		X	
Inclusion and exclusion criteria		X	
Demographic patient data		X	
Clinical characteristics		X	X
Comorbidity	X	X	X
Angioedema diagnosis		X	
Duration and severity of acute angioedema events	X		X
Treatments used in managing the acute angioedema event	X		X
Treatments used in the prophylaxis of angioedema	X		X
Validation of attacks entered by patient via "Cloud R HAE carnet de suivi"			X

9. STATISTICS

9.1 Data responsibility and flow

The registry data will be handled by Cloud-R s.r.l. accordingly to a specific contract with the financing partners that will be defined according to national country rules in compliance with the current regulation concerning sensitive data security and processing.
This contract provides that access to the registry is personal and strictly limited to authorized users. Every user of the registry acknowledges that he is the sole and exclusive responsible of all actions carried out with his own Username and Password and that he is obliged to protect their secrecy and keep them with the due care and diligence.
For a given cohort of patients, the associated center, responsible for collecting the consent from users, shall commit to transfer all obligations in terms of security and compliance regarding privacy to all operators and companies involved in the management of the registry. Access to patient's personal data present in the registry will be exclusively restricted to authorized representatives of each patient's center of reference. Within the registry each patient record is processed exclusively through an ID number univocal for the entire registry that cannot be recalled to personal data (identification patient code). Each patient is the only proprietor of his own data. The organizational model is represented in the image below. It is expected that the Registry may be open to the participation of other nations or through direct participation of single reference centers or through participation mediated by the relevant national associations in compliance with the specific applicable regulations.
The property of anonymized aggregated data is of the Register Committee that will be composed by representatives of the participating centers, patient's representatives (associations) and upon needs other relevant stakeholders. The Data Controller and the Coordinating Investigator for France will have access to the aggregated data of the Registry.



9.2 Primary and secondary measures

The quality parameters will be described by the size of the population and the percentage of available data.

9.3 Patients characteristics

The patient characteristics include anamnesis and demographic data, characterization of acute angioedema events and biochemical data.

9.4 Statistics methods

9.4.1 Primary hypothesis and significance statistical tests

The quality parameters will be described by the size of the population and the percentage of the available data. The quantitative parameters will be summarized as: population size, mean, median, standard deviation, 10th and 90th percentile and range values. Statistical analysis will be performed

on the entire cohort of patients and, where the sample size permits, in cohorts of interest (eg. children, adolescents or laryngeal attacks).
Survival analysis and further analysis will be performed according to the scientific needs of the clinical group.

9.4.2 Bias sources and related countermeasures

This is a clinical observational cohort ambispectic study. Therefore the specific purpose is to avoid statistical bias. Potential sources of bias are lack of enrollment continuity and selection of the sample. Appropriate controls will be made to minimize as much as possible this possibility.

9.4.3 Ad interim analysis

This is an observational study, and it is not planned any interim analysis. To ensure the quality and completeness of data, a continuous remote monitoring will be carried out every six months, without access to personal data of individual patients and without changing the design of the study.

9.4.4 Sample numerosity and statistical power

Given the objectives of the study, it is intended to recruit the largest number of patients with recurrent angioedema events. There is no fixed number of expected patients eligible to recruitment.

10. QUALITY CONTROL QC AND QUALITY ASSURANCE QA

Remote monitoring would occur during the data collection with ad hoc functionalities provided by the computing platform in support of quality control and completeness of data in order to ensure that all aspects of the protocol are met.

11. ETHICAL AND REGULATORY INTERNATIONAL CONSIDERATIONS

11.1 Ethical conduction of the trial

The trial will be carried out in accordance to the recommendations of the 18th WMA General Assembly, Helsinki, Finland 1964 and the local recommendations of participating centers

11.2 Competent authorities

In consideration of the nature of the study and of the underlying regulation, it is the responsibility of CHU GRENOBLE ALPES to obtain the approval of the protocol by the competent authorities in accordance to the law n ° 78-17 of January 6th, 1978 relating to the computing, the files and the freedoms modified by the law 2004 -801 of August 6, 2004 and by the law n° 2018-493 of June 20, 2018. French regulations require an authorization from CNIL (Commission Nationale de l'Informatique et des Libertés) delivered by an engagement to a Reference Methodology : MR004

11.2.1 Patients information and consent

It is the responsibility of each investigator to provide each patient, before inclusion in the study, full and adequate verbal and written information about the contents and study procedures. Patients must be informed of their right to leave the study at any time. The information sheet must be given to each patient before enrollment. In addition, it is the responsibility of each investigator to obtain the written informed consent from the patient before inclusion in the study.
Every signature must be dated by each signatory and each additional information document of the patient must be kept by the investigator as part of the study documents. A signed copy of informed consent and any additional information must be given to each patient. Patients must be informed that their medical data may be examined by an authorized monitor, by members of the IEC / IRB and by inspectors of regulatory authorities.
It is the responsibility of every investigator to comply with local rules concerning the consent and patient information as well as the authorization under the privacy legislation.

12. DATA PROCESSING AND STORAGE

12.1 Case report forms

It is required a case report electronic form (CRF) that will be completed for each patient included in the registry. The complete CRF – comprehensive of sensitive data – will be available to the patient and to the investigator of the center of reference and will not be available in any form to third parties, with the exception of authorized representatives of regulatory and health authorities.

12.1.1 Data gathered retrospectively

- Duration and severity of angioedema acute event
- Treatments used for the management of the angioedema acute event
- For patients deceased between the date of diagnosis and the activation of the registry the consent will be obtained from the family. In the case that consent is not obtainable, request is made to the regulatory authorities in order to include the data of medical reports and go back to official statistics registries to identify the cause of the decease.

12.1.2 Data gathered at opening study visit

- Signature of the informed consent
- Inclusion and exclusion criteria
- Personal and demographic patient’s data
- Clinical characteristics
- Comorbidities
- Angioedema diagnosis

12.1.3 Data gathered prospectively

- Clinical characteristics

- Comorbidities
- Angioedema diagnosis
- Duration and severity of angioedema acute event
- Treatments used for the management of the angioedema acute event
- Treatments used for angioedema prophylaxis

12.1.4 Data gathered by patient

12.2 Data Protection

Data protection will be implemented as defined at clause 9.1. Patients will be informed that:

- Data evaluated during this study will be stored electronically and used for the registry finality in anonymized format (patient identification code)
- Regulatory and health authorities are allowed to obtain information from the documents as per current regulation.

12.3 Data storage

In order to allow evaluations and/or inspections by health authorities, scientist officer shall store data including all participants' identities and all original informed consent duly signed and the CFR in electronic or printed format. In compliance with International rules, data will be stored by the investigators for 15 years.

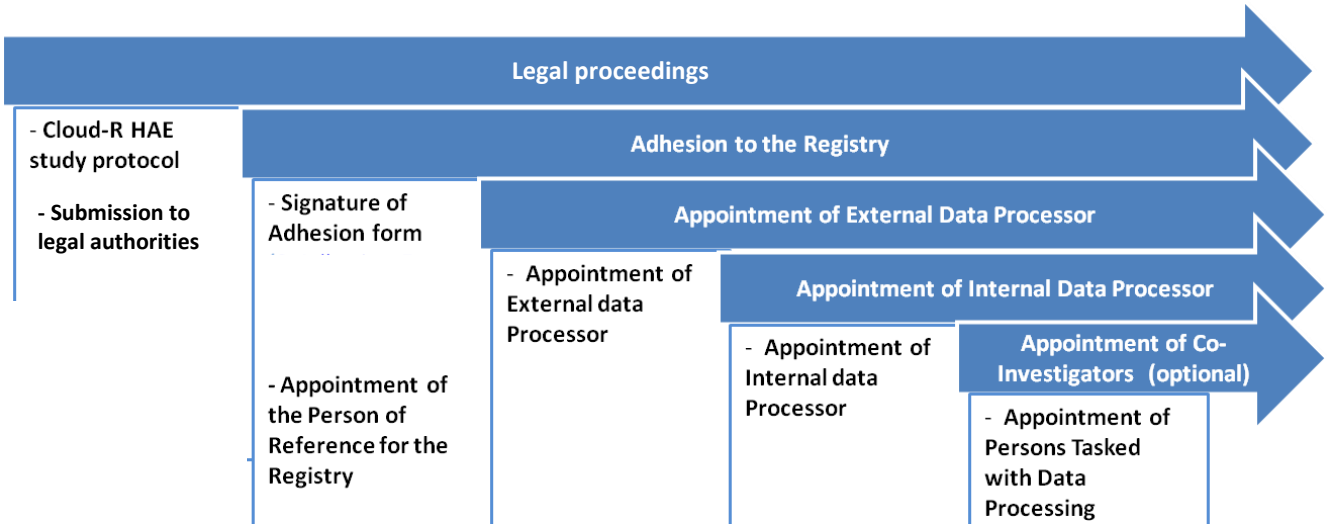
13. PUBLICATIONS

The Register Committee will agree in releasing periodic public outputs of aggregated data in form of newsletter or similar supports. For scientific publications each center or aggregation of centers (National / Regional) is allowed to use its own data without any additional permission. Each center is allowed to propose scientific publications based on aggregated data and the Register Committee will be responsible for providing the permissions.
Additional analysis required or to be presented to the health / regulatory authorities, to the IEC and to the investigators will be processed in accordance to national / regional laws.

14. FINANCIAL SUPPORT

The financial support to the study will be given by patients/scientific associations or through liberalities and/or research funds of the promoter and/or investigators.

15. DOCUMENTS FLOW OF THE PROCEDURE FOR COORDONATOR REGISTRATION TO THE STUDY



16. MANAGEMENT OF ASSOCIATED CENTERS AND ROLE OF THE COORDINATOR CENTER

16.1 Role of the National Angioedema Reference Center (CREAK)

The Grenoble center is the registry coordinator at the national level. It will contract directly with the Cloud R Company and will be in charge of coordinating the associated centers. It will therefore send the necessary documents for the good execution of the study, will ask each center to respect the current French regulatory, will organize and finance the set-up of the register in the associated centers. The coordinating center will also centralize requests for data, publications or creation of additional eCRF pages of associated centers. It will be able to organize a national scientific committee every 6 months. It will thus be the link between the French centers, the scientific committee of the registry and the company Cloud R.

The coordinating center will also be responsible for enter and reliability of patient data from it center, as well as the associated centers.

16.2 Role of associated centers

Associated Centers will be responsible for capturing and data reliability of their patients in eCRF, they will also create a personal account for each patient so that it can download the application “cloud R HAE carnet de suivi”.
Investigators referent patient will have validated at each visit or after contact with the patient crisis returned to the patient via it electronic diary.

Associated Centers will keep informed twice a year the coordinator center of the state of inclusions in the register.

17. REGULATIONS RELATED TO THE FRENCH REGISTRY

17.1 CNIL

The database will be stored, managed and analyzed by Cloud-R s.r.l as described above.
The data will be transmitted by eCRF. They will be entered on each site by the team of the local scientific officer (doctors or clinical research assistant).

The Data controller adheres to the reference methodology of the CNIL, MR004. Each associated center undertakes to respect the collection of data in accordance with the regulations in force.

17.2 Archiving

The following documents will be archived by the name of the study on service of the principal investigator center until the end of the period of practical use (at least 15 years).
These documents are:

- Protocol and annexes, possible amendments,
- Information forms and signed original consents

The personal data of the patients will be stored in their medical file.

17.3 Confidentiality of data

The data recorded during this research are the subject of a computerized treatment in compliance with the law 2018-493 of 20 June 2018 on the protection of personal data. The data processing is implemented under Article 9 of Regulation 2016/679 EU.

In accordance with current legislation (Articles L.1121-3 and R.5121-13 of the Public Health Code), persons having direct access to data will take all the necessary precautions to ensure the confidentiality of information relating to the researches, to the people who lend themselves to it and in particular as regards their identity as well as to the results obtained. These people, like the doctors themselves, are subject to professional secrecy.

During the research or its outcome, the data collected on people who are appropriate and transmitted to the controller by doctors (or other specialist stakeholders) will be made anonymous. They must not in any case show in clear the names of the persons concerned or their address.

Coding of patients will be done using the first letter of the name, then the first letter of the first name, then the number of the site that includes.
The documents establishing the correspondence between the subject's code and his identity will be kept by each site.

17.4 Information of patient

Patients should be informed fully and faithfully, in understandable terms, the objectives of the study and the nature of the information collected, and their right to object at any time to the use of collected data.

If the patient objects to the processing of his personal health data for research purposes, the opposition will be recorded in his medical file. This right of opposition is exercised at any time by any means from either the research manager or the institution holding the data that undertake to respond to this request within a maximum period of 2 months.

18.3 Amendment and modification of protocol

Any substantial modification, i.e. any modification likely to have a significant impact on the protection of persons, on the conditions of validity and on the results of research, on the interpretation of scientific documents that support the development of the research or the modalities of its conduct, is the subject of a written amendment that may be submitted to CEREES and CNIL in case of non-compliance with the MR004.

All the amendments are validated by the data controller and by all the actors concerned by the modification, before submission.
All amendments to the protocol should be made known to all investigators involved in the research agree to respect the content.

18. LIST OF ANNEXES

Annexe I : eCRF

Annexe II : Information forms and consents

19. ESSENTIAL BIBLIOGRAFY

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