SPANIK-HF Study

SPANISH MULTICENTRIC STUDY OF HYPERKALAEMIA PREVALENCE, INCIDENCE AND PROGNOSIS IN PATIENTS WITH HEART FAILURE AND REDUCED EJECTION FRACTION

[Tracking code: ESR-17-13244]

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SUMMARY

1. Promoter

Sociedad Española de Cardiología

2. Title of the study

SPANISH MULTICENTRIC STUDY OF HYPERKALAEMIA PREVALENCE, INCIDENCE AND PROGNOSIS IN PATIENTS WITH HEART FAILURE AND REDUCED EJECTION FRACTION

3. Main Researchers

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Dr. Javier Segovia, Madrid

Dr. Luis Miguel Rincón Díaz, AISEC, Madrid

5. Participant centres and researchers

20 National Public Health System hospitals. Cardiology specialist physicians

6. Clinical Research Ethics Committee (CREC)

Hospital 12 de Octubre, Madrid

7. Main goal

To estimate prevalence and, in medium term basis (12 months), incidence of hyperkalaemia in heart failure (HF) outpatients with reduced ejection fraction (REF) and its relationship with non-optimal HF therapy and clinical outcomes (mortality and hospital admission).

8. Specific goals

a. –Estimating Hyperkalaemia prevalence in these patients.

b. -Assessing the role of hyperkalaemia with the use of non-optimal therapy doses.

c. –Estimating 12 months hyperkalaemia incidence on these patients and describing the severity of the episodes.

d. -Estimating incidence of HF hospital admission and/or death in these patients on a medium term basis (12 months) and its association with existence of hyperkalaemia during follow up.

e. –Assessing hyperkalaemia risk during follow-up in relation with the existence of diabetes and/or renal failure (RF) at baseline visit.

9. Study design

National multicentric prospective observational study that includes 12 months follow-up of consecutive cases of HF outpatients with REF. Inclusion baseline visit and follow – up visits at 12 months will be scheduled for collecting clinical and blood sample data of patients.

10. Study population

The expected number of patients recruited in 20 Spanish research centres is 600.

11. Chronogram

Preparation of documentation and protocol: October31st 2018

Identification and selection of coordinators and researchers: October 2018

Submission to “Agencia Española del Medicamento y Productos Sanitarios” (AEMPS): November 2018

Presentation to Clinical Research Ethics Committees: November 2018

Contract signature: December 2018

Design of case report form (CRF) and electronic case report form (eCRF): January-March 2019

Dispatch to centres for assessment and approval: January-February 2019

Inclusion date for first patient: April 2019

Inclusion period: April 2019 – October 2019

Intermediate analysis and presentation of results: second semester 2019

End of 12 months follow up of the last patient: October 2020

Final analysis and presentation of definitive results: second semester 2020

12. Promoter and Coordinator Centre data

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1. BACKGROUND AND RATIONALE

In the last years, multiple reasons have been increasing the disease burden of heart failure (HF) in industrialised countries – also Spain -, being a very important health problem. It is foreseeable that this burden will continue increasing in our country[1].

In parallel with this evolution, several treatments already included in clinical practiceguidelines[2, 3], have proved to be effective in selected groups of patients, especially those with systolic function impairment.

These treatments that interfere with the renin-angiotensin-aldosterone system, increase hyperkalaemia risk in HF patients as much as three times[3, 4].Hyperkalaemia is associated with conduction disorders and risk of potentially life-threatening arrhythmias; it is not rare at all, as 20 years ago estimations already indicated 1-10% prevalence in hospitalised patients [5]. More recent data among ACEI new users suggest in the first year 5,6% and 1,7% for potassium values >5 and >5,5 respectively.[6] HF patients are at increased risk of hyperkalaemia, not only due to the drugs they receive (ACEIs/ARB-II, mineralocorticoids receptor antagonists (MRAs) and, more recently, sacubitril/valsartan), but also because of the frequent presence of comorbidities (diabetes or renal failure, among others).[7]

These drugs blocking the renin-angiotensin-aldosterone system have an IA indication in the clinical practice guidelines for patients with reduced ejection fraction, so their use is becoming more frequent and, subsequently, hyperkalaemia is a growing concern for treating HF patients. [7]

Despite the above mentioned, there is no evidence of prospective information for the estimation of hyperkalaemia problem in HF patients in the daily Spanish clinical practice, although some current registries allows an initial estimation of its prevalence. In a recent analysis of the patients included in Spain in the Heart Failure Registry of the European Society of Cardiology (ESC) [8] 26,3% of patients (401/1526) where MRAs are indicated (REF), but not prescribed, the underlying reason for not prescription is Hyperkalaemia in 8,5% of them (34/401). There are many “not-prescriptions” that are not adequately justified, therefore hyperkalaemia has a larger prevalence (30,6%, 34/111) among cases where a cause for avoiding MRAs does exist. At least as important is the fact that the vast majority of patients, up to 3 of 4, do not reach the

MRA goal doses and hyperkalaemia is registered as a reason in 10% of cases. This transversal information suggests that hyperkalaemia is a problem that deserves greater attention due to its negative role in HF therapy. In addition, very recent data from a single centre in Spain indicate that normalization of altered potassium levels improves prognosis.[9]

On the basis of the above described, it is proposed to carry out a prospective registry that which would help in completing the existing information for achieving the goals described later on.

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2. GOALS

2.1. Main goal

To estimate prevalence and, in medium term basis (12 months), incidence of hyperkalaemia in heart failure (HF) outpatients with reduced ejection fraction (REF) and its relationship with non-optimal HF therapy and clinical outcomes (mortality and hospital admission).

2.2. Specific goals

a. - Estimating Hyperkalaemia prevalence in these patients.

b. - Assessing the role of hyperkalaemia with the use of non-optimal therapy doses.

c. - Estimating 12 months hyperkalaemia incidence on these patients and describing the severity of the episodes.

d. - Estimating incidence of HF hospital admission and/or death in these patients on a medium term basis (12 months) and its association with existence of hyperkalaemia during follow up.

e. - Assessing hyperkalaemia risk during follow-up in relation with the existence of diabetes and/or renal failure (RF) at baseline visit.

3. STUDY DESIGN

National multicentric prospective observational study that includes 12 months follow-up of consecutive cases of HF outpatients with REF. Inclusion baseline visit and follow – up visit at 12 months will be scheduled for collecting clinical and blood sample data of patients indicated later on in this protocol.

The study will be performed in ordinary conditions of clinical practice; no additional procedures or interventions will be performed. Patients will be selected in cardiology outpatient clinics of 20 Spanish centres, including the first 30 patients meeting inclusion and exclusion criteria. All patients will undergo the common studies according to usual clinical practice and at least both, potassium and renal creatinine clearance values will be collected.

To respond to the main objective, prevalence of hyperkalaemia (as defined later in the protocol) at baseline will be determined as well as the appearance of new hyperkalaemia cases in the follow up of patients that had normal potassium levels at baseline visit; their relationship with outcomes of interest will also be determined.

Variables to be collected at each visit are indicated in appendix 1.

3. 1. Definition of the study population and selection criteria

The study population is composed of HF outpatients with REF from excellence Spanish centres.

The study will be performed in 20 Spanish centres, either SEC HF- excellence certified, integrating official research networks or with excellent performance proven in previous similar initiatives (relation of centres and researchers in Appendix 2).

Every centre will include the first 30 consecutive cardiology outpatients who fulfil the inclusion criteria and that do not present any exclusion criteria. All pre-screened patients will be indicated, together with the reason of their exemption if occurs.

Inclusion criteria

1. Patients, women or men, aged 18 or more
2. Documented HF with REF (<40%) diagnosis
3. Signed written informed consent

Exclusion criteria

1. Any type of disorder affecting the capacity to give free and informed written consent
2. Clinical trial enrolment at the moment of the inclusion
3. Patients suffering stage 5 chronic kidney disease
4. Patients with less than a year life span due to diseases different from HF
5. Not having completed HF drug titration stage at the moment of inclusion (this stage is not completed if, on doctor's judgement, possible maximum doses have not been reached in RAA system drugs and any of these drugs has been included or dose-modified in recruitment visit)
6. Informed consent refusal

At any time during follow-up patients can leave the study (and will be censored in the analysis) or retire their consent (and will be excluded from the analysis).

3. 2. Considerations about simple size

Assuming a 10% risk of outcomes (mortality or HF hospital admission) among the exposed (hyperkalaemia), 2.5% among the non-exposed and a 7:1 non-exposed/exposed ratio, 73 exposed and 511 non-exposed patients should be included to have a 80% power to detect these differences with a 95% confidence level. The recruitment goal is set at 600 patients.

This sample size allows a precision of ±2,4%, assuming a prevalence of hyperkalaemia at baseline of 10% and with a 95% confidence level. Furthermore, assuming 5% hyperkalaemia cumulative incidence through follow-up among hyperkalaemia-free patients at baseline, the proposed sample size, allows a precision of±1,8% with a 95% confidence level.

3. 3. Selection of centres

The number of participant centres throughout Spain will be 20 and a cardiologist will be the principal investigator at every centre. The centres have been selected either among those with excellence-certified HF units, included in CiberCV Consortium or

with good performance in previous similar registries; this selection is not random, but based on interest and high performance criteria in the field of HF.

3. 4.- Source of information

Data will be obtained directly from the participants at the planned visits and completed with the review of their medical records if needed.

3. 5. Variables and CRF (appendix 1)

The main outcome variables are:

a.- Hyperkalaemia. Serum Potassium (K^+) will be measured in baseline and follow-up visits, but also if there is any intermediate hospital admission. All available potassium measurements during follow-up will be reviewed and values of hyperkalaemia identified. Hyperkalaemia will be considered with (K^+) Values > 5,4 mEq/L

b.- Proportion of patients using drugs with proven efficacy for HF with REF -but also linked with hyperkalaemia- (ACEIs/ARB-II/ARNI and MRAs) and proportion of patients with use of optimal doses (based on current ESC heart failure guidelines[2]) of the same drugs; reason for not using them (or not receiving optimal doses) will be registered. Proportion of patients in the following categories will also be computed:

- No ACEi/ARB/ARNI or at less than target dose and no MRA
- ACEi/ARB/ARNI at target dose and no MRA
- ACEi/ARB/ARNI at target dose and MRA at less than target dose
- ACEi/ARB/ARNI at target dose and MRA at target dose

c.- Hospital admissions during follow-up and main cause for them. Outcomes considered will include HF admissions caused by hyperkalaemia and related events. Outcome Serum (K^+) values will be also registered.

d.- Mortality and cause.

HF (and hyperkalaemia) hospital admissions and mortality will be independently considered as outcomes; joint outcome incidence of both will be also calculated.

The remaining variables are set out in appendix 1. The most important variables are defined in section 4.

3. 6. Study development

Every participating centre will include from inclusion date (as described in section 3.1) the first 30 heart failure outpatients who fulfil the inclusion criteria and none of the exclusion ones. The excluded patients will be also registered, pointing out the reason of exclusion. The data to be collected during the initial visit will include the variables described in Appendix 1: demographic, clinical, blood sample test, and functional. A follow-up and final visit will be scheduled after 12 months for collecting all the variables the study requires (Appendix 1). Hospitalisation data since inclusion visit will be also collected, together with the information of blood sample test performed in such period for detecting hyperkalaemia episodes. Mortality data will include date and cause, where possible. If follow-up visit cannot be conducted, the reason for it will be registered. The collection and management of data is described in section 5. The envisaged length of the study is 24 months since approval date.

3. 7. Limitations

Mild elevations of serum potassium that do not lead to hospital admission between planned visits may go unnoticed.

4. DEFINITION OF VARIABLES OF INTEREST

Heart Failure (HF) with reduced ejection fraction (REF): Patients with confirmed diagnosis of HF and with ejection fraction<40%.

Hyperkalaemia: K^+values> 5,4 mEq/L.

Optimal doses: the maximum doses of renin-angiotensin-aldosterone related drugs that, according to the physician's judgement, the patient can receive. If any of these drugs (ACIEs, ARB-II, MRAs or sacubitril-valsartan) is *de novo*introducedat the initial visit, optimal doses will be not considered established.

A previous personal history of diseases and/or outcomes will be registered according to the usual practice of every centre. Some of the clarifications needed in every case are indicated as follows:

- **Coronary artery disease.** Documented existence of any of the following:acute myocardial infarction (AMI), acute coronary syndrome (ACS), coronary revascularisation (Percutaneous Coronary Angioplasty –PCA - or CABG) or coronary stenosis > 50% of arterial lumen in imaging test.
- **Cerebrovascular diseases.** History of ischaemic/haemorrhagicstroke or carotid stenosis > 50% of arterial lumen in imaging test.
- **Peripheral artery disease.** Aneurysm of thoracic/abdominal aorta or lower limb peripheral arterial disease.
- **Death due to a major cardiovascular event.** Due to ACS, HF, arrhythmia (sudden death), arterial aneurysm rupture or stoke.
- **Arterial thromboembolism.** Embolism phenomenon affecting arterial territory – (except pulmonary territory).
- **Ischaemic stroke.** Focal neurological deficit originated by cerebral ischemia; persists more than 24 hours after a sudden onset.

- **Haemorrhagic stroke:** Focal neurological deficit with sudden onset and originated by intracranial haemorrhage.
- **Acute coronary syndrome (ACS):** Acute coronary event that present typical ECG alterations and/or enzyme elevation.
- **NYHA functional class:**

Functional class I	No limitation. Ordinary physical activity does not cause dyspnoea, fatigue or palpitations.
Functional class II	Light limitation of physical activity. Everyday activities cause dyspnoea, fatigue or palpitations
Functional class III	Moderate limitation of physical activity. Activities considered less intense that everyday ones cause dyspnoea, fatigue or palpitations. Patient, however, does not present resting dyspnoea.
Functional class IV	Inability to perform activities without limitations. Symptoms may be present even at rest

- **Anaemia**

  Haemoglobin values <12 g/dl in blood sample tests performed during the previous 3 months are considered as anaemia; this is the lower value of the normal range for adult men and postmenopausal women.

- **Diabetes (and type)**

  Considered when personal history reflects diabetes diagnosis (and type).

- **Arterial hypertension**

  Personal history reflecting HTA established diagnosis and/or therapy with antihypertensive drugs

  A hypertensive patient will considered as controlled when PA<140/85 mmHg.

- **Dyslipidaemia**

  Considered when personal history reflects dyslipidaemia diagnosis.

- **Body mass index (BMI):**
  - Overweight: BMI (Kg/m^2) 25-29,9
  - Obesity: IMC (Kg/m^2) ≥30

- **Renal function**.

  It will be assessed according glomerular filtration rate as follows:

  Stage 1 (GFR>90 ml/min/1,73 m2)

  Stage 2 (GFR ≥ 60 y <90 ml/min/1,73 m2)

  Stage 3 (GFR ≥ 30 y <60 ml/min/1,73 m2)

  Stage 4 (GFR ≥ 15 y <30 ml/min/1,73 m2)

  Stage 5 (GFR <15 ml/min/1,73 m2)

  When considered as a dichotomous variable, stages 1 and 2 will be considered normal and stages 3, 4 and 5 considered as *altered renal function*.

5. DATA COLLECTION AND MANAGEMENT

5. 1. Data collection

Consecutively, every researcher will handle and explain the information sheet to the patients that might fulfil de inclusion criteria (and do not present any exclusion criteria) and will ask them to sign the informed consent. Researchers must warrant the accuracy and completion of the data collected for the study. Data registered at CRF (Appendix 1) should be consistent with source documents used for their collection.

5. 2. Data management

Data will be collected during initial and follow-up visits and they will be integrated into a unique data base of the web platform. Researchers are responsible of the information included in the database and will access by means of personal login and password. The online platform will include ranges and rules to minimize errors in data registering.

5. 3. Quality assurance

To improve uniformity of interpretation of criteria and/or procedures among centers, researchers may contact the promoter, *Sociedad Española de Cardiología* at the *Agencia de Investigación de la SEC* in order to solve any questions or problems that arise during the study:

Agencia de Investigación de la SEC. gcespedes@secardiologia.es. Tel: 91 724 23 70. Fax: 91 724 23 71

Or directly with the project office:

ODDS, S.L.; proyectos@odds.es; Telf.- 981216391; Fax.- 981217539

While there is no planned monitorization of data quality, the promoter can, if convenient, carry out an audit of the participant centres in order to ensure the compliance with best practices during the study.

6. PLAN FOR DATA ANALYSIS

Hyperkalaemia prevalence at basal visit and the rate of patients who do not receive and/or reach optimal doses of drugs of interest (ACIEs, ARB-II, MRAs) will be estimated and their corresponding 95% confidence intervals computed. The reason for not receiving and/or reaching optimal doses of drugs will be described, especially if it is due to hyperkalaemia.

For those patients who do not present hyperkalaemia at baseline, 12 month hyperkalaemia cumulative incidence (95% confidence interval) will be estimated; also it will be estimated the proportion of patients who have to modify their therapy due to hyperkalaemia.

The number of episodes of hyperkalaemia during follow-up in relation to the number of patients will be estimated and their severity and the therapy changes that induced described. Also 12 months cumulative incidence of clinical outcomes will be estimated: hospitalisation due to HF or to, hyperkalaemia (and related events) and mortality, considered as individual and composite outcomes. The association between hyperkalaemia and occurrence of outcomes will be analyses and also adjusted using potential confounding factors by means of logistic regression models

The quantitative variables will be generally described using either the mean and the standard deviation or the median and interquartile range according them following or not a normal distribution. When comparing groups, t-student test will be used for continuous variables and chi-share test for qualitative ones.

Both, intermediate and final analysis, are planned to be carried out after baseline-visit closure and at the end of follow up (12 months).

7. ETHICAL AND SECURITY ISSUES

The present study will be assessed by the Clinical Research Ethics Committee of the *Hospital 12 de octubre*, Madrid. The involved patients will sign an informed consent (Appendix 3). This study will carried out, as any other research with humans, in accordance with the ethical principles reflected in the Declaration of Helsinki and its subsequent amendments. The study will also comply with all the requirements laid down in current Spanish regulations on the subject of personal data protection.

Interference with the prescription habits of the attending physician

Given the observational nature of the study, participating in it does not interferes with the prescription habits of the attending physicians.

Control and report of adverse reactions

The main exposure of interest in this study is not a drug but in case that this study is classified as EPA-SP by AEMPS and according the legislation contained in *orden "SAS/347072009, de 16 de diciembre para estudios EPA-SP"*, the suspected adverse reactions that might be detected over the course of the study will be notified by the sponsor (*Sociedad Española de Cardiología*), following the instructions published by the AEMPS (Agencia Española del Medicamento y Productos Sanitarios). Additionally, any relevant security event detected during the study should have to be reposted to AEMPS and to the competent organs of the concerning autonomous communities (AACC).

A.- Definitions

A.1.- Adverse event

An adverse event (AE) is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, electrocardiogram). The term AE is used to include both serious and non-serious AEs.

A.2.- Serious adverse event

A serious adverse event (SAE) is an AE occurring during any study phase that fulfils one or more of the following criteria:

- Results in death.
- Is immediately life-threatening.
- Requires in-patient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital abnormality or birth defect.
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the above criteria. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

B.- Recording of adverse events

Adverse Events will be collected from time of signature of informed consent throughout the end of follow-up. All ongoing and any new AEs/SAEs identified during the follow-up period must be followed to resolution. If an Investigator learns of any SAEs, including death, at any time after a patient has completed 30 post follow-up period, and he/she considers there is a reasonable possibility that the event is causally related to the study treatment, the investigator should notify the sponsor by reporting the SAE.

The following variables will be collected for each AE:

- AE (verbatim).
- The date when the AE started and stopped.
- Whether the AE is serious or not.
- Investigator causality rating against the Investigational Product (yes or no).
- Action taken with regard to investigational product.
- Outcome.

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE.
- Date Investigator became aware of serious AE.
- AE is serious due to.
- Date of hospitalization.
- Date of discharge.
- Probable cause of death.
- Date of death.
- Autopsy performed.
- Description of AE.
- Causality assessment in relation to Study procedure(s).
- Causality assessment in relation to Other medication.

C.- Sponsor Responsibility for Reporting SUSAR´s

The investigator will report immediately (first 24 h) any SAE by means of filling and sending the corresponding form [Appendix 5] to the CRO (ODDS, S.L.) by fax [981 217539] or e-mail [proyectos@odds.es].

The sponsor/CRO must inform the AEMPS of any adverse events (AE) that occur in accordance with the reporting obligations. It is the responsibility of the sponsor to compile all necessary information and ensure that the AEMPS receives a report according to the AEMPS reporting requirement timelines.

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to the AEMPS.

All SAEs will be documented. The sponsor is responsible for informing the Regulatory Authority of the AE as per local requirements.

Risk/benefit assessment for patients

Given that the study is observational, the participation does not involve any risk for patient. A better knowledge of the pathology after the study could lead to future health benefits. The study will be carried out in the context of daily clinical practice and does not impose any restrictions to the researcher physician, with no bearing on therapy or follow-up.

Patient information and informed consent (Appendix 3)

The patients will be provided with information of the study by means of the information sheet and oral explanation. The physician will solve the doubts that may arise. All the included patients will receive an informed consent form that should be signed to participate in the study, participation that can be cancelled at anytime.

Data confidentiality

Personal data are confidential. The identity of patients cannot be revealed or disclosed except in those cases stipulated by law. Patients will be identified by means of a code that only their physician could associate with them. All data will be managed according to REGULATION (EU) 2016/679 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data.

8. PRACTICAL ISSUES

8. 1. Working plan and chronogram

Preparation of documentation and protocol: October31st 2018

Identification and selection of coordinators and researchers: October 2018

Submission to "Agencia Española del Medicamento y Productos Sanitarios" (AEMPS): November 2018

Presentation to Clinical Research Ethics Committees: November 2018

Contract signature: December 2018

Design of case report form (CRF) and electronic case report form (eCRF): January-March 2019

Dispatch to centres for assessment and approval: January-February 2019

Inclusion date for first patient: April 2019

Inclusion period: April 2019 – October 2019

Intermediate analysis and presentation of results: second semester 2019

End of 12 months follow up of the last patient: October 2020

Final analysis and presentation of definitive results: second semester 2020

8. 2. Baseline and final reports

The data will be analysed twice: after the closure of baseline visit and at the end of the study.

8. 3. Dissemination of results

The principal investigator is committed to dissemination of results through scientific journals and/or meetings and guaranteeing confidentiality of personal data. Once the statistical analysis done, the Scientific Committee will issue the Final Results Report that will be presented to all the participants following format and method previously agreed. Partial and global study data could be used in general publications and in national as well as international congresses but always referring the study. Authorship will be vested in those responsible for the preparation (Scientific Committee and/or Technical Coordination or designated researcher); the remaining participants of the study will be mentioned into a group of researchers. If publication rules allow, all the main researchers will be individually mentioned. The participant researchers could publish their individual data; in such case, the researcher/s shall notify the Scientific Committee this circumstance by sending the communication/manuscript that is being intended to publish at least 30 days prior to the presentation to the congress/meeting or journal.

8.4 Organisation of the study

8.4.1. Responsibility of *Agencia de Investigación de la SEC* (supported by the project office)

- General coordination of the study
- Control of logistics and deadline compliance
- Elaboration of the protocol (together with the main researcher) and case report form
-Logistic and administrative issues (committee submissions, contracts with researchers, economic management, communications, mail, etc.)
- Monitoring of the study
- Preparation of intermediate and final reports

8.4.2. Responsibilities of the participant researchers

- Acceptance and a commitment to follow all the rules and procedures of the study
- Facilitate data monitoring and quality control
- Compliance with ethical and legal principles of clinical research
- Collaborate with the Scientific Committee and with the *Agencia de Investigación de la SEC* when requested in order to facilitate an optimal progress of the study.

8.4.3. Functions of the Scientific Committee

- Elaboration of the protocol and case report form
- Review the documentation of the study and data base
- Assess the results of the study
- Review data analysis and prepare the conclusions and the publications