CLINICAL TRIAL PROTOCOL

"CONTROLLED, DOUBLE-BLIND, ANDA RANDOMIZED CLINICAL TRIAL FOR QUETIAPINE PROPHYLAXIS OF POSTOPERATIVE DELIRIUM IN AT-RISK SURGICAL PATIENTS."

PROMOTER: IBSAL-Instituto de Investigación Biomédica de Salamanca

PROTOCOL CODE: **QUEPRO**

EudraCT No.: 2016-004117-27

VERSION 2.0, dated April 3, 2019

PROTOCOL SIGNATURES PAGE

Promoter's Statement:

PROTOCOL TITLE: RANDOMIZED, DOUBLE-BLIND, CONTROLLED CLINICAL TRIAL FOR QUETIAPINE PROPHYLAXIS OF POSTOPERATIVE DELIRIUM IN AT-RISK SURGICAL PATIENTS

PROTOCOL CODE: **QUEPRO**

EudraCT No.: 2016-004117-27

Representative of the promoter: Rogelio González Sarmiento

_____

Company

Date

Signature of the Coordinating Researcher:

PROTOCOL TITLE: RANDOMIZED, DOUBLE-BLIND, CONTROLLED CLINICAL TRIAL FOR QUETIAPINE PROPHYLAXIS OF POSTOPERATIVE DELIRIUM IN AT-RISK SURGICAL PATIENTS

PROTOCOL CODE: **QUEPRO**

EudraCT No.: 2016-004117-27

Researcher Coordinator of the Study: Elisa Sánchez Barrado.

_____

Company

Date

Principal Investigator's Signature Page

PROTOCOL CODE: **QUEPRO**

EudraCT No.: 2016-004117-27

CONFIDENTIALITY AND DECLARATIONOF CONFORMITY OF CBS

I have read the protocol of the previous clinical study entitled: "RANDOMIZED, DOUBLE-BLIND, CONTROLLED CLINICAL TRIAL FOR QUETIAPINE PROPHYLAXIS OF POSTOPERATIVE DELIRIUM IN AT-RISK SURGICAL PATIENTS" and agree that it contains all the information necessary to conduct the study.

I hereby confirm that I have thoroughly read and understood this clinical study protocol, and I agree that my staff and I will conduct the study in accordance with the protocol and comply with its requirements, including ethical and safety considerations.
I understand that if the Promoter decides to terminate or suspend the study prematurely for any reason, such decision will be communicated to me in writing. On the contrary, if I decide to withdraw from the execution of the study, I will immediately communicate this decision to the Promoter.
I agree not to publish any part of the results of the study conducted under this clinical study protocol without the prior written consent of the Sponsor.

Principal Investigator ____

Hospital Center ____

_____

Company

_____

Date

ABBREVIATIONS

AA	Adverse Event
AAG	Serious adverse event
AEMPS	Spanish Agency for Medicines and Health Products
APACHE II	Acute Physiology And Chronic Health Evaluation II
AUC	Area under the curve
Good	Blood Urea Nitrogen
C.A.U.S.A	University Assistance Complex of Salamanca
CAM	Confussion Assessment method
CDR	Data Collection Notebook
CEIm	Committee on the Ethics of Research with Medicinal Products
IC	Confidence interval
CI	Informed consent
CTCAE	Common Toxicity Criteria for NCI Adverse Event
Cro	Contract research organisation
DRS-R-98	Delirium Rate Scale-Revised-98
DSM IV	Diagnostic and Statistical Manual of Mental Disorders
EVA	Visual Analog Scale
GBPC	Good Clinical Practice Guide
IBSAL	Biomedical Research Institute of Salamanca
Me	Resident Intern
NCI	National Cancer Institute
p.e.	For example
PCR	C-reactive protein
RAGI	Serious and Unexpected Adverse Reaction
RASS	Richmond Agitation sedation Scale
REec	Spanish Registry of Clinical Studies
SF-36	Health-Related Quality of Life Questionnaire
SNC	Central nervous system

1. SUMMARY AND GENERAL INFORMATION

1.1TYPE OF APPLICATION

Non-commercial low-intervention clinical trial

1.2IDENTIFICATION OF THE PROMOTER

Fundación Instituto de Estudios Ciencias de la Salud de Castilla y León (IECSCYL)- Instituto de Investigación Biomédica de Salamanca (IBSAL).

IECSCYL-IBSAL Foundation.

1.3TITLE OF THE CLINICAL TRIAL

Randomized, double-blind, controlled clinical trial for quetiapine prophylaxis of postoperative delirium in at-risk surgical patients.

1.4PROTOCOL CODE

QUEPRO

1.5COORDINATING AND PRINCIPAL INVESTIGATOR

Elisa Sánchez Barrado. Anesthesia, rehabilitation and pain treatment service. C.A.U.S.A

1.6CENTRES WHERE THE STUDY IS PLANNED

University Assistance Complex of Salamanca

1.7CEIM

Committee on Research Ethics with medicines Salamanca Health Area

1.8RESPONSIBLE FOR MONITORING

Monitor: Esperanza López Franco

Coordinator in the Promoter: Carmen Arias De La Fuente. Clinical Trials Area. IBSAL

RESPONSIBLE FOR PHARMACOVIGILANCE:

Patricia Rodríguez Fortúnez (UICEC H. Universitario de Canarias)

1.9.DESCRIPTIONOF STUDY PRODUCTS.

Experimental treatment and control

Quetiapina (experimental) vs placebo (control)

Route of administration: oral

Experimental: quetiapine 25 mg gelatin capsule-coated tablets. Cada tablet contains 25 mg of q uetiapina (as quetiapine fumarate). Excipient: lactose 18.5 mg

Therapeutic group: N05A H04. Antipsychotics: diazepines, oxacepines and thiazepines.

Anatomical Group: (N) Nervous system

Placebo: gelatin capsule.

1.10 CLINICAL TRIAL PHASE
Phase III

10.11OBJECTIVES
Main: to know the incidence of postoperative delirium in patients at risk, over 65 years of age, treated early with prophylactic quetiapine compared to those treated with placebo.

Side:

1. Evaluate the safety and tolerability of the medication applied
2. To compare the efficacy of medication versus placebo in relation to:
   - length of hospital stay
   - perceived quality of life
   - all-cause mortality at discharge and 28±2 days from initiation (1st dose) of quetiapine treatment.
3 In cases where delirium develops, know:
   - Time of appearance
   - the duration and severity of the same
   - Total dose of treatment with other antipsychotics.

1.12STUDY DESIGN
Prospective low-level non-commercial, balanced, randomized, double-blind clinical trial (phase III) clinical trial.

1.13STUDY DISEASE
Delirium developed during the period after surgery.
Delirium is an acute alteration of consciousness accompanied by inattention, disorganization of thought and alterations of perception that fluctuate in a short period of time (DSM IV). It is one of the most frequent complications of surgery and develops characteristically between 0-96 h after the intervention. It is associated with worse prognosis in the short and long term.

1.14STUDY VARIABLES
A. The main variable is the proportion of patients diagnosed with delirium (number of delirium cases/total number of patients) in the first 4 postoperative days in both branches.
B. Secondary variables:
   1. number of days from the start of treatment to the onset of delirium, if it appears,
   2. duration of delirium, in days,
   3. severity of delirium measured with validated scale (DRS-R-98)
   4. total dose (mg) haloperidol or another antipsychotic to control symptoms of delirium,
   5. Security variables:
      - degree of sedation: by RASS scale,
      - QTc prolongation: increase in mseg on the control ECG.
      - presence or absence of extrapyramidal symptoms (tremor, involuntary movements, stiffness)
   6. days of hospital stay since surgery,

7. perceived quality of life (through SF36 validated questionnaire) 28±2 days after initiation of treatment,
8. All-cause mortality at discharge and 28±2 days after initiation of treatment

1.15STUDY POPULATION AND TOTAL NUMBER OF PATIENTS

Patients older than or equal to 65 years of age who are going to undergo major non-cardiac surgery and who have a score equal to or greater than 5 on the Delphi scale:

- Age: 70-79 years: 1 point; >80 years: 2 points
- Physical activity: need for assistance, not self-sufficient: 2 pointss
- Alcoholism: 1 point
- Hearing deficit: 1 point
- History of delirium: 2 points
- Urgent surgery: 1 point
- Non-laparoscopic surgery: 2 points
- Admission to Critical Care Units: 3 points
- C-Reactive Protein (CRP) value > 10 mg/dL: 1 point

The necessary sample size will be 350 patients, 175 patients per branch (control and experiment).

1.16DURATION OF PROCESSING

The duration of the treatment will be three days included in the early postoperative phase. Quetiapine will be administered orally to the patientsof the experimental group 60 minutes after arrival at Resuscitation/Post-Anesthetic Recovery Unit and thereafter every 12 hours until the 3rd postoperative day. Subjects in the control group will be given placebo in the same time and form as subjects in the experimental group.

1.17 CLINICAL TRIAL SCHEDULE.

The total duration of the clinical trial will be approximately 3 years. They include the period for approvals and coordination of the project, period of recruitment and monitoring, period or analysis of results and a final period for the publication of results.

1.18COLLABORATING INVESTIGATORS OF THE TRIAL

Dr. José María Calvo Vecino. Head of Service Anesthesiology, resuscitation and pain management. C.A.U.S.A - Biomedical Research Institute of Salamanca (IBSAL)

Dr. Luis Mario Vaquero Roncero. Medical assistant to the Anesthesiology, Resuscitation and Pain Treatment Service. C.A.U.S.A. - Biomedical Research Institute of Salamanca (IBSAL).

Dr. Domingo Bustos García. Medical assistant to the Anesthesiology, Resuscitation and Pain Treatment Service. C.A.U.S.A.

Dr. Azucena Hernández Valero. Medical assistant to the Anesthesiology, Resuscitation and Pain Treatment Service. C.A.U.S.A.

Dr. Miguel Vicente Sánchez Hernández. Head of section of the Anesthesiology, Resuscitation and Pain Treatment Service. C.A.U.S.A.

Dr. Antonio Rodríguez Calvo. Medical assistant to the Anesthesiology, Resuscitation and Pain Treatment Service. C.A.U.S.A.

Dr. Carolina Jambrina. Medical assistant to the Anesthesiology, Resuscitation and Pain Treatment Service. C.A.U.S.A.

Dr. María del Carmen Vargas. Assistant Physician Anesthesiology, Resuscitation and Pain Treatment Service. C.A.U.S.A.

Dr. Cristina Morales. Medical assistant to the Anesthesiology, Resuscitation and Pain Treatment Service. C.A.U.S.A.

Dr. Isabel Pingarrón. Medical assistant to the Anesthesiology, Resuscitation and Pain Treatment Service. C.A.U.S.A.

Dr. David Sánchez Poveda. Medical assistant to the Anesthesiology, Resuscitation and Pain Treatment Service. C.A.U.S.A.

Dr. María Pilar Arribas Pérez. Medical assistant to the Anesthesiology, Resuscitation and pain treatment service. C.A.U.S.A.

2 INDEX

3 JUSTIFICATION

According to the DSM-IV, delirium is an acute alteration of consciousness accompanied by inattention, disorganization of thought and alterations of perception that fluctuate in a short period of time. Postoperative delirium is one of the most common complications of surgery, with an incidence ranging from 10-51% in elderly patients at risk and up to 80% in those requiring critical care (1). It develops characteristically between 0 and 96 hours after the intervention (2) and is associated with a worse prognosis in the short and long term, with an increase in mortality and hospital stay and, therefore, an increase in economic expenses (3,4). The antipsychotic of choice for treatment is haloperidol (5,6), although its efficacy is limited in part by its side effects (mainly extrapyramidalism and prolongation of

the QTc interval) and lack of response in some patients. To solve these problems, second-generation or atypical antipsychotics appear, which have a more favorable safety profile with similar efficacy in clinical response (7). However, despite treatment, the prognosis does not seem to improve once delirium is triggered (4,8), so prophylaxis may be essential. Thus, although non-pharmacological prophylaxis measures (respect for wake-sleep cycle, pain control, early mobilization, providing visual and auditory aids...) have shown efficacy in reducing the incidence of delirium in this type of patients (4), this decrease is closely related to the complete follow-up of all measures, which implies a very important work overload without evidence of improvement in fundamental variables at discharge, such as functional or cognitive status (9). Therefore, pharmacological prophylaxis is gaining interest (4), although the evidence in the literature is limited. It seems logical to think that, just as antipsychotics are effective for the treatment of delirium, they will also be effective for pharmacological prophylaxis.

In this regard, a number of studies with haloperidol and atypical antipsychotics have presented variable results, possibly related to the quality of the studies, variability in the tools used for the diagnosis of delirium and the selection of high-risk patients. The first large randomized clinical trial was conducted in 430 postoperative hip replacement patients. It failed to demonstrate a reduction in the incidence of delirium when 1.5 mg haloperidol was administered orally divided into three doses, but the severity and duration of delirium decreased (10). Larsen (11), in 2010, tested olanzapine 5 mg orally in 400 patients and managed to demonstrate that the risk of developing delirium in the intervention group was lower (RR 0.36, 95% CI 0.24 to 0.52), although episodes of delirium were longer lasting and severe. In 2014, Fukata (12) administered 121 patients 2.5 mg of intravenous haloperidol daily after general, trauma or other surgery, and could not demonstrate a decrease in the incidence of delirium in the intervention group. And yet, Wang (1), using haloperidol in patients undergoing noncardiac surgery, demonstrated clinically significant incidence decreases. Despite the risk of bias in these studies, there was no evidence of adverse effects with the use of these antipsychotics at low doses.

We think that, within the group of atypical antipsychotics, quetiapine, due to its pharmacological profile (low affinity for dopamine receptors and μ receptors; high affinity for serotonergic receptors), could be useful in the prophylaxis of delirium and provide sedation without causing too many extrapyramidal effects (3) or precipitating acute episodes of delirium. In the current literature, there are no clinical trials with quetiapine for postoperative delirium prophylaxis but there are for the treatment of delirium. A series of randomized trials (7, 13,14) and one open-label trial (3) suggest that quetiapine may be effective and safe. Studies show faster resolution of symptoms than with placebo and find the same efficacy of other antipsychotics such as haloperidol, with low incidence of side effects, mainly drowsiness, without finding significant differences. The average dose used in these studies ranges from 40 mg to 200 mg, because they use increasing doses until symptoms are controlled. But there are studies that show efficacy with lower doses: 25-40 mg / day. They are studies carried out in the medical population and in critical care, and have certain limitations: n small, assessment of the effectiveness of treatment with quetiapine with different scales ... Even so, they would justify the use of quetiapine as prophylaxis at doses lower than those used for treatment. In this sense, there are two international clinical trials underway on postoperative delirium prophylaxis in the population at risk in critical care units, with an initial dose of quetiapine 12.5mg, in one of them adjusting for patient weight and the other with increasing doses as needed (15,16). Taking into account, in addition, that the clearance of the drug in patients over 65 years of age is decreased and, therefore, the half-life of the drug is extended in this population, we believe that the use of doses of quetiapine of 25 mg every 12 hours during the first three days of the postoperative period in patients at risk is justified.

One aspect to take into account is to determine the population at risk (in which we would suppose greater benefit of prophylactic measures), which can be complicated since until now there is no reliable

tool to detect patients at risk of developing delirium during the postoperative period (17). More and more risk factors for this condition are known that seem to be based on three variables (18): the first is the speed of onset of surgical aggression. Thishas been demonstrated in orthopedic surgery, where several studies show that urgent surgery is associated with increased risk of delirium. The second variable is severity: the greater the surgical aggression (for example aorta surgery or neurosurgery) and the longer the intervention, the greater the risk of delirium. Although there is little evidence linking increased risk of delirium with a drug or anesthetic technique, it currently appears that anesthetic depth plays an important role in the development of postoperative delirium with sufficient evidence (17,19). The last variable is the patient, in whom several risk factors have been identified: age (the older the older the greater the risk of delirium), cognitive deficit or dementia, depression, use of psychotropic drugs, associated comorbidity, degree of functionality (independent for activities of daily living)... (17-20).

In the work on the prophylaxis of delirium with antipsychotics, different tests have been used to identify patients at risk of developing delirium after surgery. One of the first was used by Kalisvaar to identify patients at risk of developing delirium after hip replacement surgery (21). Based on a scale of a study on delirium prophylaxis in patients undergoing general surgery, it used 4 items: visual deficit (measured with the Snellen test), APACHE II >16, Minimental Test > 24 and dehydration (BUN/creatinine ratio > 18). In this way, it classified patients with intermediate risk (if they had 1 or 2 items) or high risk if they had 3 or 4 (AUC 0.73). In 2014, Harasawa (22) used a new scale to predict the development of postoperative delirium in patients undergoing cerebrovascular surgery with a sensitivity of 71% and a specificity of 85.7%, area under the curve 0.844. It considers five variables: underlying disease (comorbidity), dehydration (nitrogen/creatinine index> 18), age >70 years, alterations in consciousness (Glasgow scale) and presence of depression-anxiety. Patients with a score greater than 12 were at increased risk of delirium. In that same year, in the published protocol of the HARPOON study (9), a multicenter trial that assesses the efficacy and safety of haloperidol prophylaxis in the prevention of delirium in elderly medical and surgical patients, they used three simple questions to identify patients at risk of developing delirium: about the patient's mental state (do they have memory problems?), on the degree of functionality (have you required help for your personal care in the last 24 hours?) and on the background (have you presented a state of transitory confusion during admissions or previous illnesses?). Each positive response scores as 1, and a score equal to or greater than 1 identifies a patient at risk. Except in this last study, the use of delirium risk predictor scales is complicated by the incorporation of other scales that hinder and slow down their realization. In this sense, in 2016 a delirium prediction scale was published to identify high-risk patients based on clinical data from the perioperative period: it is the Delphi method (23). The predictors used are: age, dependence for physical activities, alcoholism, hearing deficit, history of delirium, urgent surgery, open surgery, C-reactive protein value > 10 (mg/mL) and admission to critical care unit. A score equal to or greater than 7 classifies the patient as at high risk of developing delirium during the postoperative period. This predictor scale presents an area under the curve of 0.938 (95% CI: 0.91-0.97) and identifies the patient at high risk of developing delirium with a sensitivity of 80.8% and a specificity of 95.7%. It is simple, fast and easy to perform.

Given the importance of this condition, its prevalence and its consequences, we think that prophylaxis in the population at risk (patients >65 years postoperative for non-cardiac surgery) during the first 72 hours after surgery with small doses of quetiapine can provide great benefits (decreased incidence, decreased duration and severity delirium) with a low level of risk since it has a favorable safety profile.

4 HYPOTHESES AND OBJECTIVES

Hypothesis: The prophylactic administration of an antipsychotic with fewer side effects, such as quetiapine, in patients identifiedwith a validated scale decreases the incidence of delirium during the postoperative period compared to placebo administration.

The main objective of the study is to determine the incidence of postoperative delirium in patients at risk, over 65 years of age, treated early with prophylactic quetiapine compared to those treated with placebo.

The secondary objectives are:

- eassess the safety and tolerability of the medication applied.
- cCompare the efficacy of medication versus placebo in relation to:
  - the length of hospital stay.
  - perceived quality of life at 28±2 days from the start (1st dose) of quetiapine treatment.
  - all-cause mortality at discharge and 28±2 days from initiation (1st dose) of quetiapine therapy.
- In cases where delirium develops, know:
  - Time of appearance.
  - the duration and severity of the same.
  - total treatment with other antipsychotics.

5 CLINICAL TRIAL DESIGN.

5.1 . DESCRIPTION OF VARIABLES

The main variable is the proportion of patients diagnosed with delirium (number of delirium cases/total number of patients) in the first 4 postoperative days. We will use a validated scale based on the DSM-IV definition of delirium, CAM: *Confusion Assessment Method* scale (17,24-27).

The secondary variables are:

1. Numberof days from the start of treatment to the onset of delirium, if it appears.
2. duration of delirium, in days.
3. severity of theirium measured with validated scale (DRS-R-98).
4. D Total osis (mg) haloperidol or another antipsychotic tocontrol the symptoms of delirium.
5. Security Costs:
   - Sedation degree: using RASS scale.
   - QTc prolongation: increase in mseg in the control ECG.
   - presence or absence of extrapyramidal symptoms (tremor, involuntary movements, rigidity).
6. Days ofhospital stay ofthe surgical intervention.
7. perceived quality of life (through validated questionnaire SF36 or SF 12) 28±2 days after initiation of treatment.
8. mortality from all causes at discharge and 28±2 days after initiation of treatment.

Additional variables that will also be collected:

- Baseline variables: demographic data, comorbidity, ASA classification, preoperative medication (sleep medication, antidepressants, opiates, corticosteroids), vital signs, previous baseline analysis with CRP, previous physical function (independent for daily life activities-Barthel index), previous cognitive function (assessed with MINIMental).
- Intraoperative variables: type of intervention and specialty, type of anaesthesia, intraoperative medication related in previous studies with delirium, duration of anaesthesia (min), anesthetic depth and regional cerebral oxygen saturation whenever possible, blood transfusion, degree of pain (by VAS scale) and postoperative medication related in previous studies with delirium and / or analgesic techniques usedin this period.
- Complications not associated with delirium that require medical intervention (from grade II on the Clavien-Dindo scale – ANNEX 5). They will be collected at the time of the patient's discharge and 28± 2 days after the start of treatment, in percentage. They must be registered in the corresponding section of the CRD, indicating the start date and severity according to the Clavien-Dindo scale. The list of complications to be collected is detailed in ANNEX 6 of this protocol. Inaddition, all those events that in the opinion of the researcher are relevant to the development of the study and patient safety should be collected.

5.2 STUDY DESIGN AND CONTROL METHOD.

Prospective low-intervention, non-commercial, balanced, randomized, double-blind clinical study (phase III).

5.3 PATIENT ASSIGNMENT AND IDENTIFICATION CODES.

Patientswill be identified with a code that will be generated with protocol code (QUEPRO) + correlative number, according to orrdin inclusion in the study. Example: The first patient included in the trial will receive the identification code QUEPRO-001; the second QUEPRO-002 and so on.

Once the patient accepts participation in the study by signing the informed consent, his participation has been correctly recorded in his medical history and it has been verified that he meets all the inclusion criteria and none of the exclusion criteria, the subject will be assigned an identification code and will be centrally randomized by the sponsor with a 1:1 ratio in one of the two arms of the study, placebo (control group) or quetiapine (experimental group) in a consultation prior to surgery (selection visit), in such a way that proportional groups with equal probability of permanence are generated.

5.4 DESCRIPTION OF TRIAL TREATMENTS

Quetiapine is a drug belonging to the group of atypical antipsychotics with extensive experience of use in humans. Generic presentation is currently available. The smallest dose marketed in Spain is 25 mg in the form of film-coated tablets whose composition is: 25 mg quetiapine as quetiapine fumarate and 18.5 mg lactose as excipient. It is administered orally or enterally by crushing it previously.

For the realization of this clinical trial we will use doses of 25 mg every 12 hours for 3 days, so the total dose used per patient will be 150 mg of quetiapine.

Adverse reactions reported for quetiapine:
According to the Summary of Product Characteristics published by Normon S.A. revised in July 2018, themost frequently reported adverse drug reactions (ADRs) with quetiapine (≥10%) are drowsiness, dizziness, dry mouth, headache, withdrawal symptoms (discontinuation), elevated serum triglyceride levels, elevated total cholesterol (predominantly LDL cholesterol), decreased HDL cholesterol, weight gain, decreased hemoglobin, and extrapyramidal symptoms. ANNEX 7 details the ADRs associated with quetiapine treatment and their corresponding indications. The frequencies of adverse events are classified as Very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data).

The placebo is prepared in hard gelatin capsules in such a way that the capsules are identical to those containing active ingredient so that it is impossible to differentiate. Placebo consists of microcrystalline cellulose and magnesium stearate.

5.5 MASKING TECHNIQUES AND OPENING OF MASKING CODES.

This work is designed as double-blind, so that neither the patient nor the researcher know the branch of the study assigned to each patient.
At the pre-intervention screening visit, the patient is assigned a code (identification code) and randomization is performed, all centrally. Upon arrival at Resuscitation / Post-anesthetic Recovery Unit after the intervention, the pharmacy is requested to prepare the medication corresponding to that code. The preparation will be marked as quetiapine/placebo, which will be what the doctor in charge of the patient's care writes in the treatment orders, thus respecting the masking. The active drug/placebo will be coated with an identical gelatin capsule so that neither the patient nor the patient's attending physician can identify which of the products they are administering.
The cecum will be maintained until after the data analysis is performed. The blind for a specific patient should only be broken when information about the patient's treatment protocol is considered necessary and essential. The unmasking procedure shall be requested only by the principal investigator and/or his/her representative and with the consent of the sponsor. If an urgent intervention is necessary so as not to compromise the safety and/or life of the patient, the blind can break without the express authorization of the sponsor, but must be notified within a maximum period of 24 hours.

5.6 IDENTIFICATION OF THE DATA TO BE RECORDED.

The patient data necessary to obtain the primary, secondary and complementary variables will be collected in the paper data collection notebooks (CRD) and must be documented in accordance with the guide of Good Clinical Practice, confidentiality and data protection law. The data included in the CRD, which are derived from source documents, must be consistent with those documents or otherwise justify the discrepancies.
Retention of documentation: the investigator will keep the original clinical documents of each patient in the study, which consist of all medical and demographic information including

laboratory data, electrocardiograms, etc., and a copy of the signed informed consent form, for as long as established by the legislation in force after the end or suspension of the study. Uponsigning the protocol, the researcher agrees to follow the procedures for preserving documents.

5.7 END OF ESSAY

The end of the trial will be considered the day of the final visit of the last patient included in the study.

6 PATIENT SELECTION AND WITHDRAWAL

6.1 INCLUSION CRITERIA.

Patients older than or equal to 65 years of age who are going to undergo major non-cardiac surgery and who have a score equal to or greater than 5 on the Delphi scale:

- Age: 70-79 years: 1 point; >80 years: 2 points.
- Physical activity: need for assistance, not self-sufficient: 2 pointss
- Alcoholism: 1 point.
- Hearing deficit: 1 point.
- History of delirium: 2 points.
- Urgent surgery: 1 point.
- Non-laparoscopic surgery: 2 points.
- Admission to Critical Units: 3 points.
- C-Reactive Protein (CRP) value > 10 mg/dL: 1 point.

6.2 EXCLUSION CRITERIA.

× the lergia the quetiapine.
× lactose intolerance.
× patients with a score of less than 5 on the Delphi scale.
× Diagnosis of delirium on admission.
× Cardiological diseases: QTc >460 msec in men, >470 msec in women, AMI or recent cardiac decompensation, AV block 2-3º or history of torsades de pointes arrhythmias or ventricular arrhythmias, bradycardia (<45 bpm).
× hipopotasemia <3 mEq/CLK.
× history of drug use.
× Patients on antipsychotic or antidopaminergic treatment (chlorpromazine, clozapine, olanzapine, risperidone, haloperidol, quetiapine, paliperidone, amisulpride).
× Parkinson's disease.
× Minimental < 24.
× vascular dementia or Levi's bodies.
× Disorder of movements hipokinéticos.
× History of neuroleptic malignant syndrome.
× Central anticholinergic syndrome.
× epilepsy.
× patients weighing less than 50 or more than 200 kg.

× Patients participating in or having participated in a study of an investigational drug or device within four weeks prior to administration of the first dose of study treatment.

6.3 NUMBER OF PATIENTS.

Taking into account the current published literature, the estimated incidence of delirium in this type of population is 20-25%(2). We consider that a reduction in the absolute risk of delirium of 12% is clinically relevant , being similar to the reduction of absolute risk with non-pharmacological measures (10). Therefore, a sample size of 350 patients is estimated, with 175 subjects per treatment branch (significance level 95%, power 80%, expected losses of 5%).

6.4 EXPECTED CRITERIA FOR WITHDRAWAL OF STUDY SUBJECTS.

1. Voluntary patient abandonment: patients have the right to withdraw from the study at any time and for any reason, being able to express it personally or through their representative.

2. By medical criteria (safety and efficacy):
    a. Admission to critical care units for postoperative complications.
    b. Significant prolongation of the QTc interval: prolongation greater than 60 miliseconds or QTc greater than 500 msec (1.28) during the study or appearance of ventricular tachycardias / torsades de pointes.
    c. When, for any reason, the treatment is no longer safe for the patient (for example, the patient has an allergic reaction to it), it may aggravate his disease, endanger his life or have serious consequences for him.

3. For non-compliance or violation of the rules contained in the protocol: when the patient no longer complies with the rules or proceduresestablished in this protocol or there is loss of follow-up.

6.5 FOLLOW-UP OF STUDY PATIENTS.

The monitoring of the pacientis will be done from the signing of the informed consent (CI) until the last view marked by protocol. In the case of retired patients, follow-up will be done until the date of withdrawal that will be documented in the clinical history with the reason for it, whenever possible, and a premature withdrawal visit will be made.

6.6 PREMATURE DISCONTINUATION OF THE STUDY.

This study may be stopped prematurely if in the opinion of the sponsor or regulatory authorities there is sufficient reasonable cause. The investigator will receive written notice that the terminating party documents the reason for the suspension of the study.
The circumstances justifying the suspension of the present study include, but are not limited to:

a) Identification of unforeseen, significant or unacceptable risks to patients.
b) Inability to enroll an acceptable number of patients.
c) Insufficient compliance with protocol requirements.
d) Plans for modification, suspension or discontinuation of study drug development.
e) Administrative reasons that the promoter could not solve with the health authorities.

If the trial ends early or is suspended for any reason, the investigator shall promptly inform the trial subjects, ensuring appropriate treatment and follow-up of the trial and, where required by applicable law, inform the regulatory authority.
If the investigator terminates or suspends a trial without the prior agreement of the sponsor, he or she shall promptly inform the institution, and the investigator/institution shall promptly inform thesponsor and the CEIm and provide them with written justification of the cause of such termination or suspension.
If the sponsor terminates or suspends a trial, the investigator must inform the institution where the trial is conducted and the investigator/institutionmust promptly inform the CEIm by providing written justification of the reasons for the termination or suspension.
If the Ethics Committee (CEIm) terminates or withdraws the favourable opinion of a trial, the investigator shall inform the institution and the investigator/institution shall promptly inform the sponsor and provide written justification for the cause oftermination or suspension.

7 PATIENT TREATMENT.

7.1 CLINICALTRIAL MATERIALS.

The active drugwill be supplied by the promoter (IBSAL).
The manufacture of the medication will be entrusted to an independent company (LABORATORIUM SANITATIS, S.L.) which will generate identical capsules for active drugs and placebo under rules of good manufacture of medication according to current legislation. Subsequently, they will be sent to the pharmacy service of the C.A.U.S.A. Theperson in charge of dispensing the medication will be the only one who knows if the treatment is the active drug or is the placebo. All the medication that the patient will receive together will be dispensed, in a bottle containing the 6 corresponding capsules. The treating physician will leave reflected in the treatment orders: administrar quetiapine/placebo 1 capsule orally every 12 hours. The first dose of active drug/placebo will be administered 60 minutes after arrival at the resuscitation unit and every 12 hours thereafter for the first 3 postoperative days.

7.2 SCHEDULE OF VISITS AND PROCEDURES.

See Figure 1: Outline procedures in each visit.

I. Pre-selection visit: where the patient is selected by assessing the inclusion and exclusion criteria. Itwill explain what the clinical trial consists of and give youthe documentation (information sheet and informed consent).

II. Selection visit: it will be carried out during the pre-anesthesia consultation or the day before the surgical intervention. Thefollowing procedures shall be carried out:
- signature of CI.
- Verification of compliance with selection criteria.

- Demographics.
- Relevant medical history: Preoperative comorbidity.
- ASA classification.
- Preoperative medication: sleep medication, antidepressants, opiates, corticosteroids...
- vital signs.
- complete analysis with PCR.
- previous physical function: independent for activities of daily living (Barthel index).
- Basal cognitive function (valued with MINIMental o 6 ICT).
- CAM scale.
- ECG and QTc measurement.

III. Postoperative visits: A daily personal clinical visit will be made to all randomized patients during the first four days of the postoperative period or during the duration of their admission if it is less than 4 days. In this case, the last visit during admission will be the visit to discharge.
Theseclinical visits will be listedin corresponding to the postoperative day: visit 1st day post, visit 2nd day post... so on until the 4th postoperative day.

Procedures to be performed:

- CAM scale.
- RASS scale.
- Extrapyramidal symptoms.
- vital signs.
- ECG and QTc measurement (after administration of the 4th dose).
- Complete laboratory tests (at least one during the first four days after surgery).
- VAS scale and analgesia received (opiates).

In addition, during the **1st postoperative visit**, the intraoperative variables will be collected:

- Type of surgical intervention and specialty.
- urgent ly programmed.
- anesthetic technique performed.
- Drugs used, doses and routes of administration(benzodiazepines, opiates, glucocorticoids, atropine).
- Measurement of anesthetic depth and/or regional brain oxygen saturation where possible.
- Duration anesthesia .
- EVA upon admission to URPA/Resuscitation.
- Analgesia: IV or by regional techniques(drug used, dose and administration).
- blood transfusion.

If the patient develops delirium , the daily visit will continue until the clinic disappears. In this case, the following will also be collected:

- severity of the picture using DRS scale -R- 98
- Drug used for its treatment, dose and route of administration.

IV. Discharge visit: when the patient meets criteria and is discharged. The following will be collected:
- Reason for hospital discharge.
- CAM.
- RASS.
- vital signs.
- Extrapyramidal symptoms.
- Hospital evolution including complications that have appeared and that have required medical treatment (≥ grade II Clavien-Dindo scale): blood transfusion, surgical reoperation, pneumonia ... .
- mortality.
- complete anal itatic if it has not been collected in the postoperative visits.
- If you have developed delirium:
  - × duration.
  - × Severity.
  - × Dosage and route of administration of the drug used for its treatment.

V. Premature withdrawal visit: all patients who, regardless of the cause and phase of the study in which they are, prematurely and permanently stop treatment, must complete the premature withdrawal visit, which will take place in the following 24-48 hours from the time the withdrawal is known. During the same the following procedures will be carried out:
- reason de premature interruption.
- vital signs.
- CAM.
- RASS.
- sextrapyramidal symptoms.
- Hospital evolution including complications that have appeared and that have required medical treatment (≥ grade II Clavien-Dindo scale): blood transfusion, surgical reoperation, pneumonia ... .
- if you have developed delirium:
  - × duration.
  - × severity.
  - × Dosage and route of administration of the drug used for its treatment.

VI. Final visit: It will be carried out at 28± 2 days from the start of treatment. A personal, telephone or mail follow-up will be carried out to determine the vital status (mortality) and quality of life in relation to health through the SF 36 questionnaire. Complications that have appeared during this period and that have required medical treatment (≥ grade II Clavien-Dindo scale) will also be collected.

	VISITAS								
	Preselección	Selección	1-post	2-post	3-post	4-post	Alta	Final (28± 2 días)	Retirada prematura
Criterios de selección	x	x							
Entrega de documentación	x								
Firma CI		x							
Variables demográficas		x							
Comorbilidad		x							
ASA		x							
Medicación preoperatoria		x							
CAM		x	x	x	x	x	x		x
BARTHEL		x							
MINIMETNTAL		x							
ECG con QTc		x			x				
RASS			x	x	x	x	x		x
Constantes vitales		x	x	x	x	x	x		x
Síntomas extrapiramidales			x	x	x	x	x		x
Variables intraoperatorias			x						
EVA y analgesia			x	x	x	x			
Complicaciones no relacionadas con delirio							x	x	x
Mortalidad							x	x	
SF-36								x	
Datos analíticos		x	x*	x*	x*	x*	x		
Severidad del delirio			x	x	x	x	x		x
Tratamiento del delirio			x	x	x	x	x		x
Duración del delirio							x		x

Figure 1: Outline procedures in each visit. * At least one complete analysis during the period of admission.

7.3 CONCOMITANT AND PROHIBITED TREATMENTS

All types of anesthetic drugs and analgesic techniques are allowed according to the needs of each patient, and must be reflected in the data record book: the anesthetic technique performed, the anesthetic depth and regional brain oxygen saturation, if it has been possible to measure it, and the drugs used that in previous studies have been related to delirium (benzodiazepines, opiates, corticosteroids and atropine).

The use of drugs for adequate control of pain, heart rate and blood pressure is recommended as needed, including opioids and regional analgesic techniques, leaving the drug used recorded.

According to the Technical Label ofthe investigational medicinal product, concomitant administration of cytochrome P450 3A4 inhibitors, such as HIV protease inhibitors, azole-type antifungal agents, erythromycin, clarithromycin and nefazodone, is contraindicated.

Considering the main effects of quetiapine on the central nervous system, quetiapine should be used with caution in combination with other centrally acting drugs and alcohol.

In case of developing delirium, the usual treatment will be carried out not intervening in it, leaving reflected in the CRD drug used and dosage. In this case, if it develops during the first 3 days, the study medication will be discontinued .

7.4 STORAGE, CONSERVATION AND DISPENSING OF MEDICATION

Quetiapine is a drug already marketed and with generic presentation. For our work it will be supplied free ofcharge by the promoter and manufactured by LABORATORIUM SANITATIS, S.L.
The manufacturer of the medication, will send it to the pharmacy service of the C.A.U.S.A. that will be responsible forthe storage, conservation and dispensing.
It shall be stored and kept in accordance with the particularsspecified in the data sheet and as specified by the manufacturing undertaking. The dispensing will be carried out following the randomization list provided by the promoter to the Pharmacy service.

8 N-ASSESSMENTOF EFFECTIVENESS

8.1 EFFICACY VARIABLES.

The efficacy of the treatment is given by the main variable: incidence of delirium during the postoperative period in the first 4 days in both intervention groups.
The secondary variables will be collected: number of days free of delirium, duration and severity of delirium if it finally develops; hospital stay, adverse effects, mortality at discharge and 28± 2 days, perceived quality of life at 28± 2 days.

8.2 EVALUATION METHODS.

To obtain the main variable we will use the CAM scale (Confusion Assessment Method) as a method of diagnosis of the appearance of delirium. It is a scale based on the DSM IV definition of delirium (29) and with demonstrated internal and external validity for surgical patients (17,24-27). It consists of an interview of the clinician consisting of six items: two addressed to the closest caregiver (family member or nursing technician) with which information is obtained on the beginning of the picture and the presence of fluctuations. The remaining four items are to ask the patient, to determine their cognitive impairment that evaluates attention, thinking and consciousness. In the second part of the instrument, the clinician answers a questionnaire of 4 questions (yes / no), based on the evaluation made. The diagnosis of delirium is established around the presence of its two fundamental criteria (abrupt onset with fluctuations of symptoms and loss of attention) and one of the two secondary criteria (disorganized thinking and altered level of consciousness). We will use the same scale to rule out the presence of delirium in the initial assessment of the patient and to determine the duration of the picture during the follow-up period. The assessment of the response will be carried out daily in both study groups, during the first 4 days of admission or until the patient's discharge.

We will use the RASS scale (Richmond Agitation sedation scale) to assess the degree of sedation or agitation presented by the patient. It is a 10-point scale, very intuitive in its description since the positive values indicate agitation and the negative values are used to quantify sedation, in such a way that level 0 corresponds to a calm and awake patient, level 4

to the situation of maximum agitation and level -5 to the highest depression of the level of consciousness. It also has a good correlation with the appearance of delirium when the presence or absence of attention is detected (30). It will be administered prior to CAM during the follow-up period, if -4/-5 values are obtained, it will be repeated again after two hours until it decreases to -3 values onwards. In case of development of delirium, daily follow-up (through CAM and RASS scales) will be carried out until resolution of the patient's condition or discharge and the drugs used for symptom control and the necessary doses will be recorded in the CRD.

The severity of delirium developed will be determined by the DRS-R-98 scale (31,32). Itis a scale of 16 items scored by the clinician with two sections (severity and diagnosis) and a score sheet. The 13 items in the severity section can be scored separately from the 3 items in the diagnostic section. The severity section functions as a standalone scale for repeated measurements during an episode of delirium. All items are accompanied by descriptions that serve as a guide for scoring along a continuum that moves between normality and severe involvement, scoring between 0 and 3. All available sources of information can be used for patient assessment: family, visitors, hospital staff, even the roommate can contribute more information. Some items are scored based on test and medical history, while others incorporate standardized questions (e.g., language and cognitive items). The items assessed are: circadian rhythm alteration, alteration in perception and hallucinations, delusions, affective lability, language alterations, alterations in the course of thought, agitation or motor slowdown, orientation, attention, short and long-term memory, visuospatial capacity. Only the severity section of the scale will be administered once a day for as long as you develop delirium.

At 28±2 days, the final visit (personal, telephone or email) will be made, reflecting the patient's vital status (mortality) and health-related quality of life, assessed through the SF-36 questionnaire. It is a questionnaire that should preferably be self-administered, although it is also acceptable to administer it through personal and telephone interviews, not changing its internal consistency. It consists of 36 items covering 8 scales: physical function, physical role, body pain, general health, vitality, social function, emotional role, and mental health (33,34).

9 ADVERSE EVENTS. SAFETY ASSESSMENT.

The researchers of the study will record the hospital evolution of the patients including complications and the treatments derived from them, both pharmacological and non-pharmacological through the daily visit to collect the variables during the first four days of admission or until hospital discharge.

Safety oversight in the trial will comply with the provisions of Royal Clinical Trials Decree1090/2015 on the registration, evaluation and reportingof adverse events (A A).

The sponsor, through the principal investigator of the study, will assess Serious Adverse Events (SAAs) with the safety documents of the products and will notify those AGAs that meet expedited notification criteria (serious, unexpected and treatment-related), to the Health Authorities. The notification to the competent authorities (AEMPS, CEIm, competent bodies of the Autonomous Communities) and principal investigators of any notifiable event will also be the responsibility of the sponsor,who will do so within the time limits established by the Spanish regulations in force (namely: serious and unexpected adverse reactions (RAGI) will be notified within a maximum period of 15 calendar days from when the sponsor becomes aware of it, and within 7 days if the unexpected serious adverse reaction has resulted in death or endangering the subject's life).

9.1 DEFINITIONS.

- **Adverse Event (**AA):
  Any incident harmful to health that occurs to a subject to whom a medicinal product has been administered, even if it does not necessarily have a causal relationship with it.

- **Serious adverse event (SAA**):
  Any incident harmful to health which, at any dose, necessitates hospitalisation or prolongation, results in permanent or significant disability or disability, results in a congenital anomaly or malformation, endangers life or results in death.
  Interventions scheduled prior to study inclusion will not be considered as SAAs. Nor the complications derived from the surgical process itself.
  For reporting purposes, suspected AA or RA that is considered medically important but does not meet the above criteria, including major medical events requiring intervention to prevent any of the consequences described above, shall also be treated as serious.

- **Adverse reaction (AR):**
  Any harmful and unintended response to a medicine.
- **Serious and unexpected adverse reactions (RAGI)**:
  A serious adverse reaction whose nature, severity or outcome is not consistent with the baseline safety information.

9.2 QUALIFICATIONOF AN ADVERSE EVENT.

The degree of intensity of anA A provides a qualitative assessment of the extent or intensity of an adverse event, determined by the investigator or reported by the patient. The degree of intensity does not reflect the clinical severity of the event, but only the degree or extent of grief or incidence (e.g., severe nausea, mild crisis) and does not reflect the relationship to study medication.

- Degree of intensityof an adverse event
  The researcher will assess the intensity of A A and A AG. AA intensity will be rated on a scale of 1 through 5 according to the latest version of the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCs), which are available online at NCI: http://ctep.cancer.gov/reporting/ctc.html.
  If a particular event is not listed on the NCI CTCAE toxicity scale, the following table will be used for classification:

Degree	*Definition*	*n*
1	*Mild.*	*The patient reports the sign, symptom or event, which is usually temporary and does not require special treatment or interfere with usual daily activities.*

2 Moderate. Discomfort that interferes with usual activities but usually improves with basic therapeutic measures.

3 Intense.Incapacitates and does not make it possible to perform usual activities or that significantly affects the clinical state and guarantees therapeutic intervention. Hospitalization may or may not be necessary.

4 Life-threatening. Risk of imminent death requiring hospitalization and clinical intervention.

5 Death.

- Relationship of adverse events and serious adverse events with study treatment. Imputability criteria.

  The sponsor will classify adverse events, based on their causal relationship with the drug, according to the Karch and Lasagna Algorithm (1977), as:

  • Definitive:• there is a reasonable time sequence between the administration of the drug and the appearance of AA. This event coincides with the RA described for the drug, improves with its suppression, reappears after its readministration and cannot be explained by alternative causes.

  • Probable:• there is a reasonable time sequence between drug administration and the onset of AA. This event coincides with the RAs described for the drug, improves after discontinuation of treatment and cannot be explained by other alternatives.

  • Possible:• there is a reasonable time sequence between the administration of the drug and the appearance of AA. This event coincides with the RA described for the drug but can be explained by alternative causes.

  • Conditional or •Unlikely: there is a reasonable time sequence between the administration of the drug and the appearance of AA. This event does not coincide with the ARs described for the drug and can be explained by alternative causes.

  • **Unrelated:• there is no reasonable time sequence between drug administration and the onset of AA. This event does not coincide with the ARs described for the drug and can be explained by alternative causes.**

  For expedited notification purposes, the definitive, probable and possible categories of Karch and Lasagna's (1977) algorithm will be considered as related and the conditional or improbable category of said algorithm as unrelated.

  The determination of the possible relationship to the treatment of the study is the responsibility of the principal investigator of the research center or the person designated by it.

- Actions to be taken inresponse to an adverse event

The measures to be takenbefore an RA are described on a numerical scale, from 0 to 5, which covers different possibilities. One or more of them must be selected.

0 =None
1 =Temporary dose adjustment/interruption of study medication
2 =Study medication is permanently discontinued due to AA
3 =Concomitant medication administration
4 =Administration of non-pharmacological treatment
5 =Hospitalization/prolongation of hospitalization

9.3 PROCEDURES FOR THE REGISTRATION OF AA.

All serious adverse events (SAAs) occurring during the clinical trial from the first dose of the drug until 28±2 days thereafter will be recorded in the CRD. For serious adverse events, registration should be extended until the SAA is resolved or considered clinically stable at medical discretion .

To the extent possible, each adverse event shall also be described in terms of:

- its duration (start and end dates)
- the degree of intensity (grade 1, 2, 3, 4 or 5)
- the severity of AA (severe or non-severe)
- Study drug(s) with which a causal relationship is suspected.
- the action(s) taken.

9.3.1 Responsibility for notification.

Any serious adverse events (SAAs) occurring afteradministration of the first dose and up to 28 days thereafter should be reported.

The investigator shall inform the sponsor of the AAG without undue delay and within 24 hours of becoming aware of such events, even if they do not appear to be related to the drug under study. The investigator shall, where appropriate, send the sponsor a follow-up report to enable the sponsor to assess whether the serious adverse event has an impact on the benefit-risk balanceof the clinical trial.

All AGAs should be monitored until one of the following occurs:

- Resolution of the event.
- Stabilization of the event
- Restoration of the baseline of the event, if a baseline value is available.
- The event may be attributed to products other than the study medication or to factors unrelated to the conduct of the study.
- Further information is unlikely (subject or primary care physician refuses to provide additional information, loss to follow-up after demonstration of due diligence with follow-up efforts)

AllAGs that have not been resolved at the end of the study, or that have not been resolved with withdrawal from study participation, will be monitored until any of the above situations occur. Thefollow-up information of an AG shall be communicated in the same manner as the original Serious Adverse Event, including the date of when

the initial report was reported. The new information will be sent in a form from AAG (indicating that it is a follow-up and the new date noted). Follow-up should describe whether the event has resolved or continued, whether and how it was treated, and whether or not the patient remained in the study. Both the form and the shipping confirmation sheet must be archived.
The cause of death of a subject in a clinical study, whether the expected event or not, and whether or not the event is relatedto the drug under study, is considered a serious adverse event communicable within 24 hours.
The investigator should keep a copy of allinformation relating to AG.

9.3.2 Notification to Health Authorities and Ethics Committees.

The sponsor will communicate to the competent Health Authorities (when appropriate) and to the Ethics Committees all the relevant information on serious and unexpected adverse reactions (RAGI) that are suspected to be related to the study drug and that are fatal or life-threatening, as soon as possible and in any case, within a maximum period of seven days from the moment the case is known. Follow-up information relevant to these cases shall subsequently be notified within a further period of eight days.
For the evaluation of esperability , the quetiapine summary of product characteristics shall be used.
The responsibility for assessing adverse events lies with the sponsor of the study, always taking into account the opinion of the investigator. Each AAG should be evaluated for expectability, and if it is an unexpected AGR and should be notified accordingly.
The annual safety reports that will include the RAGIs and AAGs collected in the study, will be sent by the sponsor to the AEMPS (Clinical Trials Area of the General Subdirectorate of Medicines for Human Use), to the CEIm and CCAA, within the deadlines established in current legislation.

9.4 NUMBER AND CONTACT PERSON IN TERMS OF PHARMACOVIGILANCE.

In the event of a SAA that needs to be notified to the Pharmacovigilance Unit, or a case of pregnancy is collected, a member of the research team shall complete and sign the AAG or pregnancy notification form to be faxed immediately and always within 24 hours of becoming aware of the event to:

PhD Patricia Rodríguez Fortúnez

Head of Pharmacovigilance UICEC of the University Hospital of the Canary Islands

Telephone: 922 678 117 Fax: 922 677 284

Email: patricia.rodriguez@scren.es

The Pharmacovigilance Unit shall review the form received and, if appropriate, request additional information from the investigator. Whenadditional information on the AAG is obtained, or resolves or is unlikely to change, a follow-up report should be completed and fax/e-mail also sent to the Pharmacovigilance Unit.

10 STATISTICAL ANALYSIS

A statistical analysis will be carried out after the development of a basis for the collection of patient data, by protocol and in accordance with the principle of "intention to treat".
After identifying extreme data, a subsequent analysis will be carried out to assess the normality of the variables. All variables related to efficacy and safety will be analyzed for both treatment arms.
Categorical variables shall be expressed in percentages and number of observations. Continuous variables shall be expressed as mean and standard deviation or medians and interquartile ranges (25 – 75) and/or minimum and maximum. Relative risks of the estimated effect and its 95% confidence intervals shall be calculated and presented. For the comparison of categorical variables, the Chi-square test or the Fisher's test will be used, when necessary. For the comparison of the continuous variables, the Student's "t" test or Mann-Whiteney U test will be used for both simple and paired data, or other non-parametric tests, if necessary. Multivariate and survival analyses will be used to determine whether the association between the intervention and theprimary (or secondary) objective is free from confusion. Covariates in each model will be considered as those that in the univariate analysis show a value of p <0.1
All analyses will be performed with hypothesis contrast of 2 tails and a significance level of 5%.
The statistical program used will be SPSS® 21.0.
Intermediate analyses are not planned except those indicated by the Safety Committee in order to safeguard the health of patients included in the study.

11 ETHICAL ASPECTS

This clinical trial will not start until the Spanish Agency for Medicines and Health Products (AEMPs) and the CEIm consider that all the conditions present in article 3 of RD 1090/2015 on the general requirements of clinical trials are met.
This study should be developed in accordance with the protocol and the Good Clinical Practice (GCP) standards, as described in: ICH Harmonized Tripartite Standards for Good Clinical Practice (CPMP/ICH/135/95), according to current Spanish legislation (RD1090/2015) and European regulation EU 536/2014 (Good Clinical Practice Standards for trials on medical devices in the European Community) . It will also be guided in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research on Human Subjects, approved by the General Assembly of the World Medical Association (Fortaleza, Brazil, 2013) and taking into account the Oviedo Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Applications of Biology and Medicine, as well as any other rules that may be applicable.
It can be accessed through the website of the World Medical Organization http://wma.net/es/30publications/10policies/b3.

The researcher agrees, with the signature of this protocol, to follow the instructions and procedure described therein and therefore will comply with the principles of Good Clinical Practice on which it is based.

11.1 INFORMED CONSENT

The obtaining and content of informed consent will follow the provisions of Article 29 of Regulation (EU) No. 536/2014 of the European Parliament and of the Council, of April 16, 2014, as well as Articles 8 and 9 of Law 41/2002, of November 14, as set out in RD 1090/2015 on clinical trials.
The investigator must explain to each patient (or legally authorized representative) the nature of the study, its purposes, procedures, expected duration, and the potential risks and benefits associated with participating in the study, as well as any inconvenience the study may pose. Each participant should be advised that their participation in the study is voluntary and that they may leave the study at any time, without affecting their subsequent medical treatment or their relationship with the treating physician. Informed consent will be provided by means of a standard writing, in language easily understood by the participant. The patient must write his/her name and that of the reporting physician in his/her own handwriting and date and sign the informed consent, as well as receive a copy of the signed document. If the subject cannot read or sign the documents, an oral presentation may be made or the signature of the subject's authorized legal representative may be obtained, provided that it is witnessed by a witness not involved in the study and mentioned in the same document and/or medical history. No patient may be included in the study without prior informed consent.

11.2 CONFIDENTIALITY / DATA PROTECTION.

By signing the protocol, the researcher undertakes to keep all the information provided by the Sponsor in strict confidentiality and to insist on the maintenance of it by his team. The study documents provided by the Sponsor (protocols, data sheet, CRDs and other materials) must be kept appropriately to ensure their confidentiality. Information provided by the Sponsor to the investigator may not be disclosed to third parties without the direct written permission of the investigator, except to the extent necessary to obtain the informed consent of patients who wanted to participate in this trial. Patients will be informed that all study data will be archived and treated in a strictly confidential manner, according to the Organic Law on the Protection of Personal Data (Organic Law 3/2018, of December 5, on the Protection of Personal Data and guarantee of digital rights) and its implementing regulations, as well as current European regulations on the matter.
The monitor will also assume respect for this confidentiality when, in the course of the trial, it carries out the obligatory reviews and verifications of the study data.

11.3 ACQUISITION AND DISPENSING OF THE MEDICATION UNDER STUDY.

Quetiapine is a drug alreadymarketed and comes in generic form. The promoter is responsible for supplying the drug under study, ensuring that the rules of good manufacturing, packaging and labeling have been met.
It shall be stored and stored in accordance with theparticulars specifiedin the data sheet. The preparation will be carried out by the pharmacy service in accordance with the indications reflected in the protocol in section 8.1.

All unused and unaltered study drugs may be returned to whomever the sponsor designates or destroyed in the center's Pharmacy Service if authorized. Any of the procedures should be well documented.

11.4 AUDIT AND MONITORING.

Regulatory authorities, the CEIm, and the sponsor or a designated representative may request access to all original documents, patient data collection notebooks, and other study documentation to conduct an on-site audit or inspection. The researcher must ensure direct access to these documents and collaborate at all times in carrying out these activities. In such procedures, due protection of private personal identification data will be attended to in accordance with the data protection law.

Monitoring.
Before starting the study, at the start visit of each center or at a meeting of researchers, a representative of the Sponsor will review the protocol and the data collection notebooks with the researchers and other personnel involved in the study. During the study, the monitor will regularly visit the center, to compare the data collected in the CRD with the source documents, check adherence to the protocol and the Standards of Good Clinical Practice. The investigator and trial personnel should be available to assist the monitor during these visits.

No data revealing the identity of patients should leave the participating center.

11.5 FAILURE TO COMPLY WITH PROTOCOL.

Serious breaches of the authorised protocol should be reported to the sponsor without undue delay and at the latest within three calendar days from the date on which it became aware of the non-compliance. The sponsor will communicate it to the Spanish Agency of Medicines and Health Products and the CEIm. For these purposes, a serious non-compliance is one that may significantly compromise the safety and rights of the subjects or the reliability and robustness of the data obtained in the clinical trial.
Where immediate deviation from the protocol is required to avoid immediate risks to patients, the investigator shall contact the sponsor, circumstances permitting, to discuss planned action. Any deviation from the protocol should be documented in detail in the CRD and in the original documentation.

12 FINANCINGAND INSURANCE

This is a non-commercial study. The trial will be funded for the most part by the Spanish Multimodal Rehabilitation Group. In addition, thepromoter will try to obtain funding through several calls and / or public scholarships to cover the expenses associated with the implementation and development of the study that may not be covered as well as obtain necessary material for it.

Sure.
Because the clinical trial has been requested as a low-intervention clinical trial, the sponsor takes advantage of the insurance coverage established by RD 1090/2015, of December 4, for this type of trial.

13 PUBLICATION POLICYN

13.1 PUBLICATION OF RESULTS.

Both positive and negative results of this clinical trial will be communicated in scientific congresses and/or published in scientific journals, regardless of the obligations to publish the report of the results in the Spanish Registry of Clinical Studies (REec) and the provisions of Regulation (EU) No 536/2014 of the European Parliament and of the Council, of 16 April 2014.
The final results of the trial and a manuscript of the publication will be sent by the coordinating investigator of the trial to the sponsor at least 60 days before their submission for publication. Posters, abstracts or other oral or written material related to the trial will also be communicated to the sponsor at least 5 days before submission.

13.2 AMENDMENTS TO THE PROTOCOL.

All changes to the protocol will be specified in the form of an amendment. The method of carrying out the amendments will follow the standardized procedures according to RD1090/2015. The protocol should not be modified without the consent of both the coordinating investigator and the sponsor.

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ANNEX 1

STOPOVER CAM-S

This instrument consists of two parts: an interview with questions to be asked to the patient and his closest caregiver (familymember and/or nurse) and a set of questions that the clinician must answerbased on the evaluation carried out.

Part One (interview)

A. Ask the closest caregiver (family member and/or nurse):

A1. "Have you noticed any changes in patient behaviorin the last 24 hours?" *(assessbehavioral and/or mental cambios)* **YES NO**

A 2. "These changes, do they vary throughout the day?" *(assess fluctuations in the course of the day)* **YES NO**

B. Ask the patient:

B1. "Tell us why you are admitted here.
"Do youfind me currently?"
Let the patient talk for one minute.
*Is the patient **unable** to follow the course of the conversation and give*
Andclear and logical explanations? **OTHERWISE**

B2. "Tell me: the day, the date, the m is, the season of the year , and the year we are in now."
Is there more than one wrong answer? **OTHERWISE**

B3. "Tell me the hospital (or place), plant (or service), city, province and country."
Is there more than one wrong answer? **OTHERWISE**

B4. "Repeat these numbers: **5-9-2** , now repeat them backwards"
Is the answer wrong? **YES NO**

Part Two (phase in which the clinician must respond to what is observed to define the presence or absence of *Delirium*)

1. The patient presents with a change in baseline mental status of **acute onset and fluctuating course** throughout the day.
To answer rely on Item A.1 and A.2. **YES--- NO**---

2. The patient has **difficulty maintaining attention**, is easily distracted .
To answer based on item B.1 and B.4 **YES--- NO**---

3. The patient presents a **disorganized thought**.
It will be positively valued if at any timeof the interview there is difficulty in organizing the thoughts reflected in:
Frequent topic changes
S.A.D.
Interruptions *or disconnections of speech*
Loss of speech logic (confused and/or delusional speech)
To answer rely especially on item B.1. **YES--- NO**---

4. The patient presents alteration of the **level of consciousness**:
Alteration of consciousness is considered to be any alteration of the ability to react appropriately to stimuli.
Vigil *(normal consciousness)*

S.A. Hyperalert *(vigilant, hyperreactive)*

Sleepy (falls *asleep easily)*
Stupor *(responds to verbal stimuli)*
A coma *(responds to painful stimuli)*
To answer based on item B.1- B.2 and B.3 **YES--- NO**---
Algorithm: The instrument will be positive for *Delirium* if in the second part the first two items and the third or fourth are positive.

***DELIRIUM*: YES NO**

ANNEX 2

RICHMOND AGITATION AND SEDATION SCALE: RASS

Score	Term	Description
+4	**Combative**	**Combative**, violent, immediate danger to the group
+3	**Very agitated**	The tubes or catheters are removed; aggressive
+2	**Agitated**	Frequent and purposeless movement, struggle with fan
+1	**Restless**	Anxious but no aggressive or vigorous movements
0	**Alert and calm**	
-1	**Drowsy**	Not fully alert, but stays awake (opening and eye contact) to the verbal call **(≥ 10 seconds)**
-2	**Mild sedation**	Briefly wakes up to the verbal call with eye contact **(< 10 seconds)**
-3	**Moderate sedation**	Eye movement or opening at the verbal call **(but no eye contact)**
-4	**Deep sedation**	No response to verbal call, but there is eye movement or opening to the physical stimulus
-5	No **response**	No response to voice or physical stimulus.

If RASS is -4 or - **5, stop** and **reassess** the patient later.

ANNEX 3

DELIRIUM RATING SCALE-REVISED-98

ITEMS OF SEVERIDAD.

1. Disruption of the circadian rhythm.

Value the sleep-wake pattern using all sources of information, including family, caregivers, nursing information and the patient himself. Try to distinguish sleep from rest with your eyes closed.

0. Do not present.

1. Slight disturbance of sleep continuity during the night or occasional daytime sleepiness.

2. Moderate disorganization of the sleep-wake rhythm (e.g. falling asleep during conversations, taking naps during the day or several brief awakenings during the night with confusion or changes in behavior or little sleep time during the night).

3. Severe: alteration of the sleep-wake cycle (e.g. reversal of the sleep-wake cycle, or circadian fragmentation with multiple periods of sleep and wakefulness or severe insomnia).

2. Alterations of perception and hallucinations.

Illusions and hallucinations can belong to any sensory modality. Alterations in sensoperception are "simple" when they do not have a single dimension, such as a sound, noise, color, spot, or lights, and can be "complex" when they are multidimensional, such as voices, music, people, animals, or scenes. Note if they are referred by the patient or caregiver or if they are inferred during observation.

0. In the gifts.

1. Slight perceptual alterations (e.g. feelings of derealization or depersonalization, or the patient cannot distinguish dreams from reality).

2. Presence of illusions.

3. Presence of hallucinations.

3. Delusions.

Delusions can be of any kind, but persecutory delusions are more frequent. Write down if they are referred by the patient, family, or caregiver. Value as delusional ideas that are unlikely to be true and that the patient presents an absolute certainty of their veracity and that resistance cannot be overcome with logical argumentation. Delusions cannot be explained by the patient's cultural context or religious background.

0. Do not present.

1. Slightly suspicious, hypervigilant or worried.

2. Unusual or overrated ideas that do not reach delusional proportions or may be plausible.

3. Delusions.

4. Affective lability.

Value the patient's affection as the form of manifestation and not a description of how the patient feels.

0. Absent.

1. Affection slightly altered or incongruous with the situation; changes during the course of hours; Emotions are basically under control.

2. Affection is generally inappropriate to the situation and changes intermittently within minutes; Emotions are not under control although they can be directed by others.

3. Disinhibition of emotions in a severe and consistent way; Affection changes rapidly, is inappropriate to the context, and cannot be directed by others.

5. Language.

Assess abnormalities of oral, written or sign language that cannot be attributed to dialect or stuttering. Research fluency, grammar, comprehension, semantic content and naming. Value comprehension and naming non-verbally if necessary by administering commands that the patient should follow or point to objects.

0. Normal language.

1. Slight alteration including difficulties in finding words or naming or fluency problems.

2. Moderate alteration including difficulties in understanding or deficits in communication (semantic content).

3. Severe alteration including meaningless semantic content, "word salad", mutism or severely reduced understanding.

6. Alteration of the course of thought.

Assess the alterations of the course of thought based on verbal or written language. If the patient does not speak and write, do not rate this item.

0. Normal course of thought.

1. Tangential or circumstantial thinking.

2. Occasional loss of partnerships, but still understandable.

3. Loss of partnerships most of the time.

7. Psychomotor agitation.

Assess through observation, including from other sources of observation such as visitors, family and health personnel. Do not include dyskinesia, tics or chorea.

0. No restlessness or agitation.

1. Light restlessness with rude movements or nervousness.

2. Moderate restlessness including significant limb movements, nervousness and trying to start the tracks.

3. Severe psychomotor agitation, such as aggression or need for containment or isolation.

8. Psychomotor slowdown.

Assess movements through direct observation or through other sources of observation such as family, visitors or clinical staff. Do not assess components caused by parkinsonism. Do not value drowsiness or sleep.

0. No slowing down of voluntary movements.

1. Slight reduction of the frequency, spontaneity or speed of movements to a degree that may interfere in some way with the evaluation.

2. Moderate reduction in the frequency, spontaneity or speed of movements to a degree that interferes with self-care activities.

3. Severe psychomotor slowing with few spontaneous movements.

9. Guidance.

Patients who cannot speak may be given the hearing test or visually with multiple-choice responses. Allow the patient to make mistakes up to 7 days instead of 2 if the admission is longer than 3 weeks. Disorientation in person means not recognizing familiar people and it is not scored if the patient recognizes the person even if he has made a mistake in the name. In-person disorientation is more severe if the person does not recognize themselves and is rare. Disorientation in person appears after disorientation in space and/or time.

0. Oriented in time, space and person.

1. Disoriented in time (e.g. more than 2 days or wrong month or year) or space.

(e.g. name of building, city or state) but not both.

2. Disoriented in time and space.

3. Disoriented in person.

10. Attention.

Patients with sensory deficits or who are intubated or those with limited hand movement should be evaluated with tests that do not require writing. Attention can also be assessed during the interview (e.g. verbal perseverances, distractibility and difficulty in changing the subject) and/or through the use of specific tests.

0. Alert and attentive.

1. Slightly distracted or slight difficulties in maintaining attention, but with the ability to focus it again on warning you. In tests only minor errors without significant slowing down in the answers.

2. Moderate inattention with difficulty focusing and maintaining attention. In tests it presents numerous errors or requires help to finish the task.

3. Severe difficulty focusing and maintaining attention with numerous incorrect or incomplete answers or inability to follow directions. Distracted by noises or environmental events.

11. Short-term memory.

Defined as the retrieval of information (e.g. 3 items presented verbally or visually) after 2 or 3 minutes. When it is assessed with a standardized test, it is necessary that it has previously been properly registered. The number of trials until the information is recorded, as well as the effect of giving clues can be noted on the answer sheet. The patient cannot rehearse during the waiting time and must be distracted in this period of time. The patient can speak or communicate nonverbally with the examiner to identify the correct items. Short-term deficits can also be picked up during the interview.

0. Intact short-term memory.

1. Remember 2/3 items; You may be able to remember the third item with clues.

2. Remember 1/3 items; May be able to remember the other items after clues.

3. Remember 0/3 items.

12. Long-term memory.

It can be assessed formally or through the interview remembering part of your past life (e.g. medical history or information that can be corroborated by someone else) or general information that has had relevance. When evaluating with standardized tests use 3 items that

can be presented verbally or visually, make sure they are correctly recorded and ask at least 5 minutes later. The patient should not rehearse during the waiting period. Make concessions in patients with less than 8 years of education or with mental retardation in terms of general information. The assessment of the severity of deficits includes a judgment of all long-term memory modalities that have been evaluated, including long-term and short-term memory evaluated informally during the interview and also formally tested.

0. No significant long-term memory disturbances.

1. Recalls 2/3 items and/or has minor difficulties in remembering details of long-term information.

2. Recalls 1/3 items and/or has moderate difficulty remembering long-term information details.

3. Remembers 0/3 items and/or has severe difficulties.

13. Visuospatial capacity.

Value it formally and informally. Consider the patient's difficulty in managing in their environment (e.g. getting lost). Formally evaluate by drawing, copying a design, assembling a puzzle, or drawing a map and identifying major cities, etc. Take into account visual problems that may interfere with the performance of the test.

0. No alteration.

1. Slight alteration so that most of the design, most details or parts are correct; and/or there is a small difficulty in managing around them.

2. Moderate alteration with distorted design appreciation and/or various errors in details or parts; and/or repeated need to redirect to avoid getting lost in a nine environment despite having familiar objects around.

3. Serious alteration in formal tests, and / or repeated questions or lost in the middle.

DRS-R-98 OPTIONAL ITEMS

These 3 items can be used for the differential diagnosis of delirium from other diseases as well as for diagnostic or research purposes. They are NOT included in the total severity score.

Temporary onset of symptoms.

Assess the speed of onset of the symptoms of the current episode, do not valuethe time of evolution. Distinguish the onset of symptoms attributable todelirium when they occur concomitantly with other pre-existing psychiatric pathologies. For example, if a patient with major depression is evaluated during an episode of delirium for an overdose, assess the speed of onset of delirium symptoms.

0. No significant change from baseline.

1. Gradual onset of symptoms, over a period of weeks or months.

2. Acute change in behavior orpersonhood occurring within days or a week.

3. Abrupt change in behavior orbehavior, occurring over a period of hours or a day.

Fluctuating in symptom severity.

Assess the oscillations of the symptoms individually or grouped during the chosen period of time. It is usually applied to cognition, affect, intensity of hallucinations, alteration of thought and alteration of language. Keep in mind that perceptual disturbances usually appear intermittently, but can have moments of greaterintensity when the other symptoms fluctuate in severity.

0. No fluctuation of symptoms.

1. Symptoms fluctuate in severity over hours.

2. Symptoms fluctuate in severity within minutes.

Medical illness

Assess the degree to which a physiological, medical or pharmacological problemmay be the cause of the symptoms evaluated. Many patients have these problems but there may not be a cause-and-effect relationship .

0. None present or active.

1. presence of any physical problems that interfere with mental state

2. medication, infection, metabolic disturbance, CNS injury, or any other medical problem that may specifically be involved in the cause of altered consciousness or mental status.

DRS-R-98 SPANISH VERSION

SEVERITY SCORE: _____ TOTAL SCORE: _____

Severity item ScoreAdditional information

Sleep-wake cycle 0 1 2 3 ❑ naps ❑only nocturnal disturbance ❑Night-day investment

Alterations of perception 0 1 2 3 Sensory type of illusion or hallucination: ❑auditory ❑visual ❑olfactory ❑tactile Form of illusion or hallucination: ❑simple ❑complex

Delusions 0 1 2 3 Type of delirium: ❑ persecution ❑grandiosity ❑somatic Form: ❑little systematized ❑structured

Affective Lability 0 1 2 3 Type: ❑anger ❑anxiety ❑sadness-dysphoria ❑hyperthymia ❑irritability

Language 0 1 2 3 Intubation, mutism, etc. ❑

Course of thought0 1 2 3 Intubation, mutism, etc. ❑

Motor agitation 0 1 2 3 In contention ❑ Containment type:

Psychomotor retardation 0 1 2 3 In containment ❑ Containment type:

Orientation 0 1 2 3 Date: Place: Person:

Attention 0 1 2 3

Short-term memory 0 1 2 3 memorized ❑Number of trials until items are ❑Able to remember with help

Long-term memory 0 1 2 3 with help ❑Indicate if you are able to remember

Visuospatial capacity0 1 2 3 hands ❑Indicate if you are unable to use your

Diagnostic item ScoreAdditional information

How to start the Symptoms0 1 2 3 to another psychopathology ❑Indicate if the symptoms may belong

Fluctuation in the severity of symptoms0 1 2 during the night ❑Indicate if there are symptoms that only appear

Medical pathology 0 1 2 Diseases involved

ANNEX 4

SF-36 HEALTH STATUS QUESTIONNAIRE

1. In general, you would say that your health is:

Excellent 1
Very good2
Good 3
Regular4
Bad 5

2. How would you say your health is compared to a year ago?

Much better now than a year ago 1
Somewhat better now than a year ago 2
More or less the same now as a year ago 3
Worse now than a year ago4
Much better now than a year ago 5

3. The following questions refer to activities or things you might do on a typical day. Does your current health limit you from doing those activities or things? If so, how much?

	Yes, yes, no limits me it Much	**a little**	**does not limit me limits nothing**
Activities			
Intense efforts, such as running, lifting heavy objects or participating in sports Strenuous	1	2	3
Moderate efforts, such as moving a table,1 vacuuming, bowling or walking more than an hour		2	3
Picking up or carrying the shopping bag	1	2	3
Climbing severalfloors up the stairs	1	2	3
Climbing a single floor up the staircase	1	2	3
Bending or kneeling	1	2	3
Walking one kilometre or more	1	2	3
Walk several blocks (several hundred of meters)	1	2	3
Walking a single block (about 100 meters)	1	2	3
Bathingor dressing oneself	1	2	3

4. During the last four weeks, have you had any of the followingproblems at work or in your daily activities because of your physical health?

	Yes	**No**
Did you have to reduce the time spent at work or in your activities of daily living?	1	2
Did he do less than hewould have wanted to do?	1	2
Did you have to stop doing some tasks at your job or in your activities of daily living?	1	2

Did you have difficulty doing your job or activities?
everyday (for example, did it cost you more than usual)? 1 2

5. During the past four weeks, have you had any of the following problemsat work or **in your daily activities because of any emotional problems(such as being sad**, **depressed, or nervous)?**

	Yes	**No**
Did you have to reduce the time spent at work or in your Everyday activitiesfor any emotional problems?	1	2
Did he do less than he would have wanted to do, Orany emotional problems?	1	2
Didn't you do your job or your day-to-day activities so carefully as usual, for any emotional problem?	1	2

6. Over the past four weeks, to what extent have your physical health or emotional problems hindered your usual social activities with the family, **friends, neighbours or others?**
Nothing 1
A poco2
Teamlar 3
Pretty much. 4
Mucho5

7. Did you have pain anywhere in your body during the past four weeks?
No, none 1
Yes, very little 2
Yes, a little 3
Yes, moderate 4
Yes, a lot 5
Yes, very much6

8. Over the past four weeks, how much has the pain made it difficult for you to do your usual job (including work outside the home and household chores)?
Nothing 1
A little 2
Regular 3
LowAunt 4
Mucho 5

9. The questions that follow relate to how you have felt andhow things have gone over the past four weeks. In each question, answer what most closely resembles how you have felt . During the last four weeks, how long...?

	Always	**Almost Always**	**many times**	**some**	**only some time**	**never**
Felt full of vitality	1	2	3	4	5	6
He was very nervous	1	2	3	4	5	6
I feel so low morale	1	2	3	4	5	6
that nothing could encourage him	1	2	3	4	5	6
Felt calm and calm	1	2	3	4	5	6
Had a lot of energy	1	2	3	4	5	6
Felt discouraged and sad	1	2	3	4	5	6
Felt exhausted	1	2	3	4	5	6

Felt happy 1 2 3 4 5 6
Felt tired1 2 3 4 5 6

10. Over the past four weeks, how often have physical health oremotional problems hindered your social activities (such as visiting friends or family)?
Always 1
Almost always 2
Sometimes 3
Only once 4
Never 5

11. Please say whether each of the following phrases seems true or false to you:

	Totally true	**Quite true**	**I know**	**Totally false**
I think I get sick more easily than other people	1	2	3	4 5
I'm as healthy as anyone	1	2	3	4 5
I think my health is going to get worse	1	2	3	4 5
My health is excellent	1	2	3	4 5

INSTRUCTIONS: The above questions pertain to what you think about your health. Your answers will let you know how you are doing and to what extent you are able to do your usual activities.
Answer each question as directed. If you are not sure how to answer a question, please answer what seems most true to you. Remember, you need to dial only one number per question.

TOTAL SCORE:

ANNEX 5

The Clavien-Dindo Classification

The therapy used to correct a specific complication is the basis of this classification in order to rank a complication in an objective and reproducible manner.

It consists of 7 grades (I, II, IIIa, IIIb, IVa, IVb and V). The introduction of the subclasses a and b allows a contraction of the classification into 5 grades (I, II, III, IV and V) depending on the size of the population observed or the of the focus of a study.

Complications that have the potential for long-lasting disability after patient's discharge (e.g.: paralysis of a voice cord after thyroid surgery) are highlighted in the present classification by a suffix ("d" for disability). This suffix indicates that a follow-up is required to comprehensively evaluate the outcome and related long-term quality of life.

GRADES	DEFINITION
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventionsAllowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusionsand total parenteral nutritionare also included.
Grade III	Requiring surgical, endoscopic or radiological intervention
IIIa	Intervention not under general anesthesia
IIIb	Intervention under general anesthesia
Grade IV	Life-threatening complication (including CNS complications)* requiring IC/ICU-management
VAT	single organ dysfunction (including dialysis)
IVb	multiorgandysfunction
Grade V	Death of a patient

**brain hemorrhage, ischemic stroke, subarrachnoidalbleeding,but excluding transient ischemic attacks (TIA);IC: Intermediate care; ICU: Intensive care unit.*

ANNEX 6

Complications not associated with delirium

List of complications to collect in the CRD include, but are not limited to:

1) Medical complications:

- cardiovascular events: arrhythmias, myocardial injury after non-cardiac surgery (MINS), acute myocardial infarction (AMI), acute pulmonary edema (PAD), shock any etiology, cardiac arrest...

- pulmonary: atelectasis, pleural effusion, respiratory failure, bronchoaspiration, adult respiratory distress syndrome (ARDS), fat embolism...

- gastrointestinal: paralytic ileus, diarrhea or colitis, acute dysgestive hemorrhage (HDA), intestinal ischemia...

- renal: acute retention urine, acute renal failure (classification according to AKIN scale)...

- cerebrovascular: stroke, convulsions, malignant hyperthermia...

- Infectious: urinary tract infection, pneumonia, sepsis/septic shock of any etiology...

- thrombosis: deep vein thrombosis, pulmonary thromboembolism...

-haemorrhage.

- allergic reaction.

2) Surgical complications:

- Anastomos fugue.

- Bleeding surgical site.

- Surgical site infection: which can be superficial or deep infection, infection of an organ or space.

All previous events that reach grade II Clavien-Dindo severity scale and all those events that, at the discretion of the researcher, are relevant to the development of the study and patient safety must be collected in the Data Collection Booklet, in the "Complications" section.

ANNEX 7

Adverse reactions to quetiapine (SmPC)

Sistema de clasificación de órganos	**Muy frecuentes**	**Frecuentes**	**Poco frecuentes**	**Raras**	**Muy raras**	**Frecuencia no conocida**
Trastornos de la sangre y del sistema linfático	Disminución de la hemoglobina	Leucopenia, disminución del recuento de neutrófilos, aumento de eosinófilos	Trombocito-penia, anemia, disminución del recuento de plaquetas	Agranulocitosis		Neutropenia
Trastornos del sistema inmunológico			Hipersensibi-lidad (incluyendo reacciones alérgicas en la piel)		Reacción anafiláctica	
Trastornos endocrinos		Hiperprolac-tinemia, disminución de T4 total, disminución de T4 libre, disminución de T3 total, aumento de TSH	Disminución de T3 libre, hipotiroidism o		Secreción inapropiada de la hormona antidiu-rética	
Trastornos del metabolismo y de la nutrición	Elevación de los niveles de triglicéridos séricos; Elevación del colesterol total (predominan-temente colesterol LDL); Disminución de colesterol HDL, aumento de peso	Aumento del apetito, aumento de glucosa en sangre a niveles hiperglucé-micos	Hiponatre-mia, diabetes Mellitus	Síndrome metabólico	Exacerba-ción de la diabetes pre-existente	

Sistema de clasificación de órganos	**Muy frecuentes**	**Frecuentes**	**Poco frecuentes**	**Raras**	**Muy raras**	**Frecuencia no conocida**
Trastornos psiquiátricos		Sueños anormales y pesadillas, ideación suicida y comporta-miento suicida		Sonambulismo y reacciones relacionadas tales como hablar dormido y desorden alimenticio relacionado con el sueño		
Trastornos del sistema nervioso	Mareo, somnolencia, cefalea, síntomas extrapiramidales	Disartria	Convulsiónes, síndrome de piernas inquietas, discinesia tardía,			
Trastornos cardíacos		Taquicardia, palpitaciones	Prolongación del QT, Bradicardia			
Trastornos oculares		Visión borrosa				
Trastornos vasculares	Hipotensión ortostática			Tromboembo-lismo venoso		
Trastornos respiratorios, torácicos y mediastínicos		Disnea	Rinitis			
Trastornos gastrointes-tinales	Sequedad de boca	Estreñimien-to, dispepsia, vómitos	Disfagia	Pancreatitis, Obstrucción intestinal/Íleo		
Trastornos hepatobilia-res		Elevación de la alanina-aminotransfer asa sérica (ALT), elevación de los niveles de gamma-GT	Elevación de la aspartato-aminotransfer asa sérica (AST)	Ictericia, hepatitis		

Sistema de clasificación de órganos	**Muy frecuentes**	**Frecuentes**	**Poco frecuentes**	**Raras**	**Muy raras**	**Frecuencia no conocida**
Trastornos de la piel y del tejido subcutáneo					Angioede- ma, síndrome de Stevens-Johnson	Necrolisis Epidérmica Tóxica, Eritema Multiforme; Erupción medicamentosa con eosinofilia y síntomas sistémicos (DRESS)
Trastornos musculoesqueléticos y del tejido conjuntivo					Rabdomio-lisis	
Trastornos renales y urinarios			Retención urinaria			
Embarazo, puerperio y enfermedades perinatales						Síndrome de abstinencia neonatal de fármacos
Trastornos del aparato reproductor y de la mama			Disfunción sexual	Priapismo, galactorrea, hinchazón de las mamas, trastorno menstrual		
Trastornos generales y alteraciones en el lugar de administra-ción	Síntomas de retirada (interrupción)	Astenia leve, edema periférico, irritabilidad, pirexia		Síndrome neuroléptico maligno, hipotermia		
Exploraciones complementa-rias				Elevación de creatina-fosfoquinasa en sangre		