THE GENOME-WIDE ASSOCIATION AND PHARMACOGENOMIC STUDY OF SCHIZOPHRENIA

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Study Summary

Title	*The genome-wide association and pharmacogenomic study of schizophrenia*
Short Title	*Pharmacogenomic study of the effects of antipsychotics in patients with schizophrenia*
IRB Number	*2010-18*
Methodology	*Open label; Randomized.*
Study Duration	*2010-2012*
Study Center(s)	*Five study centers*
Objectives	*Primary:* • *To investigate the relationship between the common variants and the efficacy of acute-stage antipsychotics treatment and the side-effects of antipsychotics.* *Secondary:* • *To compare the first-generation antipsychotics, haloperidol and perphenazine, with five commonly used atypical drugs in patients with acute-phase schizophrenia*
Number of Subjects	*3000 subjects expected to be enrolled across 5 sites*
Main Inclusion and Exclusion Criteria	**Inclusion Criteria:** *1. Chinese Han descents; 2. Patients diagnosed with schizophrenia with first-onset or chronic disease; 3. Patients with total scores of the PANSS more than 60; 4. Patients who give the written informed consent.* ***Exclusion Criteria****: 1. Patients who are pregnancy or breast-feeding; 2. Patients with the contraindications of the recommended drugs; 3. Patients with severe or unstable physical diseases; 4. Patients with following heart diseases: QTc>450 ms in male, or QTc>470ms in female; Decompensated and congestive heart failure; Complete left bundle branch block delay.*

Investigational Product (drug, biologic, device, etc.) **For Device include the planned use** **For Drug, food, cosmetic, etc. include the dose, route of administration and dose regiment**	*Olanzapine doses could range from 5 mg to 20 mg per day, risperidone from 2 mg to 6 mg per day, quetiapine from 400 mg to 750 mg per day, aripiprazole from 10 mg to 30 mg per day, ziprasidone from 80 mg to 160 mg per day, haloperidol from 6 mg to 20 mg per day, and perphenazine from 20 mg to 60 mg per day.*
Statistical Methodology	*We evaluate the associations between allele dosages and treatment response using linear regression under an additive genetic model implemented in PLINK v1·07. Gender, age, site of collection, and the first five principal components of population structure and other factors are used as covariates.*
Safety Evaluations	*Site investigators will be responsible for monitoring the safety of study participants. They must alert the Medical Officer of any event that seems unusual. The investigators will be responsible for appropriate medical care of study participants during the study, in connection with study procedures.*
Data and Safety Monitoring Plan	*PIs will be responsible for monitoring the data quality and the ongoing safety of subjects.*

BACKGROUND AND STUDY RATIONALE

This study will be conducted in full accordance all applicable Peking University Research Policies and Sichuan University and Procedures and all applicable Chinese laws and regulations.

Introduction

Antipsychotics are the cornerstone for clinical treatment of schizophrenia, but patients showed variations in response to antipsychotic drug treatment. Previous studies demonstrated that genetic components play a vital role in individual differences and identified several candidate genes for variabilities of treatment response. However, the vast majority of common variants were identified in Caucasian samples. Additional risk variants may be detected when increasing sample size in different samples. Therefore, the Chinese antipsychotic pharmacogenomics consortium (CAPOC) was set to understand how genetic variants influence antipsychotic treatment response and side effects.

1.1 Background and Relevant studies

Schizophrenia is a chronic and severe mental disease that affects approximately 1% of the world's population.[1] Currently, antipsychotic drugs are the mainstay treatments of schizophrenia and reduce the risks of clinical deterioration and psychotic relapse.[2] Three-quarters show low compliance for antipsychotic medications because of ineffectiveness or side-effects.[3] In turn, this may cause clinical exacerbation or psychotic relapse which often results in hospitalization and cause considerable burden on patients and their family. Antipsychotics corresponds to a considerable fraction of healthcare costs in most developed countries. [4,5] A modest improvement in outcomes may provide great benefits for the society. Therefore, it is important to understand biological mechanisms of antipsychotic treatment response.

The heritability for antipsychotic drug responses are extremely limited because of difficulties recruiting twin pairs who have received the same antipsychotic treatment.[6,7] Several twin and family studies suggest that response to antipsychotic treatment is a heritable trait. The studies on monozygotic twins observed similar response to treatment with antipsychotics and similar levels of antipsychotic-induced weight gain.[6,7] Given that schizophrenia has a high heritability, it is likely that there is a substantial genetic component to individual differences in treatment response. [8,9]

In the past decades, pharmacogenetics researches have succeeded in identifying genetic variants associated with variability in antipsychotic treatment. [10-17] These studies have focused on encoding drug targets (pharmacodynamic candidates) or for involvement in the metabolism of the drug itself (pharmacokinetic candidates). Pharmacodynamic candidates have shown positive associations with treatment response, such as dopamine receptors D2 (DRD2) and D3 (DRD3) and serotonin receptor genes, including 5-Hydroxytryptamine Receptor 2A (HTR2A) and 2C (HTR2C).[10-14] Pharmacokinetic candidate include the cytochrome P450 genes and ABCB1 transporter genes.[15-17] In contrast to candidate gene-based methods, GWAS studies could identify candidate variants without introducing prior hypothesis bias. Several groups have performed GWAS to identify candidate biomarkers for treatment response and side effect of antipsychotics. Currently, the researchers mainly used the genotyping data from the original Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study and focused on various phenotypes. For example, McClay et al[18] used Positive and Negative Syndrome Scale (PANSS) subscales as well as PANSS total as measures of treatment response and identified two intragenic

SNPs were nearly close to the significant GWAS-based threshold, including rs7968606 (ANKS1B) for negative symptom improvement with olanzapine and rs17727261 (CNTNAP5) for negative symptom improvement with risperidone. Furthermore, they focused on neurocognition and used five neurocognitive domains and a composite neurocognitive score as drug response indicators. They found that DRD2 mediated the effects of olanzapine on working memory, LPHN3 and CLDN1 mediated the effects of quetiapine on working memory.[19] Clark et al. used clinical global impression (CGI) of response scales as a measure of treatment response.[20] They found that PDE4D mediated the effects of quetiapine on patient reported severity, TJP1 mediated the effects of risperidone on patient reported severity, and PPA2 mediated the effects of risperidone on clinician reported severity.

Numerous studies have shown that antipsychotic treatment is often associated with medical complications. The first-generation antipsychotics (FGAs) could relieve a substantial proportion of schizophrenia patients to improve or relapse frequently, however, they often accompanied with significant side effects, including extrapyramidal symptoms and tardive dyskinesia. The second-generation antipsychotics (SGAs) show lower affinity for the dopamine 2 receptor and relatively greater affinities for other neuroreceptors, but they are associated with a variety of metabolic side effects such as dyslipidemia, elevated glucose levels and weight gain. Pharmacogenetic research efforts have focused on the identification of genetic variants contributing to individual variability regarding several antipsychotic-related phenotypes. Previous studies have reported using the CATIE sample to perform GWAS for antipsychotic induced side effects. Adkins et al. performed GWAS in the CATIE sample for a number of metabolic side effects.[21] GPR98 and NR3C1 genes were respectively found to be associated with HbA1c levels in schizophrenia patients treated with olanzapine and risperidone. The MEIS2 gene was identified to be correlated with waist and hip circumferences for patients treated with risperidone. Aberg et al. performed GWAS for extrapyramidal side effects in the CATIE sample.[22] They found three SNPs rs17022444, rs7669317 and rs2126709 (ZNF202) were significantly associated with movement-related adverse antipsychotic effects.

However, the vast majority of common variants associated with treatment response and side effects of antipsychotics were identified in large samples of Caucasian ancestry.[18-22] The associated variants identified in populations of Caucasian ancestry might not totally be significant in other ancestry groups because of underlying genetic heterogeneity. Therefore, large scale studies in Chinese and other non-Caucasian population are needed not only to evaluate whether the previous reported genetics variants could be generalized to the non-Caucasian population, but also to identify new associated variants for antipsychotics.

In recent years, the role of rare variants has been recognized in several neuropsychiatric disorders, including schizophrenia,[23-27] intellectual disability,[28-30] autism spectrum disorder,[31-33] and serotonin re-uptake inhibitor treatment response in major depression.[34] Since most drugs exert their effects through protein binding, whole exome sequencing (WES) offers a cost-effective strategy for investigating rare functional variants in drug response studies.[35] In addition, rare variants in specific genes or gene-sets may define a disease subtype that is relatively non-responsive to the standard drug treatment for a disorder.

1.2 Overview of Trial Design

This study is a randomized controlled trial of up to 3000 patients with schizophrenia involving the following medications: aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone, haloperidol or perphenazine. Patients will be followed for up to six weeks. Patients are enrolled form members from five research centres (Peking University

Sixth Hospital, West China Hospital of Sichuan University, the Second Xiangya Hospital of Central South University, Beijing Anding Hospital Affiliated to Capital Medical University, and Beijing HuiLongGuan Hospital). The Consortium, which leads 32 psychiatric hospitals in China, aims to understand the relationship between genetic variants and antipsychotic treatment responses in patients with schizophrenia.

2 Study Objectives

2.1 Primary Objective

- To investigate the relationship between the common variants and the efficacy of acute-stage antipsychotics treatment or the side-effects of antipsychotics.

2.2 Secondary Objectives

- To compare the first-generation antipsychotics, haloperidol and perphenazine, with five commonly used atypical drugs in patients with acute-phase schizophrenia.

3 Investigational Plan

3.1 General Design

Patients will be enrolled from five research centers (the Sixth Hospital of Peking University, the Second Xiangya Hospital of Central South University, West China Hospital of Sichuan University, Beijing Anding Hospital, and Beijing HuiLongGuan Hospital) comprised of 32 hospitals across China. As known, schizophrenia is mainly diagnosed based on subjective symptoms. Therefore, considering the importance of coherence, we will conduct five trainings for the psychiatrists and in 32 hospitals respectively. The content of training included research protocols, diagnostic criteria and instrument, scales for assessment of symptoms and side effects, blood sample collection and evaluation of inter-rater reliability as well.

Patients were initially randomly assigned to seven groups, including aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone, haloperidol and perphenazine groups. Randomization was performed as complete randomization with a 2:2:2:2:2:2:1:1 allocation. Group assignment was determined by a Microsoft Excel randomization generator. The random allocation sequence was generated by a trained research assistant. Then, we performed several assessments of baseline at the start of the study. The patients who meet the criterion are followed for up to six weeks or until treatment was discontinued for any reason.

3.1.1 Screening Phase

Subjects will be recruited through the oral explanation of the study. Interested subjects will be consented verbally over the interview, by the clinical doctor. A series of questions will be asked over the interview to determine if the potential subject is within the correct age range and geographic location. Potential subjects eligible based on these criteria will be brought in for a second screening visit at which time labs will be conducted as described in the inclusion/exclusion criteria section of the protocol. Written consent will be obtained before the screening labs are conducted.

3.1.2 Allocation to Interventional Group

The randomization algorithm will be built into the electronic data capture system, Once the randomization form is entered into the system and saved, the back end algorithm will run and a participant will be assigned a kit number corresponding to either drug. The master list of kit number assignments will be kept by the data coordinating center in a password protected and encrypted laptop.

3.2 Study Endpoints

3.2.1 Primary Study Endpoints

The primary endpoint will be % change in PANSS score between the baseline visit and last visit. The % change in PANSS score is defined as following, PANSS reductive ratio = (PANSS baseline score-PANSS follow-up score) ÷ (PANSS baseline score-30).

3.2.2 Secondary Study Endpoints

We evaluate two kinds of phenotypes for side-effects of antipsychotics: dichotomous phenotype and continuous phenotype. (i) Dichotomous phenotype: patients with metabolic syndromes (MetS) vs patients without MetS. Diagnosis of MetS is based on the definition by the International Diabetes Federation Chinese criteria. Those with central obesity assessed by waist circumference ≥ 90 cm in males and ≥ 80 cm in females, plus two of the following: elevated triglycerides level ≥ 1.7 mmol/L (or use of a fibrate), high-density lipoprotein < 1.03 mmol/L in males and < 1.29 mmol/L in females (or use of a statin), fasting glucose ≥ 5.6 mmol/L (or use of an antidiabetic drug) and systolic arterial blood pressure ≥ 130mmHg and/or diastolic arterial blood pressure ≥ 85mmHg (or use of an antihypertensive drug) were identified as having MetS. (ii) Continuous phenotype: quantifying antipsychotic-induced change in the assessments as described above, for example, change in BMI, blood lipids, glucose, and hemoglobin.

4 Study Population and Duration of Participation

4.1 Inclusion Criteria

Individuals included for the present study had a diagnosis of schizophrenia determined by the Structured Clinical Interview of DSM-IV, were 18–45 years old, and of Han Chinese ancestry, had a total score of the positive and negative syndrome scale (PANSS) more than 60, and at least three positive items cored more than four, were physically healthy and had all laboratory parameters within normal limits, had a condition appropriate for treatment with an oral medication, and provided informed consent. First-episode or relapsed patients with schizophrenia were enrolled from the inpatients departments of the psychiatric hospitals of CAPOC project. The patients were without prior antipsychotics for more than one week before enrollment. Within two weeks before the enrollment and throughout the study, patients should have not taken drugs inducing or inhibiting liver enzyme. After study entry, the antipsychotics remained unchanged throughout the study. All participants are asked to appoint a family member or close friend who is involved with the informed consent discussion and assists the patient with decision making.

4.2 Exclusion Criteria

Patients were excluded from the study if they met the following criteria: 1) diagnosed as schizoaffective disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, schizophreniform disorder, psychosis associated with substance use or medical conditions, mental retardation, pervasive developmental disorder, delirium, dementia, amnesia, or other cognitive disorders. 2) Patients with severe unstable physical diseases, such as diabetes, thyroid diseases, hypertension, cardiac diseases. 3) Patients with malignant syndrome and acute dystonia. 4) Patients with well-documented histories of epilepsy and hyperpyretic convulsion. 5) Patients with a DSM-IV diagnosis of alcohol and drug dependence. 6) Patients who require long-acting injectable medication to maintain treatment adherence. 7) Patients regularly treated with clozapine for treatment over the past month. 8) Patients who treated with electroconvulsive therapy over the last month. 9) Patients with the history of drug-induced malignant syndrome. 10) Patients who has serious suicide attempt, or severe excitement and agitation situations. 11) Patients with the following abnormity of liver or renal function examination test: Aspartate transaminase (AST) ≥ 80 U/L; Alanine transaminase (ALT) ≥ 80 U/L; Blood urea nitrogen (BUN) ≥ 9.75 mmo]/L; Urine creatinine ≥ 21.6 mmol/d. 12) Patients who have no legal guardian. 13) Patients with the following cardiac conditions: QTc prolongation (screening electrocardiogram

with QTc > 450 msec for men, QTc > 470 msec for women); history of congenital QTc prolongation; recent myocardial infarction (< 6 months); 14) Women who are pregnant or breastfeeding. 15) Patients with a contraindication to any of the drugs to which they might be assigned.

4.3 Subject Recruitment

The members of CAPOC from five research centers (the Sixth Hospital of Peking University, the Second Xiangya Hospital of Central South University, West China Hospital of Sichuan University, Beijing Anding Hospital and Beijing HuiLongGuan Hospital) are responsible for patient recruitment. Patients with schizophrenia are recruited through inpatient units from five clinical research centers. All participants are asked to appoint a family member who is involved with the informed consent discussion and assists the patient with decision making. All recruitment materials, which will be seen by potential participants, need to be approved by the IRB of each center.

4.4 Duration of Study Participation

The duration of the study subjects' participation, including screening, study intervention phase and any follow up time period, is about 6 weeks

4.5 Total Number of Subjects and Sites

500 subjects will be enrolled from each of the 5 centers.

4.6 Vulnerable Populations:

Pregnant women, fetuses, neonates, or prisoners are not included in this research study

5 Study Intervention (Study drug, device, biologic, vaccine, food etc.)

5.1 Description

Patients will take tablet, including aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone, haloperidol or perphenazine).

5.2 Intervention Regimen

Patients who met inclusion criteria were randomly assigned to six groups (aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone, and one of the first-generation antipsychotic, haloperidol or perphenazine). Within the first two weeks after enrollment, the psychiatrists from the CAPOC study adjusted drug dosages based on the treatment effectiveness following the study protocol (olanzapine 5–20 mg/d, risperidone 2–6 mg/d, quetiapine 400–750 mg/d, aripiprazole 10–30 mg/d, ziprasidone 80–160 mg/d, haloperidol 6–20 mg/d, and perphenazine 20–60 mg/d). The dosage of antipsychotics then remained unchanged throughout the study. The patients were evaluated by a participating psychiatrist at baseline, weeks 2, 4, and 6, and their PANSS scores were recorded.

5.3 Receipt

The investigational drug will be obtained from the CAPOC hospital.

5.4 Storage

The investigational drug will store in the pharmacy of each research center at room temperature, keeping in a cool dry room

5.5 Blinding

The random allocation sequence was generated by a trained research assistant who had no further role in the trial, and was concealed until after baseline assessments. The researchers doing both the baseline and the follow-up assessments were masked to the group assignments of each participant. Patients and psychiatrists were unmasked to assigned antipsychotics.

6 Study Procedures

Below is a schedule of events for the CAPOC project

TABLE 1: SCHEDULE OF STUDY PROCEDURES

	First interview (Baseline)	Second interview (14^{th} day)	Third interview (28^{th} day)	Fourth interview (42^{th} day)
Informed consent	*			
Subjects screen	*			
General information	*			
Symptoms and medical history	*			
DSM-IV-TR (SCID)	*			
Body and nervous system examination	*	*	*	*
Vital signs	*	*	*	*
Weight and waist circumference	*	*	*	*
PANSS and CGI	*	*	*	*
SAESS, BARS, AIMS and UKU	*	*	*	*
Laboratory examination	*		*	*
Electrocardiograph (ECG)	*		*	*
Blood drawing for genotyping	*			
Plasma Concentration			*	*
Concomitant medications monitoring	*	*	*	*
Adverse events	*	*	*	*
Form for the ending				*

Abbreviations: PANSS, Positive and Negative Syndrome Scale; CGI, clinical global impression; SAESS, Simpson-Angus Extrapyramidal Signs Scale; BARS, Barnes Akathisia Rating Scale; AIMS, Abnormal Involuntary Movement Scale; UKU, Udvalg for Kliniske Under-sogelser.

6.1 Screening

Participants who meet inclusion criteria that are broad and nonrestrictive will be recruited from clinical facilities that are representative of the sites where persons with schizophrenia receive mental health care in China. The sample will include 3000 patients representing the schizophrenias. The screening visit will consist of screening tests, patient history, laboratory tests, and physical and psychiatric examinations. The baseline visit will occur within 21 days of the screening visit. The results of all screening tests will be reviewed prior to the baseline visit. All inclusion and exclusion criteria will be verified at the baseline visit in order for patients to be randomly assigned to a treatment

group. Patients who do not meet all enrollment criteria at the baseline visit will not be randomized and their participation in the study will end. Patients who meet all criteria will be enrolled in the study and will be randomized to a study medication.

6.2 Study Intervention Phase

Treatment Phase begins a 6-week treatment period. Qualified patients will be assigned at the baseline visit to one of the treatment groups according to their clinical situation.
3000 patients without tardive dyskinesia will be randomly assigned to one of six treatment conditions for up to 6 months:
500 patients will begin open-label treatment with perphenazine or haloperidol;
500 patients will begin open-label treatment with olanzapine;
500 patients will begin open-label treatment with quetiapine;
500 patients will begin open-label treatment with risperidone;
500 patients will begin open-label treatment with aripiprazole;
500 patients will begin open-label treatment with ziprasidone.

6.2.1 Baseline visit

A physical exam must be conducted for screening purposed but if one was conducted within the past 30 days for standard of care purposes, this can be used for screening/eligibility.

- Informed consent
- Subjects screen
- Randomization
- General information
- Symptoms and medical history
- Vital Signs
- Weight and waist circumference
- Laboratory Tests
- PANSS and CGI
- Adverse reaction assessment
- Concomitant medications monitoring
- Electrocardiograph (ECG)
- Blood drawing for genotyping

6.2.2 Visit 2

List of all the procedures that will take place at study visit 2

- Vital Signs
- Weight and waist circumference
- PANSS and CGI
- Adverse reaction assessment
- Concomitant medications monitoring

6.2.3 Visit 3

- Vital Signs
- Weight and waist circumference
- Laboratory Tests
- PANSS and CGI
- Adverse reaction assessment
- Concomitant medications monitoring

- Electrocardiograph (ECG)

6.2.4 Visit 4

- Vital Signs
- Weight and waist circumference
- Laboratory Tests
- PANSS and CGI
- Adverse reaction assessment
- Concomitant medications monitoring
- Electrocardiograph (ECG)

6.3 Subject Withdrawal

Subjects may withdraw from the study at any time without impact to their care. They may also be discontinued from the study at the discretion of the Investigator for lack of adherence to intervention or study procedures or visit schedules, AEs, or other reasons. The Investigator may also withdraw subjects who violate the study plan, or to protect the subject for reasons of safety or for administrative reasons. It will be documented whether or not each subject completes the clinical study. If treatment was discontinued, the last observation was carried forward to represent treatment response.

7 Study Evaluations and Measurements

7.1 Medical Record Review

A list of the medical record review will be abstracted from the medical chart. Patients were excluded from the study if they were diagnosed with schizoaffective disorder, delusional disorder, brief psychotic disorder, schizophreniform disorder, psychosis associated with substance use or medical conditions, learning disability, pervasive developmental disorder, delirium, dementia, amnesia, or other cognitive disorders; had severe, unstable physical diseases (such as diabetes, thyroid diseases, hypertension, and cardiac diseases), malignant syndrome or acute dystonia, well documented histories of epilepsy and hyperpyretic convulsion, a DSM-IV diagnosis of alcohol or drug dependence, or a history of drug-induced neuroleptic.

7.2 Physical Examinations

The baseline evaluations include the medical history, physical examination, demographic characteristics (age, gender, and race) and other information that will be collected.

7.3 Laboratory Evaluations

Fasting blood glucose level, hemoglobin, lipid profile (total cholesterol, high-density lipoprotein [HDL) cholesterol, triglycerides), complete blood count, and serum prolactin level.

7.4 Pregnancy Testing

A urine pregnancy test will be performed for female subjects.

8 Statistical Plan

8.1 Sample Size and Power Determination

We calculate the power to detect the observed association findings under an additive genetic model using Quanto (version 1.2.4).

8.2 Statistical Methods

Using PLINK v1.07, we evaluated the association between allele dosages and the dichotomous phenotype by logistic regression, and the association between allele dosages and the quantitative phenotype by linear regression. We also used gender, age, site of collection and the first four principal components of population structure as a covariate. We

respectively examine the associations between the common variants and side-effects in the pooled antipsychotics treatment groups (seven drugs) and single antipsychotics.
For rare variants, variant-based, gene-based and get set based association analyses will be used and statistical tools included PLINK/SEQ, KGGSEQ AND RVTEST, etc. in addition, the data of KEGG and MGI will be used to explore gene set analyses.

8.2.1 Baseline Data

Baseline and demographic characteristics will be summarized by standard descriptive statistics (including mean and standard deviation for continuous variables such as age and standard percentages for categorical variables such as gender.

8.2.2 Efficacy Analysis

We use the PANSS reductive ratio for the evaluation of acute-stage treatment response to antipsychotic medications. The reductive ratio is defined as following, PANSS reductive ratio = (PANSS baseline score−PANSS follow − up score) ÷ (PANSS baseline score−30).

8.2.3 Interim Analysis

An interim analysis will be performed after the first 300 subjects are enrolled in the trial. At this time the safety and tolerability of the study dose will be assessed and if, deemed safe and appropriate, enrollment will continue.

8.2.4 Safety Analysis

All subjects entered into the study and randomized at the baseline visit will have detailed information collected on adverse events for the overall study safety analysis

9 Safety and Adverse Events

9.1 Definitions

9.1.1 Adverse Event

An **adverse event** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

9.1.2 Serious Adverse Event

Serious Adverse Event

Adverse events are classified as serious or non-serious. A **serious adverse event** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance.
- They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.
- All adverse events that do not meet any of the criteria for serious should be regarded as **non-serious adverse events**.

9.2 Adverse Event Process and Handling

At each contact with the subject, the investigator will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should record in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period will be recorded. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study intervention or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study intervention or study participation will be recorded and reported immediately.

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