Universitat de Girona

FINAL DEGREE PROJECT

ADVERSE DRUG REACTIONS AS A CAUSE OF ADMISSION TO HOSPITAL JOSEP TRUETA:

AN EPIDEMIOLOGICAL ANALYSIS

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0. ABSTRACT

Title

Adverse drug reactions as a cause of admission to Hospital Josep Trueta: an epidemiological analysis.

Background

Any substance that is capable of producing a therapeutic effect can also produce unwanted or adverse effects, affecting any body system and having different clinical presentations. Adverse Drugs Reactions (ADRs) are defined as a "response to a medicinal product which is noxious and unintended" and they are considered to be one of the major public health problems because of their impact in terms of morbidity, mortality and economic cost. However, despite the great number of methods proposed, assessing the causal role of a drug in thr occurrence of an adverse medical event remains one of the most controversial issues.

Objectives

To assess the prevalence of possible adverse drug reaction (ADR) as a reason of admission in Hospital Josep Trueta Emergency Department. Secondary objectives are to analyze the main factors, to identify the most common drugs implicated and to assess preventability and the patient's outcome related to ADR emergency admissions in Hospital Josep Trueta.

Methodology

Observational cross-sectional study performed in the Emergency Department of Hospital Josep Trueta. Prospective data from all suspected patients presenting an ADR as a reason of admission in the Emergency Department will be recorded for a posterior association assessment following WHO causality criteria. Information about age, gender, polypharmacy, preventability and the outcome will be also collected for further analysis.

Keywords

Adverse drug reaction, drug related admission, drug toxicity, polipharmacy, pharmacovigilance

ABBREVIATIONS

ADR: Adverse Drug Reaction

AEMPS: Agencia Española de Medicamentos y Productos Sanitarios

ATC: Anatomical Therapeutic Chemical Classification

CEIC: Comitè d'Ètica i Investigació Clínica

COPD: Cronic Obstructive Pulmonary Disease

ED: Emergency Department

EPA: Estudi Post-Autorització

EU: European Union

ICD: International Statistical Clasification of Diseases and Related Health Problems

ID: identification

NSAID: Non-Steroidal Antiinflammatory Drugs

OTC: Over The Counter

RAS: Renin-Angiotensin System

SDI: Suspected Drug Information

SPhVS: Spanish Pharmacovigilance System

SSRI: Selective Serotonin Reuptake Inhibitors

UMC: WHO-Uppsala Monitoring Centre

WHO: World Health Organization

WMA: World Medical Association

1. INTRODUCTION

1.1. GENERALITIES

Medicines are considered effective and safe treatments for the majority of diseases, one of the reasons why nowadays medication therapy is the most common form of therapy in health care (1). Nevertheless, adverse drug reactions (ADRs) are one of the major public health problems because of their impact in terms of morbidity, mortality and economic cost (1–9).

Any substance that is capable of producing a therapeutic effect can also produce unwanted or adverse effects. A drug has been tested in a limited number of patients before its commercialization. The information collected during the drug development pre-marketing phase is inevitably incomplete and it only allows for the discovery of the most common adverse reactions of that drug. At least 30,000 people should be treated with the drug to be sure that any patient with an ADR with an incidence of 1 in 10,000 exposed is not missed (9,10).

ADR was redefined as a "response to a medicinal product which is noxious and unintended" in 2010 by the European Pharmacovigilance legislation[1] (after the World Health Organization (WHO) first definition in 1972). With "Response", it is understood that a causal relationship between a medicinal product and an ADR is at least a reasonable possibility.

ADR can affect any body system and may have different clinical presentations. They may arise from the use of the drug within or outside[2] the terms of the marketing authorization, as well as from occupational exposure (3,11–13). For that reason, when a patient who is taking a drug is admitted to the Emergency Department (ED), the possibility of an ADR should be always included in the differential diagnosis, also assessing the use of over-the-counter[3] (OTC) drugs and complementary medicines as they are often not documented (6).

[1] Directiva 2010/84/UE del Parlamento Europeo y del Consejo de 15 de diciembre de 2010 *http://ec.europa.eu/health/files/eudralex/vol-1/dir_2010_84/dir_2010_84_es.pdf*

[2] Off-label use, overdose, misuse, abuse and medication errors

[3] Over-the-counter: drugs that can be bought without a medical prescription

The prevalence of ADR as a consultation reason in the Emergency Department has been extensively studied worldwide and it is estimated at approximately 5% of all consultations (1–4,7,14–18).

However, there are huge differences in the prevalence of ADR related admissions among those studies (prevalence varies from 0.6% to 20.9%) that can be easily explained by differences in their designs, types of studied events, definition of ADR applied, methods of identifying cases and methods for assessing causality (2,4,16).

Sometimes, although the ADR is recognized, it is not well codified, which can underestimate the number of ADRs as a cause of hospital admission increasing the difficulty to perform studies (4).

For these reasons, comparisons and extrapolations can be difficult to be done (3,6,16).

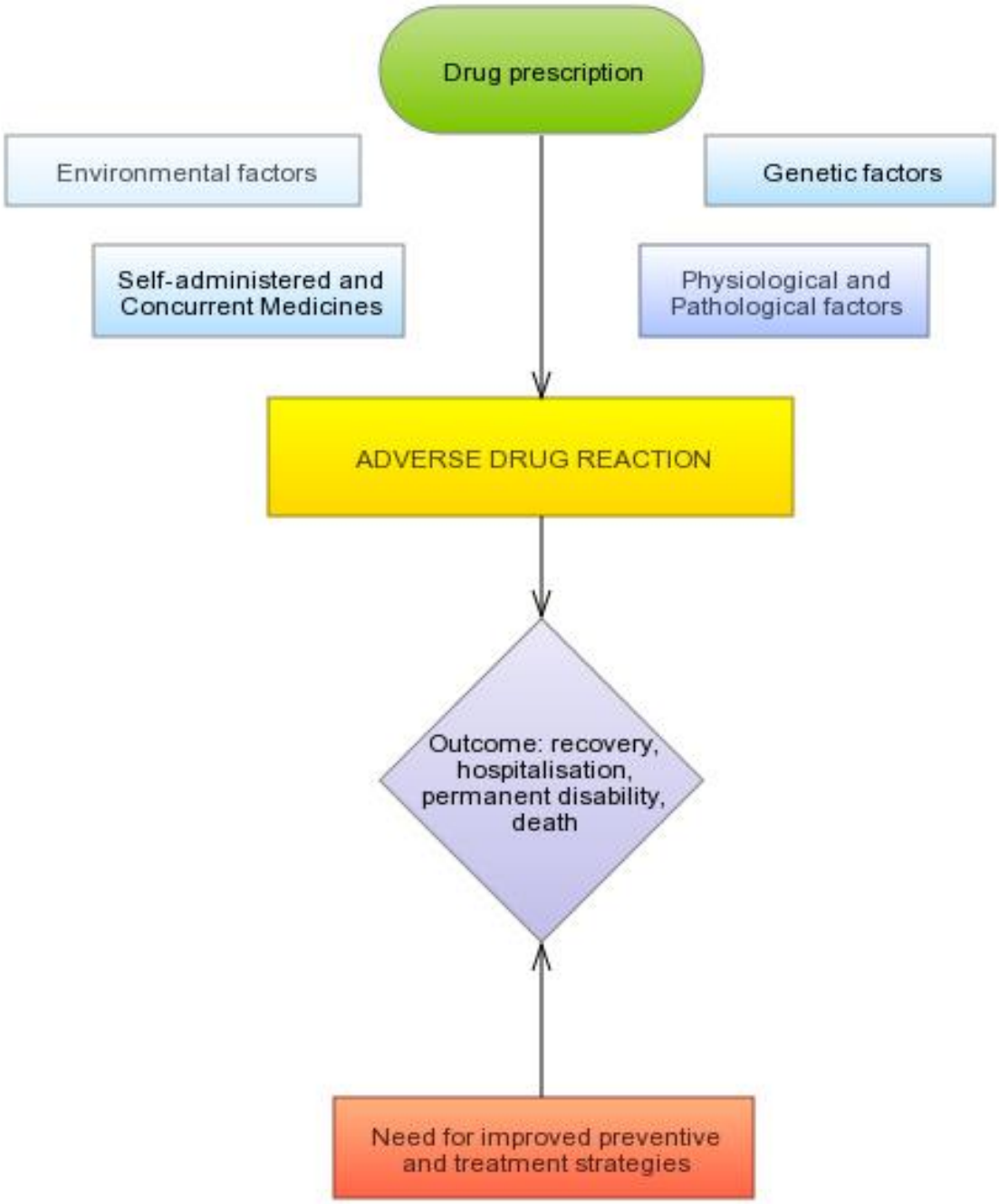
There are also some disagreements between countries (4,9) that can be related to differences in prevalent diseases, method of prescribing, genetics, drug distribution (also doses and availability), and use of traditional and complementary drugs *(figure 1)*.

In the attempt of identifying which are the most frequent drugs linked to ADR cases, huge differences between studies already performed have again been noticed. As it was mentioned above, this fact could be explained due to hospital and population differential characteristics. However, the most common drugs found in the studies are diuretics, antithrombotic drugs, renin-angiotensin system (RAS) inhibitors, non-steroidal anti-inflammatory drugs (NSAID), corticosteroids, β-adrenoreceptor blocking agents, analgesics, psycholeptics, antibiotics, antineoplastic, vaccines and immunosuppressive agents (2–4,7,14–17,19).

From here we can affirm that systems of pharmacovigilance[4] are needed in every country owing to the fact that information obtained from one country may not be relevant to other parts of the world, and also for the urgent elaboration of better local preventive strategies with the objective of reducing the burden of ADR that might be different depending on the country characteristics (6,9) *(figure 1)*.

[4] Activities related to detection, assessment, comprehension and prevention of drug related problems (see part 1.6)

Figure 1: Adverse drug reaction scheme (6)



1.2. DEFINITIONS

A) *Adverse effect / reaction*: unwanted effects, making no assumptions about the mechanism. They are interchangeable, except that an adverse effect is seen from the point of view of the drug, whereas an adverse reaction is seen from the point of view of the patient (12).

B) *Adverse event*: any unfavorable and unintended sign, symptom, or disease that may present during a treatment with a medicinal product but which does not necessarily have a causal relationship with it (9,20).

C) *Association*: events associated in time but not necessarily linked as cause and effect relation (20).

D) *Medication error*: mishaps that occur during prescribing, transcribing, dispensing, administering, adherence, or monitoring a drug. Not all medication errors lead to adverse outcomes. Those that are stopped before harm occur are sometimes called “near misses” or “close calls” or more formally, a potential adverse drug event (21).

E) *Side effect*: a known effect, not associated with the one primarily intended, related to the pharmacological drug properties, which may be beneficial as well as harmful. It can be dose-related or not (13).

F) *Toxic effect*: effect that occurs as an exaggeration of the desired therapeutic effect, and which is not common at normal doses. It occurs by the same mechanism as the therapeutic effect. It is always dose-related (12).

1.3. CLASSIFICATION OF ADR

The first ADR classification was performed by Rawlins and Thompson in 1977 as type A and type B reactions (6,22). There have been further attempts to extend and to redefine the classification and finally, we can divide an ADR into 6 different groups *(table 1).* However, type A and type B still being the most common way of classification.

Table 1. Classification of ADR (12,13,22,23)

Type of reaction	Characteristics	Management	Examples
A: Dose related (**A**ugmented)	◦ Common ◦ Enhance the normal therapeutic effect of a drug (known pharmacological action) ◦ Low mortality ◦ Predictable ◦ Can be replicated and studied experimentally	◦ Reduce dose or withhold ◦ Dose adjustment if renal/hepatic impairment	◦ Toxic effects: digoxin toxicity, serotonin syndrome with SSRIs ◦ Side effects: anticholinergic effects of tricyclic antidepressants ◦ Overdose due to renal or hepatic disease (pharmacokinetic alterations)
B: Non-dose-related (**B**izarre)	◦ Uncommon ◦ Neither related to a pharmacological drug action, nor to dose ◦ High mortality ◦ Unpredictable ◦ Can be immunological (hypersensitivity) or non-immunological ◦ Depend on individual patients' response to specific drugs	◦ Withhold and avoid in future	◦ Immunological reactions: penicillin hypersensitivity ◦ Idiosyncratic reactions: acute porphyria, malignant hyperthermia, pseudoallergy

C: Dose-related and time-related (**C**hronic)	◦ Uncommon ◦ Related to long term drug exposure (cumulative dose) ◦ Serious effects	◦ Reduce dose or withhold: withdrawal may have to be prolonged	◦ Analgesic nephropathy ◦ Some extrapyramidal effects ◦ Hypothalamic-pituitary-adrenal axis suppression by corticosteroids
D: Time-related (**D**elayed)	◦ Uncommon ◦ Usually dose-related ◦ Occurs or becomes apparent some time after starting drug use	◦ Often intractable	◦ Secondary neoplasia due to alkylating agents (cyclophosphamide) ◦ Teratogenesis ◦ Tardive dyskinesia
E: Withdrawal (**E**nd of use)	◦ Uncommon ◦ Occurs fastly after sudden drug withdrawal	◦ Reintroduce or withdraw slowly	◦ Opiate withdrawal syndrome ◦ Myocardial ischaemia (βeta-blocker withdrawal) ◦ Seizures (anticonvulsant withdrawal) ◦ Adrenocortical insufficiency (corticosteroids withdrawal)
F: Unexpected failure or theraphy (**F**ailure)	◦ Common ◦ Usually dose-related ◦ Often caused by drug interactions	◦ Increase dosage ◦ Consider the effects of concomitant therapy	◦ Inadequate dosage of an oral contraceptive, particularly when used with specific enzyme inducers

Sometimes it is difficult to classify an adverse drug reaction into one of these categories. For that reason, in our study it is important to focus mainly on type A and type B reactions, which will guide us to define if they are preventable or not due to its predictability.

It has already been proved that type A reactions are much more frequent than type B (2,7,17,24) and, in general, they are preventable.

1.4. DIAGNOSIS AND ATTRIBUTION OF CAUSALITY

When considering prospective studies of acute admissions in the context of adverse reactions, a key factor affecting ADR frequency is the drug causality assessment. It has been defined by WHO-Uppsala Monitoring Centre (UMC) as the evaluation of the likelihood that a particular treatment is the cause of an observed adverse event (25).

To attribute causality between a symptom and a drug, the first step is to find out if a patient is taking a medicinal product (including OTC, traditional and herbal remedies, recreational drugs and long-term treatments) and then, to find out whether the effect could be due to the medicine or not (12).
Sometimes, it is difficult to decide whether an adverse clinical event is an ADR or is a consequence of possible current illness deterioration. If it is an ADR, it is also challenging to determine which drug caused it, as ADR manifestations can be usually non-specific (8,9,18).

However, despite the huge range of different causality assessment methods there is no unique operational tool providing an indisputable gold standard for drug causation assessment (3,8,18). None of them have been universally accepted because there are no defined diagnostic criteria or categories, and inter-rater and intra-rater variability can be large causing a reproducibility[5] and validity[6] deficiency.

Causality has been assessed in a variety of ways:

- Expert Judgement: the process of assessing causality is done without any standardized tool rather than previous knowledge and experience in the field.
  In fact, the first step in ADR recognition depends always on a clinical judgement (8,15).
- Operational algorithms: specific questions associated to scores are used to calculate the likelihood of a drug being the cause of an adverse reaction. Those parameters are similar to the ones that expert judgment may evaluate (sequential time, previous history, dechallenge and rechallenge…)
  All cases are approached in a similar way; therefore, the degree of consistency and reproducibility is higher (8). Nevertheless, clinical judgement is as well needed in some parts of the procedure.

[5] Reproducibility ensures an identical result, regardless of who the user is and when he uses it

[6] Validity means the ability of the method to distinguish cases where the drug is responsible from those cases where it is not (8)

There are a huge number of different algorithms to assess causality, but none of them can in itself prove or disprove causality (18).

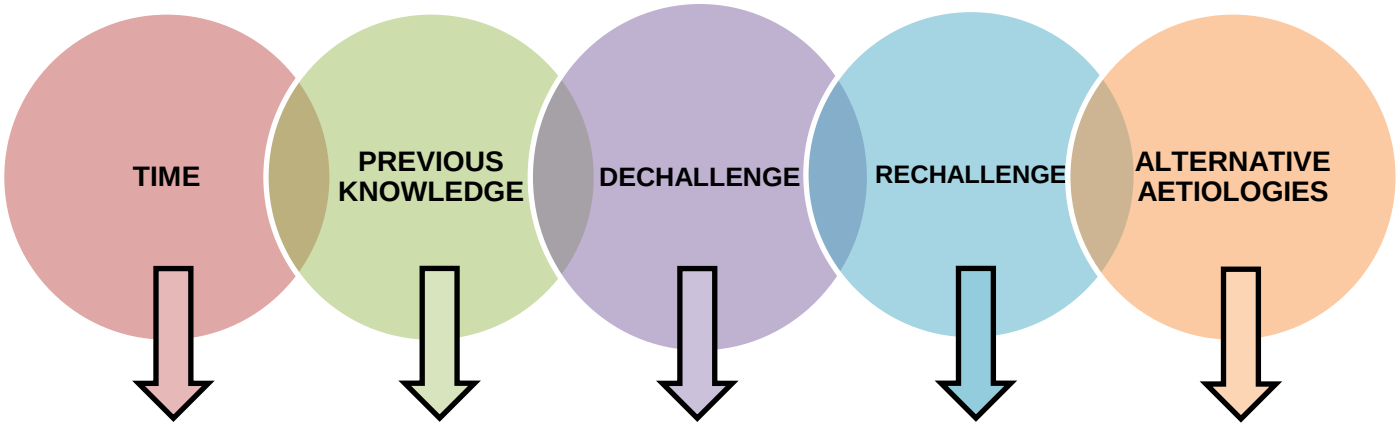
Some examples of operational algorithms are “Naranjo et al. method” (26), “Kramer et al. method” (27) or “Dangaumou’s French method” (28).

- Probabilistic approaches: specific case findings allow the estimation of drug cause probability (from a prior probability calculated with epidemiological data to a posterior probability).

  An example of probabilistic approache method is the “Australian method” (29).

The Spanish Pharmacovigilance System (SPhVS) assesses causality using an operational algorithm based on the different questions in the WHO-UMC causality assessment method *(figure 2)*. The main items to take into account defining causality are common in both methods (wider possible answers in SPhVS method) and are the following ones:

Figure 2. Causality assessment items (30)



The level of causal association is grouped into six categories which are based on the above criteria being fulfilled *(table 2).*

Table 2. WHO-UMC causality assessment method (8,25,30)

Categories	Time sequence	Dechallenge[7]	Rechallenge[8]	Alternative aetiologies
Certain	Plausible	Yes	Yes	No
Probable	Reasonable	Yes	-	Unlikely
Possible	Reasonable	-	-	Yes
Unlikely	Improbable	No	No	Yes
Unclassified/Conditional	Further data is needed			
Unclassificable	Incomplete, contradictory or unverified information			

Rechallenge often does not occur in the clinical practice for a number of reasons: for many serious ADRs, rechallenge might be considered unethical, since it may pose a considerable risk to the patient. Sometimes it is the patient who refuses it, and this is also difficult to perform in the Emergency Department. It is for that reason that more than a "probable" conclusion is difficult to achieve (3,18).

[7] To withdraw/discontinue a drug treatment

[8] Deliberated or unnoticed administration of a further dose of the medicinal product to a person who has previously experienced an ADR that might be drug related

1.5. RISK FACTORS FOR ADVERSE DRUG REACTIONS

In order to reduce the number of ADRs many authors have searched for a relationship between patient-related risk factors and ADRs. However, the evidence remains controversial, probably due to differences in definitions (31).
The most studied risk factors which have been mainly associated with an increased risk of ADRs are the following ones:

- Age

ADRs are more frequent in the elderly because of polypharmacy, poor compliance, concurrent medical illnesses and alteration in pharmacokinetics and pharmacodynamics parameters (2–4,9,10,32), that can be explained by the following statements:

- Disruption of some regulatory processes between cells and organs and a decrease of body system functions, resulting in increased drug bioavailability, slower first pass metabolism and reduced clearance of renal-cleared drugs (7).
- Increase of body fat proportion and decrease in total body water (less volume of distribution for water soluble drugs which increases drug free concentration).

- Gender

Several studies reveal a difference between men and women in the ADR prevalence (more frequently seen in females rather than males) (2,6,24,31,33). However, this is not a global uniform result. Conversely, some other studies have not found that association and conclude that there are no differences due to gender (2,3,31).
Possible reasons for gender as a risk factor might be:

- Differences in perception of ADRs
- Differences in kinetics, such as different volume of distribution
- Hormonal differences

- Polypharmacy

An exponential relationship between the number of concurrently used drugs and the likelihood of an ADR has been described, being the most frequently documented independent patient-related risk factor for serious ADRs (31).
It is accepted though, that patients taking more medications suffer from more ADRs (2,6,7,14,31).

1.6. PHARMACOVIGILANCE

Pharmacovigilance can be understood as the activities related to the detection, assessment, comprehension and prevention of adverse effects or any other medicine related problem (20,34).

Post-marketing drug safety monitoring programs through pharmacovigilance activities, spontaneous ADR reporting and observational studies, are important tools for detection, assessment and prevention of ADRs (7,9).

Nevertheless, ADRs are vastly under-reported due to a number of reasons. On one hand reporting is not mandatory to clinicians and so it is likely to be forgotten. Reported information depends on the willingness and awareness of reporters, taking into consideration that between 85% and 98% of physicians have never reported an ADR to their national authority (6,7,18). On the other hand, clinicians may have problems recognizing the scenario as an ADR on account of its heterogeneity.

Although the yellow card[9] (or other similar schemes worldwide) has been successful, under-reporting makes them unsuitable when recording epidemiological data of ADR (6).

PHARMACOVIGILANCE IN SPAIN

The Pharmacovigilance program in Spain was initiated in 1985 by “Dirección General de Farmacia y Productos Sanitarios del Ministerio de Sanidad y Consumo” aimed at having an easier way to collect information about all adverse reactions that might have been caused by drugs.

Every autonomous community in Spain has a pharmacovigilance centre, where collection, analysis, evaluation and storage of notifications from their community are performed. A database called “FEDRA” has been created to register all data, and it gathers it for the collection of information about patients presenting the same disease related to specific drug exposure. It is a faster way to generate new causal-effect hypothesis. As a result, it helps with the discovery of new ADRs, and changing intensities and frequencies in the old ones.

[9] Reporting data form. See Annex 5

In December 2012 there were more than 200,000 data registrations for ADR suspicion (35).
Afterwards, it is AEMPS (Agencia Española de Medicamentos y Productos Sanitarios) job to determine if the authorization conditions should be modified, or if a reevaluation of the harm-benefit ratio is needed.

All the information is sent to the European Medicines Agency and to the WHO International Coordinating Centre (WHO-Uppsala Monitoring Centre).

WHO-UPPSALA MONITORING CENTRE (UMC)

Since 1978, UMC has managed primary aspects for expanding pharmacovigilance worldwide. Nowadays, more than 130 countries form part of the program, known as the WHO Program for International Drug Monitoring.
Data from September 2015 shows that 122 countries have already joined the program and in addition 29 'associate members' are awaiting full membership (36).

The main functions of WHO - UMC are related to new ADR identification and analysis, the setup and maintenance of a database for further investigation (vigiBase[10]), information exchange between WHO, UMC, and National Centres, publication of guidelines and other tools for pharmacovigilance management, health professionals training, computer software for case report (vigiFlow), annual meetings, research, etc.

WHO CAN REPORT SUSPECTED ADRs?

- Doctors
- Pharmacists
- Nurses
- Odontologists
- Chiropodists
- Other sanitary professionals, according to the Law 44/2003, of arrangement (ordination) of the sanitary professions
- Citizens (from July 2012)

[10] VigiBase: is a computerized WHO database for pharmacovigilance, in which information is recorded since 1968 in a structured, hierarchical form to allow an easiest and flexible retrieval and analysis of the data. By May 2015 over 11 million reports were contained in it

WHAT SHOULD BE REPORTED? (9)

All types of notifications are welcomed, but those which refer to huge sever reactions, unexpected reactions or recent commercialized drugs are the most interesting ones.

- For “new” drugs, all suspected reactions, including minor ones, should be reported (drugs are considered “new” up to five years after marketing authorization)
- For established or well-known drugs, all serious or unexpected suspected ADRs should be reported
- Increased frequency of a given reaction
- All suspected ADRs associated with drug-drug, drug-food or drug-food supplements (including herbal and complementary products) interactions
- ADRs in special fields such as drug abuse and drug use in pregnancy and during lactation
- ADRs associated with drug withdrawals
- ADRs occurring from overdose or medication error
- Lack of efficacy or when suspected pharmaceutical defects are observed

It does not matter if causality cannot be totally assessed before reporting it (18,35). Just if the health professional or even the patient has the suspicion, the reaction has to be notified. Nevertheless, there are some factors[11] that may help in order to evaluate the drug possible function in producing the symptomatology.

[11] Those factors are the ones already explained above, in causality assessment (introduction part 1.4.)

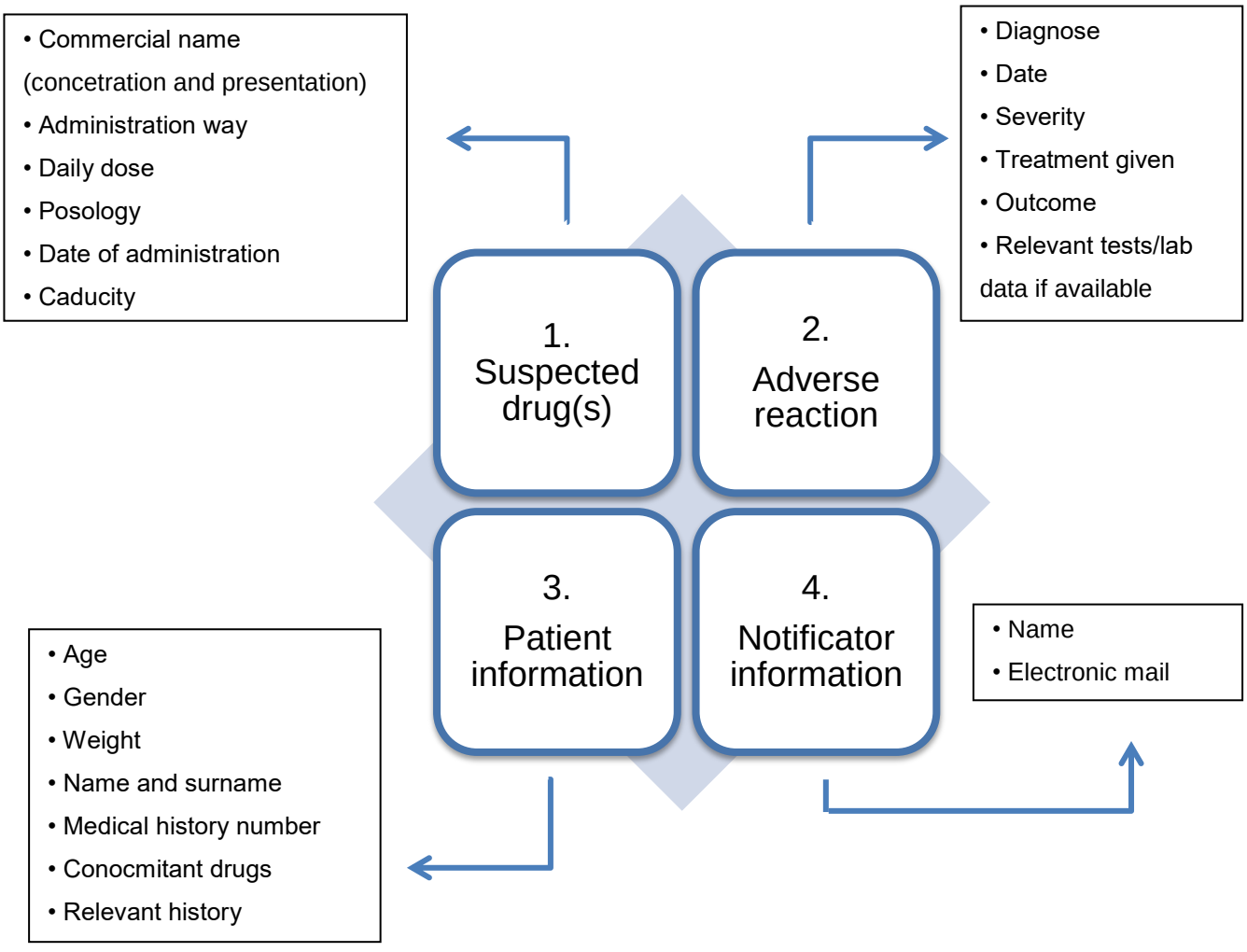
HOW TO REPORT?

There are different methods (see annex 5):

a) On-line: https://www.notificaRAM.es

b) Postal mail using the **yellow card** from each autonomous community. There are four different parts to be fulfilled when a case report is made *(figure 3)*.

Figure 3: Needed data to report a suspected ADR (9)



Other information: drugs taken during the last three months before the adverse reaction (prescribed, over the counter, medicinal plants...), information about rechallenge, medical past history (including allergies), test abnormalities results, moment of pregnancy administration if congenital disease, other documents, photos, etc.

2. JUSTIFICATION

Adverse drug reactions (ADRs) have been regarded as a major public health problem for their impact in terms of morbidity, mortality and economic costs (1–9). Although there are high differences between all performed studies, it has been estimated that approximately 5% of all hospital admissions are caused by ADRs (1–4,7,14–18,37) and that ADRs cause 197,000 deaths annually throughout the European Union (EU) (38).

Report and follow-up of suspected ADRs should be part of routine medical practice. Although health professionals are in the best position to detect and report ADRs, we have to bear in mind that the number of voluntary reports of events suspected to be ADRs are not as high as they should be. The databases of those spontaneous reports might underestimate the burden of drug-induced disorders as a cause of hospital admission (4), and furthermore, they tend to include less information than the necessary one. With the aim of improving our patient's quality of life (minimizing sequelae) and reducing mortality, correct ADRs reporting should be improved in all possible centres.

Other systematic reviews of studies of ADRs leading to hospital admission in different places all over Europe have already shown their results regarding prevalence, associated risk factors and the most frequent drugs involved. However, we have a lack of data in this field in Hospital Josep Trueta as it has not yet been studied.

Taking into account that hospital emergency departments have been considered as an observatory of the severe consequences of drug use and that the consumption of drugs can vary from region to region, it would be very useful to identify the ADRs that lead to hospital admission in our milieu not only to identify the prevalence of this public health problem but also to identify areas of improvement in the use of drugs in our province.

In conclusion, for all those reasons exposed we considered that initial studies on this field are more than justified.

3. HYPOTHESIS

The prevalence of possible ADR in Hospital Josep Trueta's Emergency Department is 5% (value suggested after reviewing similar studies already performed in other hospitals with similar characteristics)

4. OBJECTIVE

Main objective

To assess the prevalence of possible adverse drug reaction (ADR) as a reason of admission to Hospital Josep Trueta Emergency Department.

Secondary objectives

- To analyze the main factors related to ADR emergency admissions in Hospital Josep Trueta (age, gender, polypharmacy).

- To identify the most common drugs implicated in ADR emergency admissions in Hospital Josep Trueta.

- To assess preventability and outcome of ADR presented in the Emergency Deparment of Hospital Josep Trueta.

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5. METHODOLOGY

5.1. STUDY DESIGN

This study is designed as an observational, descriptive, cross-sectional, prospectively performed study in which we will assess the prevalence of possible ADR as a cause of urgent admission to the Emergency Department.

With this study typology we will be able to generate other hypothesis for further studies.

5.2. SETTING

The study will be carried out with data from patients consulting the Emergency Department of a second B level[12] hospital, concretely, at Hospital Josep Trueta in Girona, during 29 full days distributed over a one-year period.

5.3. POPULATION

The reference population of the study will include all patients being admitted to the general Emergency Department of Hospital Josep Trueta during the time mentioned above.

- Inclusion criteria:
    1. Presenting one of the pre-defined signs – symptoms – diagnoses

       Prior to the data collection period, a pre-defined list of the most frequent pathologies potentially caused by drugs seen as a cause of admission in the Emergency Department will be elaborated (see annex 1). This list will be defined according to previous data obtained from other already performed studies in similar hospitals and population characteristics (2–4,7,17).

       Data from patients presenting one of those signs – symptoms – or diagnoses will be included in the study for a posterior drug association assessment.

       As we will not know who of those patients will be finally considered as "presenting a possible ADR", information about the study will be given and informed consent will be asked to all of them.

[12] Data from CatSalut webpage
catsalut.gencat.cat/web/content/minisite/catsalut/proveidors_professionals/normatives_instruccions/any_2015/instruccio_11_2015/annex5.pdf

2. If inclusion criteria number 1 is fulfilled, data will be transferred to an ad-hoc created committee in order to apply the criteria used by the WHO to evaluate causality. With the information collected, the suspected ADRs will be classified as “certain”, “probable”, “possible”, “unlikely”, “unclassified” or “unclassificable” according to the WHO causality classification *(table 2)*.
   Patients presenting an ADR classified as “certain”, “probable” or “possible” will be included in the study. Additionally, ADRs will be classified as type A or type B reactions according to the Rawlins and Thompson classification (22).

- Exclusion criteria:
  1. Patients directly derived to one of the following departments (which have their own Emergency Department in Hospital Josep Trueta):
     - Obstetrics and gynecology
     - Pediatrics
     - Orthopedics
     - Otorhinolaryngology
     - Ophthalmology
  2. Deliberate or intentional overdoses
  3. Relapse because of non-compliance
  4. Admissions with insufficient information for a reliable assessment
  5. Unlikely, conditional or unclassifiable ADR classification cases
  6. Drug dependence and withdrawal syndrome
  7. Patients who will not give the informed consent

5.4. SAMPLE SELECTION

Sample recruitment will take place during a one year period. Patient selection will be performed during a complete journal day (24h), every 13 days during one year: 29 full days in total, from April 2016 to March 2017.
In this way, we will have data collected from each day of the week, and we will also avoid seasonal bias and day-night bias.

A non-probabilistic consecutive sampling-method will be performed, including all patients in Hospital Josep Trueta who fulfil the inclusion criteria during the period established before. Patients who fulfill any of the exclusion criteria will not be recruited.

5.5. SAMPLE SIZE

We expect a prevalence of 5% ADRs-related admissions in the Emergency Department based on the results of previous systematic reviews published.

Taking into account this data, we have calculated the sample size needed, with the help of a free online software from Regicor called GRANMO. The result was that a sample size of 2024 subjects randomly selected will suffice to estimate with a 95% confidence and with a precision ± 1% a population percentage (patients presenting a possible ADR) considered to be around 5%. A replacement rate of 10% has been anticipated.

In the Emergency Department in Hospital Josep Trueta (services with own Emergency Department excluded), a mean of approximately 100 patients are admitted during one full day. According to this information, we would need around 20 days to obtain our calculated sample. Despite this calculation, we are going to include all patients who fulfil the inclusion criteria previously explained during 29 full days as we are not inducing harm to the patient or changing the validity of our study.

5.6. VARIABLES

Taking into account the objectives of this study, we define below the different variables that are going to be studied. As it is a cross-sectional study we do not have an independent and dependent variable. We have described them as the main variable to be studied and covariables. A synthesis of all defined variables has been attached at the end of this part *(table 3)*.

A data record form has been elaborated to facilitate data collection (see annex 2).

5.6.1. Main variable

The main variable to record in the study is “to present a possible ADR”. This item is defined as a “response to a medicinal product which is noxious and unintended”. It is the definition used by the Spanish Pharmacovigilance System (SPhVS) which is the one described in the regulatory framework of the European Union.

It will be measured as a nominal dichotomous qualitative variable (Yes / No).

We assume that ADR is positive (YES) if the conclusion of the WHO criteria[13] application leads to “certain”, “probable” or “possible”.

[13] See *table 2*

However, we will consider as a negative ADR (NO) if the association criteria leads to an "unlikely", "conditional/unclassified" or "unassessible/unclassifiable".

We will take into account only the cases where an Emergency Department admission is needed. Data from out of hospital patients or already in hospital patients will not be included in this study.

The prevalence of admissions related to possible ADRs will be referred as the ratio of the number of possible ADR related admissions to the total number of general Emergency Department admissions.

It will be expressed as a percentage (%).

MAIN VARIABLE CHARACTERISTICS

To perform WHO causality criteria in order to define and classify a possible ADR we need the following information:

- *Timing:* it will be referred to the time between the hour/day/month when the patient started the treatment and the ADR occurrence.
  This information will be obtained from the clinical interview with the patient.
  It will be expressed in hours/days/months, depending on each case.

- *Suspected drug(s) information (SDI):*
  Dose: We will ask the patient which quantity of the drug is he/she taking and it will be expressed as µg, mg, g, ml, etc depending on the drug.
  Posology: We will ask the patient how many times per day/week/month is he/she taking the drug.

  We should not forget about products that may not be thought of as medicines (such as herbal or traditional remedies) and long-term treatments that might have been forgotten by the patient during the clinical interview (12,19).

  Drugs associated with each ADR will be classified according to the anatomical therapeutic chemical classification (ATC).
  This will be useful to achieve our secondary target about having data from which are the most common drugs implicated in ADR emergency admissions in Hospital Josep Trueta.

- *Relation with drug dose:* we should notice if there is a relationship with the dose reaching steady state, dose reduction or withdrawal. It can be also determined in blood and urine tests. If it is a congenital abnormality, we should assess if the exposure happened at the appropriate gestational time.

- *Dechallenge:* we assumed YES if a symptom(s) improvement is seen while stopping drug and NO if no changes happen.

- *Rechallenge:* we assumed YES if the symptom(s) reappear(s) after reintroducing the suspected drug and NO if no changes happen.

- *Mechanism:* although having 6 different groups[14] (from A to F depending on which is the specific mechanism), we will only classify the ADR into type A or type B, which are the most frequent ones (2,7,17) and which will be also useful to have information about preventability.
  We can obtain this information mainly from the interview with the patient.
  It will be expressed as type A or type B.

- *Alternative etiologies*: it is important because when the causality assessment will have to be performed, we will have to discard other causes as the reason of admission.
  This information will be collected from the clinical interview with the patient and from the medical records.

5.6.2. Covariables

❖ Age: it will be measured as a discrete quantitative variable (number of years old).

The patient's age at the time of hospital admission will be measured in one year intervals according to the date of birth. It will be collected from the identification card (ID) of the patient or other official documentation given by the patient at the admission department.
It is important to take the age of the patient into account because a high relationship between age and ADR has been already proved in other studies.
It will be expressed as mean and standard deviation.

[14] See *table 1*

- Gender: it will be measured as a nominal dichotomous qualitative variable (Male/Female).

It will be collected from the ID card of the patient or other official documentation given by the patient at the admission department.

We want to have this information because there is no agreement on whether gender is or is not related to a high incidence of ADR.

It will be expressed as a percentage.

- Polypharmacy: it will be measured as a discrete quantitative variable (number of taken drugs).

It will be collected from the clinical interview with the patient and the medical records.

It will be expressed as mean and standard deviation.

Again, we should not forget about products that may not be thought of as medicines (such as herbal or traditional remedies) and long-term treatments that might have been forgotten by the patient.

- Preventability*:* it is a nominal dichotomous qualitative variable (Yes / No).

It will be assessed with the ADR mechanism classification which represents an approach to it *(table 1)*. Type A reactions will be considered predictable (Yes) and type B reactions will be considered unpredictable[15] (No).

It will be expressed as a percentage.

The main characteristics (age, gender, drugs involved, polypharmacy, and outcome) of type A or type B ADR will be compared.

- *Outcome:* it is a nominal qualitative variable.

It will be referred according to the patient's evolution in the Emergency Department. Different options have been contemplated: discharge, hospital admission, death because of the possible ADR, death from other causes or unknown.

It will be expressed as a percentage.

[15] Except if previous reactions with the same drug were already seen in the patient

Table 3. Summary of variables

	VARIABLE	TYPE	VALUES	MEASUREMENT
Related to the ADR	ADR	Nominal dichotomous qualitative	Yes - Certain - Probable - Possible No - Unlikely - Conditional - Unclassifiable	WHO causality criteria
	Preventability	Nominal dichotomous qualitative	Yes: mechanism type A No: mechanism type B	From mechanism information
	Outcome	Nominal qualitative	Discharge Hospital admission Death because of the ADR Death from other causes Unknown	Medical record
Related to the patient	Age	Discrete quantitative	Number of years old	ID card or other documentation of the patient
	Gender	Nominal dichotomous qualitative	Male / Female	ID card or other documentation of the patient
	Polypharmacy	Discrete quantitative	Number of taken drugs	Clinical interview or medical records

5.7. DATA COLLECTION AND STUDY CIRCUIT

For data collection, special permission will be asked to the Emergency Department head due to the fact that the whole service represents one of the most important parts of our study. All of the Emergency Department working team will be informed about the objectives of the study as well as about the procedure and ethical aspects of it.

To record all needed data, a questionnaire has been created (annex 2). It has been called Adverse Drug Reaction Case Record Form and it has been elaborated after a review of items required to assess ADR causality as well as for the already known or suspected risk factors evaluation.

We cannot record data from all patients because of a lack of feasibility. For that reason, only patients presenting one of the pre-defined list signs, symptoms or diagnoses related to ADRs (annex 1) will be interviewed. Information will be obtained basically from the patient interview and from medical records about the patient.
Homogeneity in data collection will be ensured, as just one person will perform this task.

To maintain data anonymity and confidentiality, the form will only include an identification number for each patient. No personal data will be included. If later contact with the patient is needed, this identification number and date of admission will help us to access the Emergency Department database to search for further information about the patient.

After every day shift, answered questionnaires will be transferred to an ad-hoc committee. This committee will have the task of establishing an association between the suspected drug and the ADR. This procedure will be done following WHO causality criteria.

If there is a lack of information regarding any of the items, this will be noted on the questionnaire and the committee will decide if the information is or is not enough to apply WHO criteria. If there is not, the patient will be excluded from the study.

If the patient is considered to present a possible ADR by the committee (“certain”, “probable” or “possible” ADR conclusion), data of those specific patients will be included prospectively in a previously created database which will classify information for further analysis (ensuring the highest level of security established by the “Ley Orgánica de Protección de Datos” LOPD 15/1999).

The following data will be collected: age, gender, past medical history, total number of regular medications on admission, culprit medication(s), primary diagnosis for the admission, main physical examination and laboratory abnormalities, treatment needed, final diagnosis and outcome.
Preventability classification will also be performed.

We will need a computer with database creator software tools (concretely, OpenOffice Calc software will be used).

A pre-test will be done in order to evaluate the questionnaire. It will be useful to evaluate data recording difficulties and to detect errors or missing data.

All identified cases of suspected ADRs will be reported to the Spanish Pharmacovigilance System (SPhVS) following the methods already explained.

6. STATISTICAL ANALYSIS

All the statistical variables analysis will be performed using SPSS version 22.0 (IBM, Armonk, NY, US). Statistical significance will be considered at a p value <0.05 and the confidence intervals will be calculated at 95%.

In the context of our project, we cannot technically define our variables as independent and dependent due to the study design. However, for the analysis, we will define variables consisting of age, gender, polypharmacy as independent variables and the variable "to present a possible ADR" as the dependent one.

Descriptive analysis

The prevalence of ADR-related admission will be calculated by dividing the number of patients classified as "presenting, at least, a possible ADR" by the total number of admissions through the Emergency Department.

For qualitative variables (gender, preventability, outcome), results will be expressed as percentages (with a 95% confidence interval) and relative frequencies.

For quantitative variables (age, polypharmacy), mean with their standard deviation will be estimated, assuming it is normally distributed. In case it does not follow a normal distribution, arithmetic median with percentiles will be calculated.

Bivariate analysis

It will show if any relationship exists between our independent and dependent variables.

Chi-squared test ($\chi 2$) method will be used to compare the distribution of qualitative variables (gender) to "presenting a possible ADR".

For the analysis between a quantitative variable (age, polypharmacy) and qualitative variable (to present a possible ADR) Student's T test or Mann-Whitney test (if normality assumption does not hold) will be performed.

Multivariate analysis

Multivariate logistic regression analysis will be conducted to adjust for potential confounders co-variables and also to assess the association between ADR admission and age, gender and polypharmacy.

Statistics of patient characteristics admitted due to an ADR and patients without an ADR on admission will be compiled by multivariate logistic regression analysis.

7. ETHICAL CONSIDERATIONS

Patients will be informed orally and with an elaborated information document about the study (annex 3). They will be asked to sign an informed consent (annex 4) authorizing the maintenance of a secure computerized database with their personal data for further investigations, before being included in the study.

The protocol will be submitted to the Clinical Research Ethics Committee, "CEIC"[16] of the Hospital Josep Trueta, in order to be evaluated and approved before starting recording data. The recommendations given by the committee will be taken into account.
The protocol will be also sent to the "Direcció General de Recursos Sanitaris de Catalunya" and to the "Agencia Española del Medicamento y Productos Sanitarios" for their authorization.

This study is designed in accordance with the medical ethics requirements defined by the World Medical Association (WMA) in the Declaration of Helsinki for Ethical Principles for Medical Research Involving Human Subjects (Asamblea General, Fortaleza, Brasil, October 2013)

As it is a post-authorization drug observational study (Estudio Post-Autorización, EPA) we will take into account the "Orden SAS/3470/2009" of 16th December.

The information of clinical history, names and surnames, will be confidential, guaranteeing the anonymity of the patients involved in the study, according to "Ley Orgánica 15/1999 of December 13, Protección de Datos de Carácter Personal (Real Decreto 1720/2007 del 21 de diciembre)". The right of access to any kind of information concerning the patient is guaranteed as well as the participants' right to consult, modify or erase the personal data from their personal file.
All of the information will only be used for the purpose of the research.

Investigators of the project will have to declare they have no conflicts of interest with any party or organ related to this study.

[16] CEIC: Comitè d'Ètica i Investigació Clínica

8. WORK PLAN

The study will be totally achieved in approximately 2 years and the sequence of activities developed, as well as the personal responsible for them is detailed below:

A. RESEARCH TEAM

It will be composed of the coordination team (CT), the data collection person (DCP), the investigation team (IT) and the statistical specialist (SS).

- Coordination team (CT)
  - General Practitioner
  - Internal medicine specialist 1
  - Emergency Department associated doctor 1
  - Clinical pharmacologist

They will carry out the tasks of study work-planning and coordination. They will also be in charge of results discussion, interpretation, publication and dissemination. Other tasks are database elaboration and economic management. They will be the reference contacts if any trouble arises during the study, as well as the group evaluations performance in every step of the study.

- Data collection in-charge person (DCP)
  - Student / Intern fellow

This activity concerns the collection of needed data for the study. Data will be obtained in the Emergency Department from patients consulting during the agreed time (medical records or direct interview) presenting one of the signs/symptoms/diagnoses included on the list previously elaborated (annex 1), using a case recording form (annex 2).

- Investigation team (IT)
  - Internal medicine specialist 1 – 2 – 3
  - Emergency Department associated doctor 1 – 2
  - Clinical pharmacologist
  - Hospital pharmacist
  - General Practitioner

A team comprising different specialists will be specifically created in order to extract data from the questionnaires and to assess the possible connection between all included cases and the respective(s) suspected drug(s) *(table 2)*.

They will have to classify them according to the level of causal association (certain, probable, possible) and according to the type of ADR (A or B) and also to introduce the data of patients presenting, at least, a possible ADR into a database for further results discussion.

❖ Statistical specialist (SS)

Her/his task will be the database control and the performance of all posterior data statistical analysis.

B. STAGES

❖ **STAGE 1: initiation process** (November 2015 – March 2016)

1. *Coordination and preparation phase*. Development of the theoretical framework and definitive protocol. (November 2015 – January 2016):
    - Bibliographic research and protocol elaboration: our objectives and hypotheses are based upon the knowledge obtained from previous studies done in this field. The goal is to try to avoid the problems other authors may have found performing similar studies. Beside this first part, more bibliography will also be consulted during other phases of the study if needed.

2. *Ethical evaluation of the protocol* (February 2016)
    - Request approval of the Clinical Research Ethics Committee "CEIC" from Hospital Josep Trueta.
    - The study protocol will be also sent to AEMPS for being classificated as a post-commercialization study related to drugs.

3. Emergency Department request (February 2016)
    - Permission will be asked to the Emergency Department head, in order to perform the study in the service.
    - We will ask him as well to communicate all-working people in the Emergency Department about the study performance.

4. *Initial coordination meeting (all-member meeting 1)* (March 2016)
    - An all-member meeting will be performed before starting the project in order to define task organization and coordination.

      Explanations about the project design, execution plan, the system and procedures of patient selection, anonymization methods, data management and recruitment will be explained.
    - The person in charge of collecting data will be specially trained and case record form will be shown.
    - Other coordination meetings will be scheduled during the study to discuss and solve any problem if presented and also if any modification needs to be done.
    - During all the study, regular feedback will be provided and suitable methods of communication will be established among all the whole research team related to the study.

❖ **STAGE 2: data extraction and processing database** (April 2016 – March 2017)

1. Data collection and processing database

The DRC will offer to the patients the possibility of joining the study, and will make them sign the informed consent according to the inclusion/exclusion criteria above explained. Information provided by patients who accomplish the inclusion criteria will be collected.

The person in charge of data collection is responsible to ensure that all data is complete and exact, in an accurate and timely manner and he has to be sure to guarantee the data availability for the IT.

IT will meet every two weeks in order to assess the causality between the suspected ADR and drug therapy. They will also detect possible additional ADRs and will assess preventability and outcome. Conflicting assessment will be solved by consensus.

The whole information obtained will be organized in a database by the IT in order to organize data for further analysis.

2. Pilot study

After the first three months (end of June 2016), a results simulation will be undertaken in order to correct or to improve possible mistakes or deficiencies in the study design. This can allow for feedback from and for all the teams and also, initial results.

This data will be also used for the final results performance.

3. Evaluation of data collection

A further evaluation and validation of the data collection method will be required. Meetings will be held between DCP, IT and the CT in order to verify the correctly completeness of questionnaires and the correct computerization of data with the objective of detecting mistakes and making the appropriate corrections. Initially, it will take place every month (April-May-June) and then every three months.

- **STAGE 3: Statistical analysis and results analysis** (April 2017 – July 2017)

1. Statistical analysis[17]

After processing the database, all data collected will be analyzed using the appropriate software and statistical tests. A minimum of three months will be required to perform the final statistical analysis previously exposed.

2. Analysis of the results (all-member meeting 2)

A second all-member meeting will take place in order to perform the final data evaluation, with the aim of detecting the final protocol limitations.

The coordination team will keep in contact and will meet to analyze and interpret the results of statistical analysis performance.

- **STAGE 4: Final article elaboration and results publication** (August 2017 – October 2017)

The coordination team will write a final report describing, evaluating and interpreting the results. They will disseminate them as well. The final article will be published in different medical journals in order to make a correct diffusion of the results.

- **STAGE 5: Scientific diffusion and further research** (November 2017 – x)

Dissemination strategy includes conference presentations, meetings, and training sessions. It is important to think about implementing other strategies or making other reflections once the results of the study appear.

Further studies, taking into account the results of this study should be done for assessing the main repercussions that ADR can cause to the patients and the hospital, such as preventability studies or cost studies.

[17] After the first three months a statistical analysis will be also performed

9. CHRONOGRAM

STAGES	2015		2016												2017												2018		PERSONAL
	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	
STAGE 1: INITIATION PROCESS (November 2015 – March 2016)																													
- Protocol elaboration																													CT
- Ethical approval (CEIC)																													CEIC, AEMPS
- ED permission + communication																													CT – ED head
- All-member meeting 1 (Initial coordination meeting)																													All members (CT, DCP, IT, SS)
STAGE 2: DATA EXTRACTION AND PROCESSING DATABASE (April 2016 – March 2017)																													
- Data collection / Case recording																													DCP
- Drug association + database																													IT
- Pilot study																													All members
- Evaluation of data collection																													DCP + IT + CT
STAGE 3: STATISTICAL ANALYSIS AND RESULTS ANALYSIS (April 2017 – July 2017)																													
- Statistical analysis																													SS
- All-member meeting 2 (Final evaluation meeting)																													All members (CT, DCP, IT , SS)
- Analysis of the results																													CT + SS
STAGE 4: FINAL ARTICLE ELABORATION AND RESULTS PUBLICATION (August 2017 – October 2017)																													
- Final article elaboration																													CT
- Results publication																													CT
STAGE 5: SCIENTIFIC DIFFUSION AND FURTHER RESEARCH																													
- Conferences, meetings, sessions																													CT

10. BUDGET

STUDY BUDGET	**COST**
1. PERSONAL EXPENSES • Qualified statistician …… (35€/h per 40h) ……...…..	1.400 €
The DCP, IT and CT are not receiving any financial compensation for their contribution to the study.	
2. MATERIAL RESOURCES *No extra money will be needed for material. All clinical techniques needed will be performed following current protocols of Hospital Josep Trueta.*	-
3. PUBLICATION FEES	1.000 €
4. NATIONAL CONFERENCES ATTENDANCE *(TOTAL FOR 2 PEOPLE)* • Inscription…….... • Transport costs……... • Accomodation……..	2.000 € 450€ / person 200€ / person 350€ / person
TOTAL	**4.400 €**

11. STUDY STRENGTHS AND LIMITATIONS

Some limitations have been detected and taken into account while analyzing our study. The most relevant ones are those explained below:

1. Our study is designed as a descriptive cross-sectional study. With this type of study we can only suggest a relationship between the ADR and the suspected drug. Evaluation of the influence of independent variables, the confounding nature of these and the possible interactions among them can be difficult.
   Nevertheless, it is really difficult to be absolutely certain of a causal link between a drug and an ADR (3,17,18). This is the reason why our goal was also to include all probable and possible cases. Then, we can assign association of the factors, but not causality.

2. Overattribution of ADR may happen. Bias of WHO assessment causality is inherent to our methodology performed. We decided to use WHO criteria, although there are other methods that might be even better, because it is the one used in the Spanish Pharmacovigilance System for reporting suspected cases, and so being able to report them in an easier way.

3. Confusion bias. It is possible to have covariables producing confusion, which we have not considered before in the multivariate analysis.

4. Information bias. Patients will be asked to remember when the symptomatology started, which was the drug used, what was the dosage, etc. Those with neurocognitive problems or those who have been taking the drug for a very long time may not be able to answer.
   Moreover, symptoms of an ADR might not be communicated to care providers or care providers might not have recorded it. Non prescribed and complementary drugs can be less reported.
   Furthermore, we have to take into account that research in the Emergency Department is sometimes more complicated due to the fast environment and the usual lack of time.
   The objective is to compensate for these failings, providing an excellent education to all participants of the study as well as an excellent performance of data recording.

5. The sample of the study refers to the health Region of Girona. That means it can only be extrapolated to very similar sanitary regions or communities. As it has been explained before, every region might have differences regarding prescription methods, genetic factors, population characteristics that impede general extrapolation.

6. Selection bias. Some patients will be initially rejected from the study. Those are the patients who consult directly to the orthopedic, gynecologic and ophthalmologic department, although they are also Emergency Departments. In addition, our inclusion criteria are only focused on some pre-defined signs, symptoms and diagnoses. That means there is a possibility of losing ADRs clinically different from those items and consequently, infra-estimation of the number of ADRs.

Some strengths of our study are:

- Prospective design which allows a more accurate recording of both the drug history and symptoms.
- One full-year period
- Single collecting data person (ensuring consistency of methods and fiability)
- Seasonality bias avoided
- Extrapolation to similar centres
- High feasibly: low budget needed and most of resources available

12. CLINICAL AND HEALTHCARE IMPACT

Once we have the results of our study, general information for the hospital, professionals and patients can be obtained regarding related risk factors, preventability, main symptomatology and main drugs involved. The presentation of the study results to health professionals of the hospital as well as to primary care physicians of Girona and province would be helpful to increase their awareness about ADRs and about the approaches to reduce them. Moreover, it will allow an increased pool of available data for further analysis in this area.

The prevalence of ADRs can only be reduced by prevention. With increasing knowledge in this field, new prevention strategies elaboration could be considered in order to create safer and higher quality healthcare systems. With better policies of prevention and risk factors awareness (which implies an easier identification of risk patients), lower prevalence may occur and consequently lower rate of sequelae and mortality. To sum up, a better medical practice.

Methods for improving communications in pharmacovigilance must be created or reinforced. The main point for achieving it, is to involve all health workers to ADR reporting. Having data from their own hospital is a good way to do it. If all suspected ADRs were reported, new ADRs could be discovered and better evaluation of drug risk-benefit profiles could be performed.

Prevalence information can lead to an exhaustive ADR related cost study for hospital management and could help to decrease sanitary expenses derived from it.

We will be able to re-demonstrate how heterogeneous ADRs can be. Not only with this study but in addition to all the other ones already performed, it might be a tool for better definitions and classifications.

Nowadays there is not a validated protocol regarding ADR admission. Once we obtain our results it is important to assess if the design of a protocol could be helpful to improve professional's skills to achieve an early warning of ADRs, to easily detect that kind of related pathology and to facilitate the information recording and reporting.

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ANNEXES

- Annex 1: Pre-defined list of signs – symptoms – diagnoses that are potential ADR
- Annex 2: ADR Case record form
- Annex 3: Information document (Informació al participant)
- Annex 4: Informed consent (Consentiment informat)
- Annex 5: Pharmacovigilance notification (Yellow card + online reporting form)

ANNEX 1: PRE-DEFINED LIST OF SIGNS – SYMPTOMS - DIAGNOSES THAT ARE POTENTIAL ADVERSE DRUG REACTIONS

- Rash
- Vasculitis
- Erythema nodosum
- Lupus erythematosus
- Angioedema
- Anaphylactic shock
- Allergic reaction
- Parkinsonism
- Coma
- Encephalopathy
- Confusional state
- Aseptic meningitis
- Guillain-Barré syndrome
- Neuropathy
- Seizure
- Haemorrhagic CVA
- Heart block
- Sincope
- Arrhythmia
- Cardiorespiratory arrest
- Multiorganic failure
- Pulmonary thromboembolism
- Thrombosis
- Heart failure
- Cardiomyopathy
- Hypertension
- Hypotension
- Pneumonitis
- Pulmonary fibrosis
- COPD aggravated
- Bronchospasm
- Dyspnea
- Respiratory insufficiency
- Abdominal pain
- Vomiting
- Pancreatitis
- Gastrointestinal bleeding
- Gastric or duodenal ulcer
- Gastrointestinal perforation
- Hepatitis
- Jaundice
- Hepatic function test abnormalities
- Hyponatremia
- SIADH
- Hypokalemia
- Hyperkalemia
- Hypocalcaemia
- Acidosis
- Cushing’s syndrome
- Hypoglycaemia
- Hyperglycaemia
- Dehydration
- Pancytopenia
- Anaemia
- Leukopenia, agranulocytosis
- Thrombocytopenia
- Haematoma, haemorrhage
- Acute renal failure
- Nephropathy
- Diplopia
- Optic neuritis
- Myopathy
- Rhabdomyolysis
- Osteonecrosis
- Fever in immunosuppression
- Opportunistic infection

<u>ANNEX 2</u>: ADVERSE DRUG REACTION CASE RECORD FORM

- PATIENT ID (clinical history): …….....
- Date of admission (DD/MM/YYYY): __ __ / __ __ / __ __ __ __
- Date of birth (DD/MM/YYYY): __ __ / __ __ / __ __ __ __
- Gender: ☐ Female ☐ Male

- Cause of admission: …….....

- Personal known diseases: ……...……..……
  ……...……..……
  ……..……
  ……
  ☐ No data

- Current treatments (including drug with prescription, without prescription or medicinal plants)
  ……
  ……
  ……
  ……
  ☐ No other treatments
  ☐ No data

- Adverse drug reaction
  - Describe briefly: ……...……....
  - Symptomatology starts (day and hour): ……...……
  - Treatment given: …….....
    ☐ None needed
  - Outcome
    ☐ Discharged ☐ Hospital admission ☐ Unknown
    ☐ Death from the ADR ☐ Death from other causes

- Further relevant information:
  - Physical examination abnormalities: .....….....….....
    ……..……..……...
    ……
  - Abnormal LAB tests results: ……..…
  - Other:…….……..…….....
    .....…….....
    ☐ No data

- Suspected drug(s)

Drug Name	Code[18]	Dose Posology	Adm[19].	Initial time	Final time	Dech[20].			Rech[21].			Causality conclusion *(to be fulfilled by the comitee)*
						Ye	No	Un	Ye	No	Un	
				Day: Hour:	D: H:	☐	☐	☐	☐	☐	☐	
				D: H:	D: H:	☐	☐	☐	☐	☐	☐	
				D: H:	D: H:	☐	☐	☐	☐	☐	☐	
				D: H:	D: H:	☐	☐	☐	☐	☐	☐	

- Time between initial treatment and symptomatology (min/hours/days/months)
  ____ minutes // ____ hours // ____ days // ____ months

- Could the ADR have been prevented? *(to be fulfilled by the comitee)*
  ☐ Yes (type A reaction) ☐ No (type B reaction)

- Final diagnose[22]: ……..……ICD-10: ☐☐☐☐

[18] According to ATC
[19] Administration way
[20] Dechallenge
[21] Rechallenge
[22] ICD-10: 10th revision of International Statistical Clasification of Diseases and Related Health Problems

ANNEX 3: INFORMATION DOCUMENT (INFORMACIÓ AL PARTICIPANT)

A) Generalitats del projecte. El present estudi es titula "Adverse drug reactions as a cause of admission to hospital josep trueta: an epidemiological analysis" i es portarà a terme al servei d'Urgències de l'Hospital Universitari Dr. Josep Trueta de Girona, en un període de temps aproximat de dos anys. El projecte en qüestió ha estat valorat i aprovat pel Comitè Ètic d'Investigació Clínica (CEIC) d'aquest mateix hospital.

B) Objectius i finalitats de l'estudi. L'estudi té com a principal objectiu estudiar la prevalença de consultes al servei d'Urgències degudes a reaccions adverses per medicaments. Secundàriament, es vol estudiar quines són les principals característiques del pacient que presenti les reaccions adverses observades i amb quins fàrmacs són més freqüents així com la seva possible prevenció i la seva repercussió clínica.

Per tant, no pretén modificar ni introduir cap pràctica nova sinó que vol analitzar la situació actual pel que fa a l'anteriorment descrit.

C) Participació. La seva participació a l'estudi és totalment voluntària. Vostè seguirà el procediment diagnòstic i terapèutic habitual segons el protocol establert pel servei d'Urgències de l'Hospital Universitari Dr. Josep Trueta de Girona. Per tant, no suposarà cap procediment diagnòstic ni terapèutic addicional.

De la mateixa manera, vostè és lliure de renunciar o abandonar l'estudi, si així ho desitja, en qualsevol moment, sense necessitat de justificacions ni repercussions a la seva assistència sanitària. La participació a l'estudi és totalment gratuïta i no s'obtindrà cap compensació econòmica.

D) Confidencialitat i protecció de dades. En tot moment s'adoptaran les mesures per garantir la confidencialitat de les seves dades en compliment de la *Llei Orgànica de Protecció de dades* 15/1999. La informació serà emmagatzemada en una base de dades anonimitzada que només serà utilitzada per la finalitat d'aquest estudi.

Vostè té el dret a sol·licitar als investigadors de l'estudi l'eliminació de les seves dades, en qualsevol moment i sense necessitat d'especificar el motiu.

E) Dubtes. L'equip que en forma part li respondrà qualsevol dubte o qüestió que li pugui sorgir abans o després de firmar aquest document (del qual se'n quedarà una còpia). En tot moment podrà consultar amb altres professionals si ho considera oportú.

Nom i cognoms:…….....….....

Signatura:

Data: __ __ / __ __ / __ __ __ __ Agraïm la seva col·laboració en aquest estudi.

ANNEX 4: INFORMED CONSENT (CONSENTIMENT INFORMAT)

Declaro que:

- He llegit la fulla informativa sobre l'estudi que se m'ha entregat
- He estat informat pel professional de salut que signa aquest consentiment:
  - De les finalitats i implicacions del present estudi;
  - Del procés d'obtenció, emmagatzematge i processament de les meves dades;
  - Que està garantit el compliment de la llei de protecció de dades (15/1999);
  - Que pot ser necessari consultar la informació relacionada amb aquest estudi del meu historial clínic;
  - Que la participació és voluntària i que en qualsevol moment puc revocar el meu consentiment i sol·licitar l'eliminació de les meves dades personals sense cap justificació ni repercussió en l'atenció sanitària posterior;
- SÍ / NO accepto que els investigadors principals del projecte puguin contactar amb mi si en un futur es considera oportú.
- He pogut fer les preguntes que he considerat oportunes.

Nom:…….....……

Signatura:

Data: ……/……/…….

Declaració del professional de salut mèdica de que ha informat al participant.

Nom:……

Signatura:

Data: ……/……/…….

APARTAT PER A LA REVOCACIÓ DEL CONSENTIMENT

Jo, ……., revoco el consentiment de participació a l'estudi anteriorment indicat.

Signatura:

Data: ……/……/…….

ANNEX 5: PHARMACOVIGILANCE NOTIFICATION (Yellow card + online form)

YELLOW CARD

NOTIFICACIÓN DE SOSPECHA DE REACCIONES ADVERSAS A UN MEDICAMENTO

Por favor, notifique las reacciones adversas a fármacos recientemente introducidos en el mercado. También las reacciones graves o raras a otros fármacos. Se consideran medicamentos las vacunas, los productos estomatológicos y quirúrgicos, los DIU, las suturas, las lentes de contacto y los líquidos. En el caso de las vacunas, indique el número de lote.
No deje de notificar por desconocer una parte de la información que le pedimos.

NOMBRE DEL PACIENTE (Los datos de identificación del paciente permiten saber si se ha repetido alguna reacción; esta información será tratada de manera estrictamente confidencial)				
.....	Sexo	Edad	Peso (Kg)	Paciente hospitalizado .....
Núm. de historia clínica:	....	....	.....	☐ No ☐ Sí

MEDICAMENTO* (indique el nombre comercial)	Dosis diaria y vía admón.	Fechas		Motivo de la prescripción
		Comienzo	Final	

* En la primera línea notifique el fármaco que considere más sospechoso de haber producido la reacción. Si cree que hay más de uno, ponga un asterisco junto al nombre de los medicamentos sospechosos. Notifique todos los demás fármacos, incluidos los de automedicación, tomados en los tres meses anteriores.

REACCIÓN	Fechas	Desenlace

	Comienzo	Final	(recuperado, mortal, secuelas, etc.)

OBSERVACIONES ADICIONALES

MÉDICO ☐
FARMACÉUTICO ☐ QUE NOTIFICA

(esta información será tratada de manera estrictamente confidencial)

Nombre
Dirección
Población
Teléfono
E-mail

..... Firma

...../...../..... Fecha

☐ Necesito que me envíen más tarjetas

☐ Deseo recibir más información sobre las reacciones notificadas, hasta ahora, para este fármaco

También puede notificar por teléfono 93 427 46 46

ONLINE FORM

Notificació de ciutadà

Pacient | Medicament | Altra Medicació | Reaccions | Notificador

Informació sobre la persona que ha presentat la reacció adversa al medicament (Pacient)

Nom (*)

Cognom 1 (*)

Cognom 2

Qui ha presentat la reacció adversa? *

Sexe (*)

Edat / Grup d'edat (*) — Edat / Grup d'edat

Pes — kg

Alçada — cm

Pateix alguna altra malaltia? — No

Següent

Pacient | Medicament | Altra Medicació | Reaccions | Notificador

Informació sobre el medicament que ha pogut causar la reacció adversa

Codi Nacional

Nom del Medicament *

Lot i data de caducitat

Per a què va utilitzar el medicament?

Com ha utilitzat el medicament? (Dosi, posologia)

Dosi

Freqüència

Via d'administració

Quan va començar a utilitzar-lo?

Què ha passat amb el medicament?

- L'ha deixat d'utilitzar?
- El va deixar d'utilitzar i l'ha tornat a prendre?
- Segueix utilitzant-lo?
- N'ha disminuït la dosi?

Afegiu medicament

Anterior Següent

Pacient | Medicament | Altra Medicació | Reaccions | Notificador

Si ha pres alguna altra medicació en els últims 3 mesos (inclou medicaments amb recepta, sense recepta, publicitaris o productes amb plantes medicinals) encara que pensi que no estan relacionats amb la reacció.

Codi Nacional

Nom de la medicació *

Posologia

Dosi

Freqüència

Quan va començar a utilitzar-la?

Quan ha deixat d'utilitzar-la?

Per a què utilitza la medicació?

Afegiu medicació

Anterior Següent

Notificació de ciutadà

Pacient | Medicament | Altra Medicació | Reaccions | Notificador

Pensa que les reaccions que comunica...? *

- Han posat en perill la seva vida
- Han estat la causa de l'hospitalització
- Han allargat l'ingrés a l'hospital
- Han provocat una incapacitat persistent o greu
- Han causat defecte o anomalia congènita
- Han causat la mort del pacient
- No han causat res de l'anterior però considero que és greu
- No han causat res de l'anterior però considereu que NO és greu

Error de medicació

Informació sobre la reacció adversa (Poden ser més d'una)

Indiqui els símptomes que li han fet sospitar la reacció adversa *

Quan han començat els símptomes?

Quan han finalitzat els símptomes, si és que han acabat?

Quin és l'estat actual de la persona afectada?

Ha seguit algun tractament per millorar els símptomes de la reacció adversa? No

Afegiu la reacció adversa

Anterior Següent

Pacient | Medicament | Altra Medicació | Reaccions | Notificador

Informació sobre la persona que fa la notificació

Nom *

Cognom 1 *

Cognom 2

Correu Electrònic *

Confirmació de correu *

Adreça *

Província *

Codi Postal

Població

Telèfon de contacte

Ha notificat al seu metge o farmacèutic la reacció adversa? No

Consentiment contacte

Sí, dono el meu consentiment

Altres dades d'interès que vulgui afegir