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### ► To cite this version:

Kim An Nguyen, Yanis Mimouni, Elham Jabet, Nathalie Paret, Inesse Boussaha, et al.. Relationship between adverse drug reactions and unlicensed/off-label drug use in hospitalized children (EREMI): A study protocol. *Therapies*, 2021, 76 (6), pp.675-685. 10.1016/j.therap.2021.01.057 . hal-04549757

HAL Id: hal-04549757

<https://hal.science/hal-04549757v1>

Submitted on 22 Jul 2024

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## THERAPIES

### HEADING: Pharmacovigilance

## Relationship between adverse drug reactions and unlicensed/off-label drug use in hospitalized children (EREMI): A study protocol

Adverse drug reactions and unlicensed/off-label drug use

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Received August 27, 2020; accepted January 26, 2021

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## Summary

*Introduction.-* To date, few studies have shown a significant association between off-label drug use and adverse drug reactions (ADRs). The main aims of this study is to evaluate the relationship between adverse drug reactions and unlicensed or off-label drugs in hospitalized children and to provide more information on prescribing practice, the amplitude, consequences of unlicensed or off-label drug use in pediatric inpatients. *Methods.-* In this multicenter prospective study started from 2013, we use the French summaries of product characteristics in Theriaque (*a prescription products guide*) as a primary reference source for determining pediatric drug labeling. The detection of ADRs is carried out spontaneously by health professionals and actively by research groups using a trigger tool and patients' electronic health records. The causality between suspected ADRs and medication is evaluated using the Naranjo and the French methods of imputability independently by pharmacovigilance center. All suspected ADRs are submitted for a second evaluation by an independent pharmacovigilance experts. *Strength and limitations of this study.-*

For our best knowledge, EREMI is the first large multicenter prospective and objective study in France with an active ADRs monitoring and independent ADRs validation. This study identifies the risk factors that could be used to adjust preventive actions in children`s care, guides future research in the field and increases the awareness of physicians in off-label drug use and in detecting and declaring ADRs. As data are obtained through extraction of information from hospital database and medical records, there is likely to be some under-reporting of items or missing data. In this study the field specialists detect all adverse events, experts in pharmacovigilance centers assess them and finally only the ADRs assessed by the independent committee are confirmed.

Although we recruit a high number of patients, this observational study is subject to different confounders.

## KEYWORDS

Adverse drug reactions; Unlicensed drugs; Off-label drugs; Children; Inpatients

## **Abbreviations**

ADE: adverse drug event

ADR: adverse drug reaction

ATC: anatomical therapeutic chemical “classification system”

CI: confidence interval

CRF: case report form

IPB: independent pharmacovigilance board

PPV: positive predictive value

UK: United Kingdom

## Background

Medications are the most commonly used clinical intervention and complications associated with their use, are one of the most common causes of adverse events in health care. Adverse drug reactions (ADRs) are a major cause of morbidity and pose a substantial burden on limited health care resources [1]. Many drugs used to treat children in hospitals are either not licensed for use in children or are prescribed outside the terms of their product license (off-label prescribing). This is due to the lack of clinical trials in this population, and practical difficulties and ethical considerations arising from involving children in clinical research. Drugs used within the specifications of the product license should therefore be less likely to cause ADRs compared to drugs that are either unlicensed or off-label for use in children [2].

### Unlicensed or off-label drugs in hospitalized children

Most patients expect to only take medicines which have been shown to be well tolerated, effective, and of high quality. The licensing process to which most drugs are subjected gives the best assurance available that these criteria are met. However, children are required to take medicines everyday which are either not licensed, or are being used outside the terms of their license. This situation exists wherever children are treated around the world and whether they are in the hospital or treated at home. These are routinely prescribed drugs and many are the mainstay of pediatric therapeutics. Many problems arise from this situation, including the lack of availability of appropriate pediatric drug formulations, poor prescribing information, an increased risk of medication errors, and unanticipated adverse drug reactions [3].

A recent systematic review of studies on unlicensed and off-label drug use in children included 34 studies. Concerning prescriptions, 12.2 to 70.6% were for off-label drugs and 0.2 to 47.9 % for unlicensed drugs. The range of children receiving at least one unlicensed and/or off-label drug was from 42.0 to 100%, and the highest rate of prescriptions was for newborn. The purpose of off-label prescriptions was dose modification (7.1-73.1%) and the use of unlicensed prescriptions was for formulation modification (3.6-100%) [4].

A prospective study involving six pediatric and neonatal centers in the Sicilian region, Italy reviewed the prescriptions of 5,060 patients who were classified according to age

(newborn, infant, children, and adolescents). At least one off-label drug had been received by 454 patients [9%] in a total of 14,916 prescriptions. The risk of adverse drug reactions was notably higher in patients who received off-label drug treatment [7.3% vs. 1.2%;  $p < 0.01$ ] [5].

A study using an administrative database containing hospitalized patients aged 18 years or younger, from January 1 to December 31, 2004, from 31 tertiary care pediatric hospitals in the United States showed that at least 1 drug was used off-label in 297,592 (78.7%) of 355,409 patients discharged during the study. Off-label use accounted for \$270,275,849 (40.5%) of the total amount spent on these medications. Medications classified as central or autonomic nervous system agents, fluids, nutrients, or gastrointestinal tract agents were the most commonly used off-label drugs, whereas antineoplastic agents were rarely used off-label [6].

### **ADRs and the use of unlicensed or off-label drugs**

Drug safety monitoring is important in children. Young age, polypharmacy, prolonged hospitalization, being critically ill, and the use of unlicensed and off-label drugs have been identified as risk factors which predispose a child to experiencing an adverse drug reaction [7].

There have been few studies done on the relationship between the use of unlicensed and off-label drugs and ADRs in the pediatric population.

A systematic review included nine studies about unlicensed/off-label drug use on the occurrence of adverse events in hospitals. The percentage of unlicensed and/or off-label prescriptions involved in an adverse drug reaction ranged between 23 and 60% [8].

A prospective study conducted at a pediatric ward of a public teaching hospital, assessed the incidence, severity and predictors of adverse events related to off-label use of drugs. According to the results, the use of off-label drugs induced 34 (67%) ADRs and medicines without complete pediatric labeling were associated with higher risk of ADRs with the odds ratio (OR) 2.84; (95% confidence interval (CI) 1.37 to 7.09) [9].

To determine the incidence of ADRs to unlicensed and off-label drugs used in pediatric inpatients, Turner et al, carried out prospective surveillance on five different pediatric wards in a regional children's hospital for 13 weeks. ADRs occurred in 116 (11%) of

1,046 admitted patient. ADRs were associated with 112 (3.9%) of 2,881 licensed drug prescriptions and 95 (6%) of 1,574 unlicensed or off-label drug prescriptions [10].

A prospective study evaluating the potential relationship between off-label drug use and adverse drug reactions in a general ward of a pediatric reference hospital in Brazil during 5 months showed that 82.6% of children received at least one unlicensed or off-label drug, and 17% received both an unlicensed and an off-label drug. Off-label drug use was significantly associated with adverse drug reactions (unadjusted relative risk 2.44; 95% CI 2.12 to 2.89) [11].

In order to determine the incidence of ADRs to unlicensed and off-label drugs used in pediatric inpatients, Bellis et al carried out a nested case control study within a prospective study. Based on the results obtained from 10,699 medicine courses were applied to 1,388 patients, the odds ratio of an unlicensed/off-label medicine being implicated in an ADR was 2.25 compared to an authorized medicine (95% CI 1.95 to 2.59). Medicines which were licensed in children but were given to a child under the minimum age or weight had the highest odds of being implicated in an ADR (19% of courses in this category were implicated, OR 3.54; (95% CI 2.82 to 4.44). Each extra unlicensed/off-label medicine given increased the hazard of an ADR greatly (hazard ratio (HR) 1.3; 95% CI 1.2 to 1.3, P <0.001) [12].

The median incidence and the incidence of ADRs in hospitalized patients was estimated at 6.3% (interquartile range [IQR] 3.3 - 16.3) and 17% (95% CI 13.5 to 20.2%) respectively by two systematic reviews [13, 14]. The fatal ADR incidence was 0.08% (95% CI 0.00 to 0.15%) for hospitalized patients [13]. Another prospective cohort study evaluating 3157 patients during 6 months showed that the overall incidence of suspected ADRs was 1.6% [15].

Some studies demonstrated that the ADRs occurred more often in younger children. Morales et al. analyzed case reports of children in the Spanish Pharmacovigilance System over a 10-year period and showed that the absolute number of reports is higher in children between one and four years of age (37.9%) [16].

A prospective study of 703 patients, observed that 17.7% of children under the age of one year experienced an ADR [17].

Newborns with renal and hepatic immaturity are especially exposed to the risk of ADRs. According to a retrospective study of all reports of suspected ADRs with a fatal outcome in children received by the UK Committee on Safety of Medicines through its

Yellow Card Scheme from 1964 until December 2000, more than 8% of 331 fatal ADRs concerned newborns [18].

A prospective observational study of 1082 patients observed that the incidence of ADRs was 5% and infants were more at risk of ADRs (37%) [19].

In addition, in another observational study, among a total of 30 ADRs a highest percentage (60%) happened under the age of 1 year [20].

Aagaard L et al, characterized ADRs in children reported in Denmark over a period of one decade, showing that among 2437 ADR reports corresponding to 4500 ADRs, half of ADRs happened in infants under 2 years old age [21].

## Studies in France

In France, data concerning unlicensed or off-label drugs in hospitalized children is insufficient. A prospective study published in 2006, showed that 90% (53/57) of child patients received at least one unlicensed or off-label drug in pediatric units of hematology and oncology [22].

Avenel et al, in a prospective study, published in 2000, in a tertiary neonatal intensive care unit, reported that 257 prescriptions were administered with 55 different types of drugs during a one-month period. Ten percent of the prescribed drugs had no product license. Sixty-two percent were off-label for premature infants and 64% for newborns: 90% due to age, 9.3% due to dose and 0.7% to method of administration. No therapeutic alternatives to these prescriptions were found among the few available licensed drugs [23].

Another prospective analysis of psychotropic drug prescriptions was conducted for all patients hospitalized in two acute psychiatric hospitalization units of a pediatric teaching hospital in Paris, France. The authors reported that 46% of 187 children received at least one dose of psychotropic medication and 69% of the 421 prescriptions were off-label use. The percentage distribution of off-label prescriptions by medication class was as follows: antipsychotic drugs, 90%; anxiolytics, 28%; stimulants, 26%; antidepressants, 89%; antiepileptic drugs, 89% and antiparkinsonian drugs, 91% [24].



A prospective study (PEDIAD trial) [25] was realized in 14 hospitals by direct observation to identify and to quantify difficulties that nurses had when administering drugs orally or parenterally to pediatric inpatients. The observer followed one or several nurses for at least two hours with a questionnaire and noted all oral or injectable administrations. A total of 1,946 observations were recorded. The children were 12.6 +/- 17 months old, and weighed 8.5 +/- 9.4 kg. From 35 to 77% administered drugs were off-label in any formulations.

In summary, this wide-spread use of off-label and unlicensed prescribing for children is reported all over the world. Clinicians argued that these prescriptions are almost inevitable, given the lack of RCTs for many drugs in children and the need to treat serious diseases or in urgent situation without alternative licensed drugs. However, children are not simply adults in miniature, and the extrapolation of adult data to children mostly based on assumptions. Drug dosages for different age groups are adjusted on the basis of weight or surface body. The maturation of the liver and kidneys in children depend on their age. There are different profiles and evolution of disease in children compared with adults. Furthermore, there is a lack of information on adverse reactions and potential long-term toxicity from medicines in children. There are controversial data and few evidence about the risks of serious adverse reactions from the use of off-label and unlicensed medicines in children. In this context, we aim to carry out a large multicenter and prospective study in France that evaluates the relationship between adverse drug reactions and unlicensed/off-label drugs in hospitalized children.

## Objectives

### Primary objective

To compare the probability of occurrence of an ADR after a licensed prescription drug versus the probability of occurrence of an ADR after prescribing a drug unlicensed or off-label in patients aged 0-15 years hospitalized at least three days.

## **Secondary objectives**

- Compare the proportion of hospitalized children presenting at least one ADR following at least one unlicensed or off-label prescription with those presenting at least one ADR with all licensed prescriptions.
- Describe conditions and indications for which drugs are prescribed in terms of licensed/unlicensed/off-label manner by age group.
- Identify factors influencing the risk of developing ADRs after prescription.
- Estimate the severity and avoidability of ADRs based on the French pharmacovigilance criteria.

## **Methods and analysis**

### **Study design**

This is a multicenter, prospective, observational study involving hospitals that have implemented electronic patient's files and prescriptions.

### **Setting**

Two pediatric university hospitals (Lyon and Paris) in France are included. Both participating centers and selected wards have implemented electronic prescriptions available. The study began on January 2013. The total duration of the study is planned for 3 years. We follow up every included inpatient until discharge. We will follow up all patients presenting at least one ADRs during hospital stay and one month after discharge.

## **Participants**

All eligible children are recruited consecutively according to their admission. The detection of eligible patients is automated in each center through the exploitation of the hospitals information systems as soon as the duration of stay is over three days and the patients receive at least one medication.

## **Inclusion and exclusion criteria**

### Inclusion criteria

- Hospitalized children from 0 to 15 years old (including term and preterm newborn infants)
- At least three days of hospitalization.
- Received at least one drugs during hospital stay

### Exclusion criteria

- Children from 15 to 18 years old (this age group has a high death rate caused by accidents, violence and suicide instead of diseases requiring hospitalization).
- Patients hospitalized for an ADR or undergoing voluntary drug detoxification.
- Patients who did not take any drugs during their hospital stay.

## **Collection of patient data**

Patient data (age, date of birth, diagnoses, drugs administered, routes of administration, doses, and indications for use) from the hospital database of each center is sent each month for Lyon and every two months for Paris in the central database of the study (EREMI centralised

database\_ClinInfo). The data could be viewed or adjusted using a standard electronic case report form (eCRF).

Prescriptions for parenteral nutrition, standard crystalloid intravenous fluids, oxygen, and drugs used in research studies are collected but will not be considered.

Automated calculation of estimated glomerular filtration rate (i.e. creatinine clearance) using the modified Schwartz formula is implemented within the study database [26].

### **Definition of unlicensed or off-label drugs**

As Turner [10], we consider as unlicensed i) the modified use of licensed drugs (such as crushing tablets to prepare a suspension), ii) drugs that are licensed but the formulation is manufactured under a special license (such as the liquid preparation of a drug that is licensed only in tablet form), iii) use of chemicals as drugs when no pharmaceutical grade preparation is available, iv) drugs used before a license has been granted, v) imported drugs (drugs imported from a country where they are licensed); and vi) drugs without any product license.

In off-label analysis for age, we will use the corrected postnatal age in the preterm group. All suspected drugs ADR are assessed for unlicensed or off-label use by a trained research team using a common classification system.

The primary reference sources for determining licensed indications are the product characteristic summaries of marketing authorizations in the Thériaque database [www.theriaque.org](http://www.theriaque.org) (*French-drug database* [27]). Licensed drugs include medicines following the terms of the marketing authorization.

An automated algorithm was developed to determine unlicensed and off-label drug use within the study database using information processed from Thériaque database. This algorithm classifies the use of all drugs under temporary use authorization as unlicensed. Off-label drug use is detected by the algorithm using Thériaque information on age, route of administration, renal contraindication (with the use of the calculated creatinine clearance), and contraindicated drug-drug interaction.

One percent of prescriptions and all of the prescriptions related to any ADRs would be verified by a trained research team using a common classification system and validated by independent pharmacovigilance board (IPB) [see figure 1 study organization].

## Method for detecting ADRs

In 2008, Takata et al. developed a pediatric-focused tool for adverse drug event detection. Their review of 960 randomly selected charts from 12 children's hospitals revealed 2,388 triggers (2.49 per patient) and 107 unique adverse drug events. Mean adverse drug event rates were 11.1 per 100 patients, 15.7 per 1000 patient-days, and 1.23 per 1000 medication doses [28].

A trigger is defined as a data element within a health record that identify the presence of an adverse drug event (ADE) which has occurred or about to occur. A trigger is called positive when it has been identified in a patient health record. Typically, these triggers are derived from clinical, medication or laboratory tests [29].

A trigger tool is a targeted medical record review, either manually or automatically executed. The manual review of triggers is a sampling method based on the evaluation of a limited number of health records. The medical team decides the triggers to be taken on in the chart analysis and defines the procedure for charts to be analysed, ideally selected at random. Each chart randomly selected is screened only through triggers. Once a trigger is detected, a more in-depth review is undertaken to examine the potential for an ADE. Triggers performance is usually evaluated using positive predictive value (PPV), which is the percentage of patients with a positive trigger who actually have an ADE, while negative predictive value is percentage of patients with a negative trigger who do not have an ADE. The risk analyses through trigger tools can be computerised and systematised through algorithms as soon as electronic health records are available. These charts have to be further manually analysed by an experienced professional [29,30]. Traditionally, clinical trials and spontaneous reporting systems are the main sources for detecting ADEs in post-marketing phases. However, due to a lack of time and motivation, ADEs are underreported by healthcare professionals in their routine practice which results in underestimating the actual rate of ADEs, especially in children [31]. Therefore, four widely recommended proactive medication safety assessment techniques have been proposed: spontaneous reporting or incident report review, direct observation, chart review and trigger tools. A systematic review of the literature performed by Meyer *et al.* comparing these methods showed that the trigger tool method is the most effective and labor-efficient method to detect ADEs [30].

We used the trigger tool method with chart review of medical health records to detect ADRs in our study. The detection would be done by two methods: i) “*spontaneous detection*” by physicians or nurses in their routine practice during their rounds. Any detected ADR is sent to the local pharmacovigilance according to the usual practices. Spontaneous reporting is encouraged and helped by local coordinating center; ii) “*active detection*” by clinical research team using electronic health records (drug administration charts, laboratory results, health parameters monitoring results, electronic clinical notes and hospital discharge reports) and trigger tool every week. We organize training sessions on how to use the chart review in each center. All detected potential ADRs are confirmed with a physician from the clinical ward of onset before declaration to the regional centers of pharmacovigilance for evaluation. At the same time, EREMI team sent all declared ADRs to the IPB for final validation (Figure 2 and Figure 3)

We chose a list of trigger tool validated and reported in studies in pediatric patients and having at least a PPV of 10%. Overall, we selected 37 triggers in 3 categories as clinical, biological and medication triggers (Table 1) [28,29,32-39].

Only one clinical trigger (number 7) has not been validated in literature but suggested by our experts of IPC.

All suspected ADRs are transferred to the CRPV (Regional Pharmacovigilance center) for assessment. The center validates the nature (i.e. the MedDRA Low Level Term coding), the seriousness and the evolution of the ADRs, the suspected drugs; assessed causality using the French [40] and Naranjo Methods [41].

All of the ADRs that are assessed by the regional centers of pharmacovigilance are submitted to the IPB for final validation. ADRs that are not retained (not confirmed) by the regional centers are also submitted to this board.

Independent pharmacovigilance board (IPB) included seven experts: 4 clinicians-professors in pediatric, 1 pediatrician and pharmacologist, 1 hospital pharmacist and 2 pharmacovigilance experts.

The IPB reassesses the ADRs following the same criteria used by the regional centers of pharmacovigilance (except the French method for causality assessment). In addition, the board determines suspected drugs causality using the visual analogue scale of Arimone et al. [42], ADRs severity using Hartwig et al. method [43] and suspected drugs preventability using the French scale of Olivier et al (Fig. 3) [44].

A follow-up of the evolution of unresolved ADRs will be performed during the whole hospitalization period. After hospital discharge, the undetermined evolution would be sought during one month through any subsequent medical record or through a physician phone call to the patient's family or legal representative.

Every six months, the coordinating center organizes an ADR validation committee meeting with experts in pharmacovigilance, pharmacology and the examined disease in order to centrally validate all declared ADRs, precise whether they are serious, expected or avoidable and confirm unlicensed/off-label status of the drugs

### **Sample size**

The determination of the appropriate sample size is based on a test of comparison of two proportions between two groups. 1500 prescriptions by group (total of 3000) will be necessary with the hypothesis of a risk of ADRs of 5% in the group of "licensed drugs" and 8% in the group of "unlicensed/off-label drugs" (two-sided alpha = 0.05; power = 90%). This corresponds to an OR = 1.65 with a 95% confidence that the estimate of this OR will be comprised between 1.2 and 2.2. However, in this observational study, the statistical analysis will have to deal with various confounding and/or interacting factors. Thus, the number of prescriptions needed is higher than 3000. It depends on the number of factors and their correlation [39]. It is theoretically possible to apply a multiplying factor corresponding to a "Variance Inflating factor" (VIF) in order to take into account this phenomenon. However, in our context, it is not possible to anticipate the value of this VIF (no available data). For that reason, we decided to recruit the maximal number of patients in the study period which is estimated about 3000. With 3000 patients, about 9000 to 10000 prescriptions is expected, providing high power for the multivariate analysis.

### **Statistical analysis**

The statistical analysis would be performed following a plan established before month six of the study by the department of biostatistics of our hospital university center.

We will first describe patients` characteristics at inclusion. Quantitative variables will be described by their means, their standard deviations, their quartiles and their minimum or maximum values. Qualitative characteristics will be described using the frequency and percentages for each category. The following characteristics will be described: demographic data, medical history, the reason for hospitalization, characteristics of drugs and their status (licensed, unlicensed and/or off-label), ADRs declared (nature, severity, degree of imputability established by the pharmacovigilance committee).

The analysis of the primary objective will explore the effect of prescribing unlicensed or off label drugs on the probability of occurrence of ADRs. A logistic regression model will be used, the statistical unit being the prescription: the occurrence (yes/no) of ADRs attributable to the prescription will be the dependent binary variable and the characteristic of the prescription “licensed” vs “unlicensed/off-label” will be the binary (predictor) variable of interest.

Patient having a different risk of ADR, a random effect “patient” that takes into account this heterogeneity will be added to the model. Furthermore, the model will also contain potentially confounding - or interacting - covariates: age, sex, concomitant treatments, duration of stay, the severity of the disease, and recruitment centers.

## **Ethics**

Study ethics approval was obtained on 20 July 2016 (CECIC Rhône-Alpes-Auvergne, Clermont-Ferrand, IRB 5891).

## **Potential impact of the results**

The EREMI project will improve our understanding of the risk associated with unlicensed or off-label use of medicine in children, and contribute to describe prescription practices in hospitalized children. Information concerning the consequences of unlicensed and off-label drugs use, identification of risk factors of ADRs could help elaborate strategies for preventing them. The results could also help identify unmet medical needs in children that require further research. Finally, the study will encourage physicians to more actively declare ADRs, raise



their awareness, and improve our understanding of obstacles for efficient drug surveillance in hospitalized children. The data generated from the study will be made available for other researcher in the field to explore new hypotheses.

### **Advantages and limits**

In the reported studies so far, the relationship between ADRs and unlicensed/off-label drugs was documented using the chart review method. The causality was assessed by pharmacoepidemiologists or pediatric clinical pharmacologist. Only in the study of Bellis et al [4], three investigators independently assessed causality for all possible ADR cases, agreement on causality category between all three investigators was taken as accepted consensus.

In our study all adverse events are detected by the field specialist assisted by study teams using hospital databases and listing all drugs administered, all biological measurements and we have access to all medical records including routine clinical notes, vital signs and final medical report at discharge. Furthermore, experts in two independent pharmacovigilance centers, one in Paris and one in Lyon, assess the reported ADRs. Finally, an independent team of pediatricians and pharmacovigilance experts independently review and assess all ADRs. Only the ADRs assessed by the independent committee are confirmed.

Our study is observational and thus suffers from the limits of observational studies such as selection, confounding, measurement or follow-up bias. The objective remains, however to describe the potential burden due to unlicensed or off-label use of drugs in hospitalized children in order to take appropriate actions in terms of surveillance, training or research to improve the situation. In order to avoid selection bias all patients staying at the hospital are enrolled consecutively. Follow-up and measurement bias are reduced by the local central monitoring of the events occurring during hospitalization, this central monitoring is not applied to the ADRs that are caused by treatment prescribed before hospitalization. The telephone calls aiming to explore the consequences of ADRs, one month after hospital discharge, could also suffer from loss from follow-up, confounding or measurement biases. Finally, our study will not be able to answer to the question of hospitalization due to ADRs.

## **Innovative aspects**

The innovative aspect of our study is the use of hospital Information Technology (IT) to perform a large observational study which involves two major pediatric hospitals in France. The availability of IT tools highly impacts the feasibility of continuous monitoring of drugs. The quality of the study is assured by the implication of expertise necessary to build a well-designed research protocol and clinical research professionals on the field to support clinicians.

Implementing large studies in children remains difficult but mandatory to adequately answer to many health issues faced today in pediatrics.

## **Acknowledgments**

The authors would like to acknowledge the nursing and physicians staff in all departments of two pediatric hospitals - *Hôpital Femme Mère Enfant* of Lyon, and *Hôpital Robert Debré* of Paris, France. We are thankful for the contribution of all collaborators: C Castellan, A. Portefaix, E. Javouhey, A. Lachaux, P. Cochat, S. Di Filippo, V. Desportes, M. Nicolino, P. Reix, P. Fourneret, X. Dode, A. Duclos, A.M. Schott, C. Carcel, D. Floret, O. Claris

We are thankful for the contribution of all experts of independent pharmacovigilance board: Prof Daniel Floret, Prof Vincent Gadjos, Dr Jean Stagnara, Dr Jean Paul Langhendries, Dr A Portefaix, Mrs Claire GUY, Mrs Celine Vilier and Mrs Nathalie Bleyzac (pharmacists and pharmacovigilance experts)

## **Funding**

This study is funded by l'ANSM (French national agency of drug security) –Grant AAP 2012.

## **Financial disclosure**

The authors have no financial relationships relevant to this article to disclose.

## **Ethics and dissemination**

This study ethics approval was obtained on 20 July 2016 (CECIC Rhône-Alpes-Auvergne, Clermont-Ferrand, IRB 5891)

## **ClinicalTrials.gov identifier**

NCT02852590

## **Disclosure of interests**

Authors have no conflicts of interest relevant to this article to disclose

### Contributions of authors

- Conceiving and designing of study: Kim An Nguyen, B. Kassai
- Coordinating the study: Kim An Nguyen, Y Mimouni, B Kassai
- Data collection: Kim An Nguyen, Y Mimouni, E Jacqz-Aigrain, C Alberti, L Guittard
- Data management for analysis: Kim An Nguyen, Y Mimouni , I Boussaha, Elham Jaberi
- Analysis of data: N Bossard, L Roche, L Remontet
- Interpretation of data: all authors
- Pharmacovigilance centre of Lyon: N Paret, T Vial, Corine Carcel ;
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- Independent evaluation of all cases of suspected ADRs: Pr Daniel Floret, Dr A Portefaix, Prof Vincent Gadjos, Dr Jean Stagnara, Dr Jean Paul Langhendries, Mrs Claire GUY, Mrs Celine Vilier and Mrs Nathalie Bleyzac (pharmacists and pharmacovigilance experts)
- Update literature and writing the first draft of this manuscript: Kim An Nguyen, Elham Jaberi, Behrouz Kassai
- Review for final version of this manuscript: all authors

### References

- [1] Kaufman G. Adverse drug reactions: classification, susceptibility and reporting. *Nurs Stand* 2016;30(50):53-63.
- [2] Mason J, Pirmohamed M, Nunn T. Off-label and unlicensed medicine use and adverse drug reactions in children: a narrative review of the literature. *Eur J Clin Pharmacol* 2012;68(1):21-8.
- [3] Joseph PD, Craig JC, Caldwell PH. Clinical trials in children. *Br J Clin Pharmacol* 2015;79(3):357-69.
- [4] Magalhaes J, Rodrigues AT, Roque F, Figueiras A, Falcao A, Herdeiro MT. Use of off-label and unlicensed drugs in hospitalised paediatric patients: a systematic review. *Eur J Clin Pharmacol* 2015;71(1):1-13.

- [5] Pratico AD, Longo L, Mansueto S, Gozzo L, Barberi I, Tiralongo V, et al. Off-label use of drugs and adverse drug reactions in pediatric units: a prospective, multicenter study. *Curr Drug Saf* 2018;13(3):200-7.
- [6] Shah SS, Hall M, Goodman DM, Feuer P, Sharma V, Fargason C, Jr., et al. Off-label drug use in hospitalized children. *Arch Pediatr Adolesc Med* 2007;161(3):282-90.
- [7] Lee JH, Byon HJ, Choi S, Jang YE, Kim EH, Kim JT, et al. Safety and efficacy of off-label and unlicensed medicines in children. *J Korean Med Sci* 2018;33(37):e227.
- [8] Cuzzolin L, Atzei A, Fanos V. Off-label and unlicensed prescribing for newborns and children in different settings: a review of the literature and a consideration about drug safety. *Expert Opin Drug Saf* 2006;5(5):703-18.
- [9] Saiyed MM, Lalwani T, Rana D. Is off-label use a risk factor for adverse drug reactions in pediatric patients? A prospective study in an Indian tertiary care hospital. *Int J Risk Saf Med* 2015;27(1):45-53.
- [10] Turner S, Nunn AJ, Fielding K, Choonara I. Adverse drug reactions to unlicensed and off-label drugs on paediatric wards: a prospective study. *Acta Paediatr* 1999;88(9):965-8.
- [11] Santos DB, Clavenna A, Bonati M, Coelho HLL. Off-label and unlicensed drug utilization in hospitalized children in Fortaleza, Brazil. *Eur J Clin Pharmacol* 2008;64(11):1111-8.
- [12] Bellis JR, Kirkham JJ, Thiesen S, Conroy EJ, Bracken LE, Mannix HL, et al. Adverse drug reactions and off-label and unlicensed medicines in children: a nested case-control study of inpatients in a pediatric hospital. *BMC Med* 2013;11:238.
- [13] Miguel A, Azevedo LF, Araujo M, Pereira AC. Frequency of adverse drug reactions in hospitalized patients: a systematic review and meta-analysis. *Pharmacoepidemiol Drug Saf* 2012;21(11):1139-54.
- [14] Patel TK, Patel PB. Incidence of adverse drug reactions in indian hospitals: a systematic review of prospective studies. *Curr Drug Saf* 2016;11(2):128-36.
- [15] Sundaran S, Udayan A, Hareendranath K, Eliyas B, Ganesan B, Hassan A, et al. Study on the classification, causality, preventability and severity of adverse drug reaction using spontaneous reporting system in hospitalized patients. *Pharmacy (Basel)* 2018;6(4):108.
- [16] Morales-Olivas FJ, Martínez-Mir I, Ferrer JM, Rubio E, Palop V. Adverse drug reactions in children reported by means of the yellow card in Spain. *J Clin Epidemiol* 2000;53(10):1076-80.
- [17] Haffner S, von Laue N, Wirth S, Thürmann PA. Detecting adverse drug reactions on paediatric wards: intensified surveillance versus computerised screening of laboratory values. *Drug Saf* 2005;28(5):453-64.

- [18] Clarkson A, Choonara I. Surveillance for fatal suspected adverse drug reactions in the UK. *Arch Dis Child* 2002;87(6):462-6.
- [19] Kurian J, Mathew J, Sowjanya K, Chaitanya KR, Ramesh M, Sebastian J, et al. Adverse drug reactions in hospitalized pediatric patients: a prospective observational study. *Indian J Pediatr* 2016;83(5):414-9.
- [20] Priyadharsini R, Surendiran A, Adithan C, Sreenivasan S, Sahoo FK. A study of adverse drug reactions in pediatric patients. *J Pharmacol Pharmacother* 2011;2(4):277-80.
- [21] Aagaard L, Weber CB, Hansen EH. Adverse drug reactions in the paediatric population in Denmark: a retrospective analysis of reports made to the Danish Medicines Agency from 1998 to 2007. *Drug Saf* 2010;33(4):327-39.
- [22] Le Guyader N, Pouliquen AL, Benoit G, Leverger G. Off label drugs and pediatric hematology-oncology practices. *Arch Pediatr* 2006;13(9):1267-8.
- [23] Avenel S, Bomkratz A, Dassieu G, Janaud JC, Danan C. The incidence of prescriptions without marketing product license in a neonatal intensive care unit. *Arch Pediatr* 2000;7(2):143-7.
- [24] Winterfeld U, Le Heuzey MF, Acquaviva E, Mouren MC, Brion F, Bourdon O. Psychotropic medication use in the child and adolescent psychiatry wards of a French hospital. *Pharm World Sci* 2008;30(5):600-4.
- [25] Fontan JE, Mille F, Brion F, Aubin F, Ballereau F, Benoît G, et al. Drug administration to paediatric inpatient. *Arch Pediatr* 2004;11(10):1173-84.
- [26] De Souza VC, Rabilloud M, Cochat P, Selistre L, Hadj-Aissa A, Kassai B, et al. Schwartz formula: is one k-coefficient adequate for all children? *PLoS One* 2012;7(12):e53439.
- [27] Banque de données sur les médicaments Thériaque. 2021. <http://www.theriaque.org>. [Accessed January 28, 2021].
- [28] Takata GS, Mason W, Taketomo C, Logsdon T, Sharek PJ. Development, testing, and findings of a pediatric-focused trigger tool to identify medication-related harm in US children's hospitals. *Pediatrics* 2008;121(4):e927-35.
- [29] Matlow AG, Cronin CMG, Flintoft V, Nijssen-Jordan C, Fleming M, Brady-Fryer B, et al. Description of the development and validation of the Canadian Paediatric Trigger Tool. *BMJ Qual Saf* 2011;20(5):416-23.
- [30] Meyer-Masseti C, Cheng CM, Schwappach DL, Paulsen L, Ide B, Meier CR, et al. Systematic review of medication safety assessment methods. *Am J Health Syst Pharm* 2011;68(3):227-40.

- [31] Murff HJ, Patel VL, Hripcsak G, Bates DW. Detecting adverse events for patient safety research: a review of current methodologies. *J Biomed Inform* 2003;36(1-2):131-43.
- [32] Davenport MC, Domínguez PA, Ferreira JP, Kannemann AL, Paganini A, Torres FA. Measuring adverse events in pediatric inpatients with the Global Trigger Tool. *Arch Argent Pediatr* 2017;115(4):357-63.
- [33] Fortenberry M, Odinet J, Shah P, McKinzie C, Murphy K, Faircloth CB, et al. Development of an electronic trigger tool at a children's hospital within an academic medical center. *Am J Health Syst Pharm* 2019;76(Supplement\_4):S107-S13.
- [34] Ji HH, Song L, Xiao JW, Guo YX, Wei P, Tang TT, et al. Adverse drug events in Chinese pediatric inpatients and associated risk factors: a retrospective review using the Global Trigger Tool. *Sci Rep* 2018;8(1):2573.
- [35] Kilbridge PM, Noirod LA, Reichley RM, Berchelmann KM, Schneider C, Heard KM, et al. Computerized surveillance for adverse drug events in a pediatric hospital. *J Am Med Inform Assoc* 2009;16(5):607-12.
- [36] Matlow A, Flintoft V, Orrbine E, Brady-Fryer B, Cronin CMG, Nijssen-Jordan C, et al. The development of the Canadian paediatric trigger tool for identifying potential adverse events. *Healthc Q* 2005;8 Spec No:90-3.
- [37] Stockwell DC, Bisarya H, Classen DC, Kirkendall ES, Landrigan CP, Lemon V, et al. A trigger tool to detect harm in pediatric inpatient settings. *Pediatrics* 2015;135(6):1036-42.
- [38] Stockwell DC, Kirkendall E, Muething SE, Kloppenborg E, Vinodrao H, Jacobs BR. Automated adverse event detection collaborative: electronic adverse event identification, classification, and corrective actions across academic pediatric institutions. *J Patient Saf* 2013;9(4):203-10.
- [39] Unbeck M, Lindemalm S, Nydert P, Ygge BM, Nylén U, Berglund C, et al. Validation of triggers and development of a pediatric trigger tool to identify adverse events. *BMC Health Serv Res* 2014;14:655.
- [40] Bégaud B, Evreux JC, Jouglard J, Lagier G. Imputation of the unexpected or toxic effects of drugs. Actualization of the method used in France. *Thérapie* 1985;40(2):111-8.
- [41] Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;30(2):239-45.
- [42] Arimone Y, Bégaud B, Miremont-Salamé G, Fourrier-Reglat A, Moore N, Molimard M, et al. Agreement of expert judgment in causality assessment of adverse drug reactions. *Eur J Clin Pharmacol* 2005;61(3):169-73.
- [43] Hartwig SC, Siegel J, Schneider PJ. Preventability and severity assessment in reporting adverse drug reactions. *Am J Hosp Pharm* 1992;49(9):2229-32.

[44] Olivier P, Caron J, Haramburu F, Imbs JL, Jonville-Bera AP, Lagier G, et al. Validation of a measurement scale: example of a French Adverse Drug Reactions Preventability Scale. *Therapie* 2005;60(1):39-45.

### **Legends of figures**

Figure 1. Study organisation

Figure 2. Medical chart review using trigger tool for active ADRs detection

ADRs: adverse drug reactions

Figure 3. Detection and validation of ADRs

ADRs: adverse drug reactions

### **Legends of tables**

Table 1. Trigger tool

**Figure 1.** Study organisation

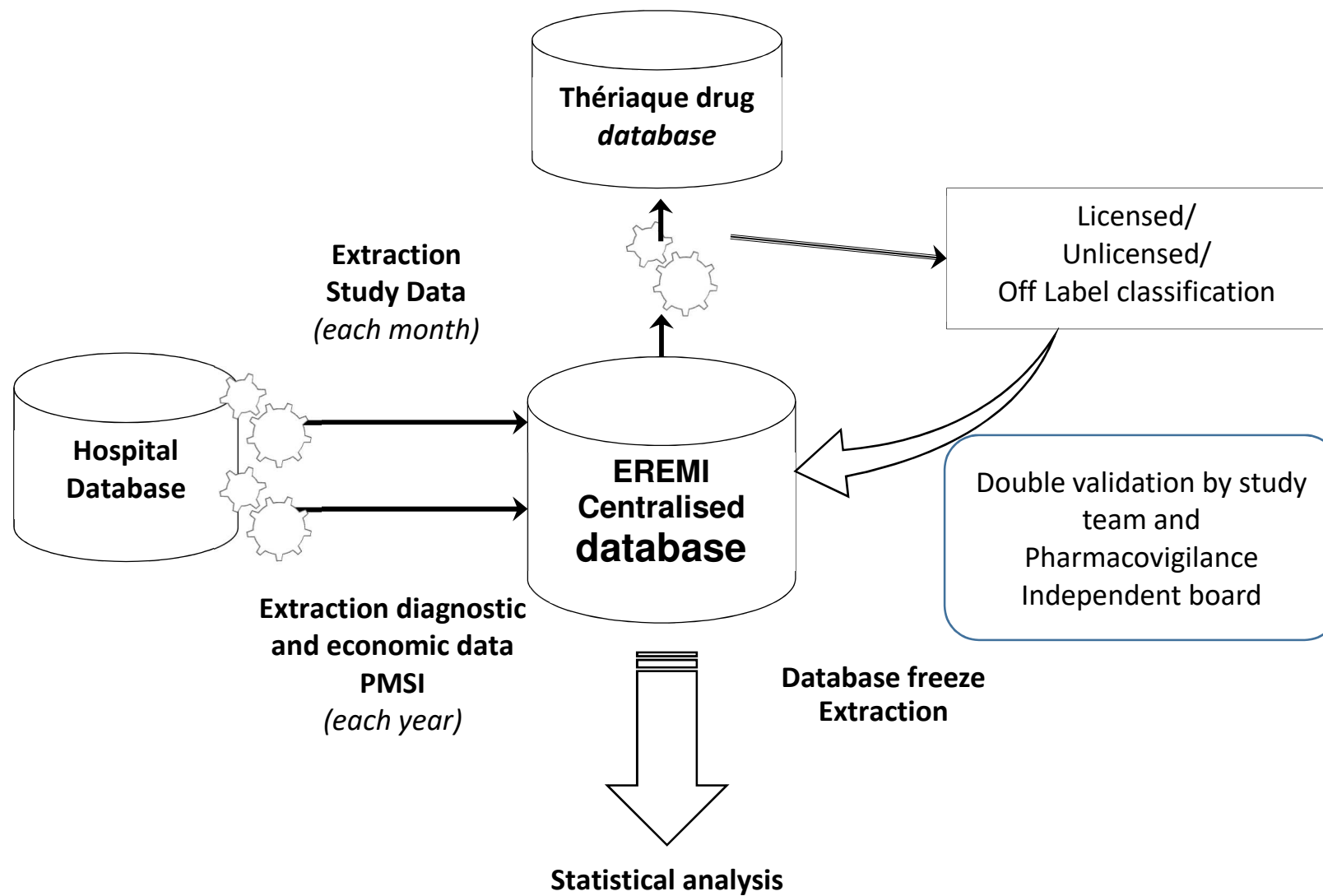
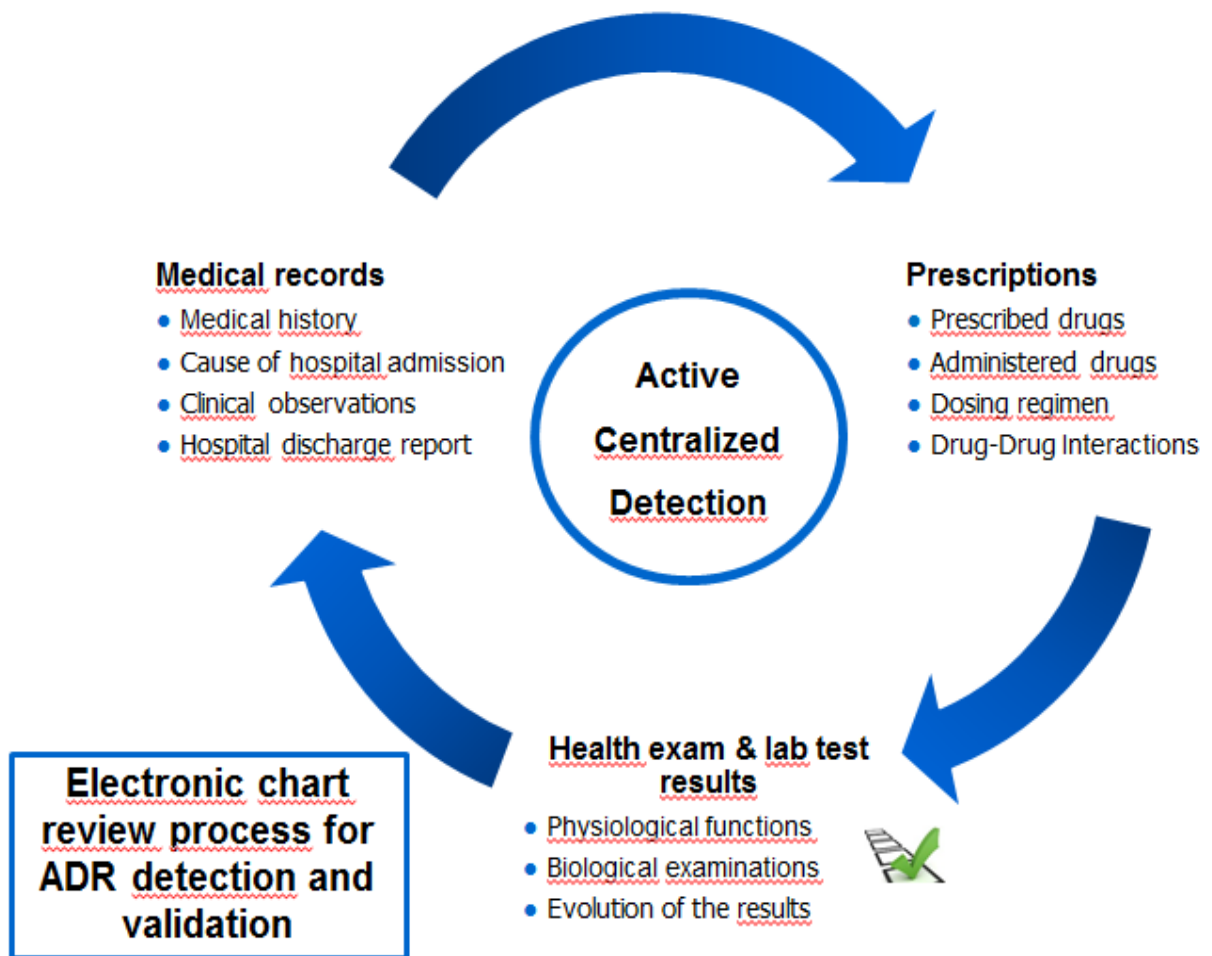
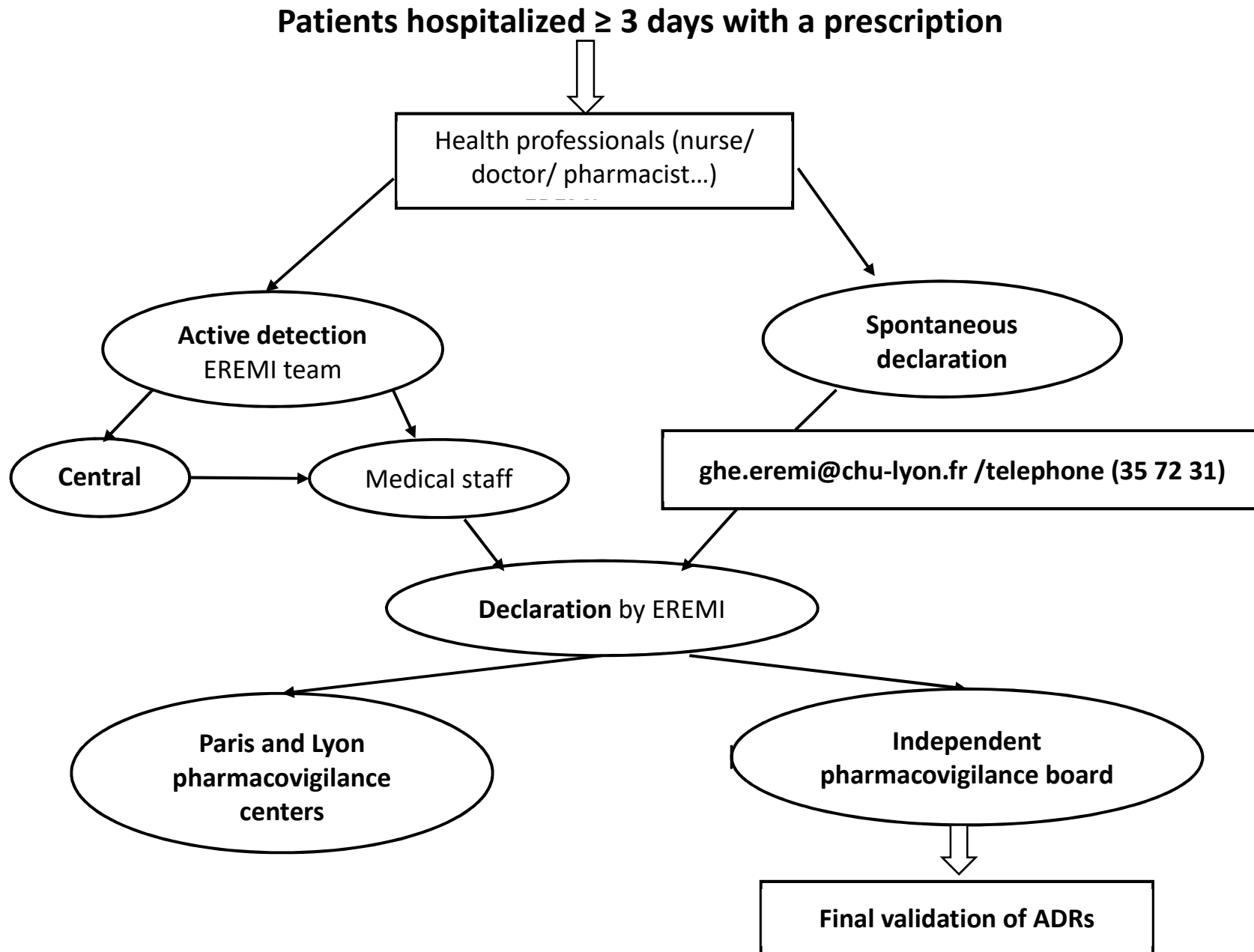




Figure 2. Medical chart review using trigger tool for active ADRs detection



**Figure 3.** Detection and Validation of adverse drug reactions



Triggers	PPV	Validation method	Reference
<b>Clinical triggers</b>			
1. Skin rash	12.7	manual	Takata, 2008
2. Extreme temperature: ≤35 ° C or ≥40 ° C	35.5	manual	Matlow, 2011
3. Hyporesponsiveness/hypotension / lethargy	14.9	manual	Takata, 2008
4. Hypoxia (SpO2 <75%) without explanation	48.1	manual	Matlow, 2011
5. Withdrawal syndrome	66.7	manual	Unbeck, 2014
6. Urinary retention/urinary catheter	71.4	manual	Stockwell, 2013
7. Anuria / Oliguria (<1 mL/kg/h) unexpectedly	unknown	manual	local expert recommendation
8. Transfusion / labile blood products	42.7	manual	Matlow, 2011
9. Emergency Code (Anaphylactic shock ...)	50	manual	Matlow, 2011
10. Stroke during hospitalization	33.3	manual	Matlow, 2011
11. Mutation to the next level (unforeseen incident, resuscitation)	45.8	manual	Matlow, 2011
12. Necrotizing enterocolitis	66.7	manual	Matlow, 2011
13. MRI/CT scan in children <3 months	38.8	manual	Matlow, 2011
14. Unscheduled surgery or return to surgery (unforeseen incident)	77.8	manual	Matlow, 2011
15. Unexpected death	80	manual	Matlow, 2011
<b>Biological triggers</b>			
16. Hemoglobin/ Hematocrit: sudden drop ≥25%	48.8	manual	Matlow, 2011
17. Platelets: <50,000/mm <sup>3</sup> or 50 × 10 <sup>9</sup> /L	55.6	manual	Matlow, 2011
18. TCA > 100 s or INR > 6	66.7	manual	Matlow, 2011
19. Leukopenia ≤5000/mm <sup>3</sup> (or ≤5 × 10 <sup>9</sup> /L) and/or neutropenia ≤1500/mm <sup>3</sup> (≤1.5 × 10 <sup>9</sup> /L)	18.8	manual	Matlow, 2011
20. positive D-dimer	62.5	manual	Matlow, 2011

21. 120 mmol/L $\geq$ Na $\geq$ 150 mmol/L	46.2	manual	Matlow, 2011
22. 3 mmol/L $\geq$ K $\geq$ 7 mmol/L	35.6	manual	Matlow, 2011
23. Ca $\geq$ 2.8mmol/L	13.3	automated	Stockwell, 2013
24. Increased urea / creatinine: twice the normal value (or sudden increase in kidney disease)	68.5	manual	Matlow, 2011
25. Increased transaminases: twice the normal value (or sudden increase in case of hepatic pathology)	12.2	manual	Matlow, 2011
26. PTT of >100 s	16.7	manual	Takata, 2008
<b>Medication triggers</b>			
27. Use of antidotes: ex Naloxone: antidote for opioids	12.1	manual	Takata, 2008
28. Stopping an unexpected medicine	19.7	manual	Takata, 2008
29. Per operative use of epinephrine, norepinephrine, naloxone, flumazenil	63.6	manual	Matlow, 2011
30. Gentamicin / tobramycin: peak >10 mg/L	44	manual	Matlow, 2011
31. Use of Vitamin K (Newborn excluded)	28.6	manual	Matlow, 2011
32. Vancomycin peak > 20 mg/L	21	automated	Kilbridge, 2009
33. Use of heparin or LMWH	52.4	manual	Matlow, 2011
34. Unexpected use of Kayexalate	20	manual	Takata, 2008
35. Unexpected use of antiemetics	20	manual	Matlow, 2011
36. Use of antihistamines	18.2	manual	Matlow, 2011