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Title

The clinical pharmacist's role in enhancing the relevance of a clinical decision support system.

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Structured abstract:

Background: Clinical decision support systems (CDSSs) can improve the quality of patient care by helping physicians to review their prescriptions and thus to optimize drug treatments. Nevertheless, the “alert fatigue” brought on by a large number of irrelevant alerts can decrease a CDSS’s effectiveness and thus clinical value. Involving a clinical pharmacist in the development and management of a CDSS can reduce the number of irrelevant alerts presented to physicians. Clinical pharmacists screen alerts and suggest PIs for physicians, corresponding to any proposed therapeutic change about health products, only for relevant alerts could improve the relevance and the acceptance of the information given to physicians about the risks faced by their patients.

Objective: To assess the value of involving clinical pharmacists in the development and maintenance of decision support rules for generating alerts and pharmaceutical interventions (PIs) and to describe the level of acceptance of these PIs by the physicians.

Method: In a retrospective, single-centre study, we evaluated the number of PIs accepted from alerts generated by the CDSS when a clinical pharmacist had developed and managed this tool. During the first 7 months of development of the CDSS, a clinical pharmacist analyzed alerts triggered by the CDSS according to its technical validity and pharmaceutical relevance. Lastly, for alerts that led to a PI, the level of acceptance by physicians was documented.

Results: During the study, 1,430 alerts were analyzed: 186 (13%) were considered to be technically invalid - mainly due to the characteristics of the interface. Of the 1,244 (87.0%) technically valid alerts, 353 (24.6%) were pharmaceutically relevant and led to a PI. The three main causes of pharmaceutical irrelevance were a lack of

specificity in the CDSS (70.8%), lack of relevance with regard to the ward's habits (15.6%), and the pharmacist's decision to recommend monitoring for the patient rather than sending a PI immediately (10.8%). 64.6% of the submitted PIs were accepted by the physicians.

Conclusion: The standardized analysis of alerts by a clinical pharmacist appears to be a good way of improving the development of CDSS by limiting the generation of irrelevant alerts and the latter's transmission to physicians. The involvement of a clinical pharmacist in the development and implementation of a CDSS appears to be novel and may help to optimize drug treatment.

Keywords: clinical pharmacist, clinical decision support system, prescription drug monitoring program, evidence-based pharmacy practice, adverse drug event, alert fatigue

Abbreviations

PI: pharmaceutical intervention

SFCP: *Société Française de Pharmacie Clinique* (French College of Clinical Pharmacy)

Word count: 2902/3000

Introduction

As a complement to computerized physician order entry (CPOE), a clinical decision support system (CDSS) can help to detect situations with a risk of adverse drug reactions. A CDSS can therefore improve the safety and efficiency of in-hospital CPOE [1;2]. A variety of drug-related and laboratory variables can be used to create clinical rules that will generate specific drug safety alerts for medication surveillance and prescription optimization [3].

A CDSS's effectiveness can nevertheless be limited by various factors, such as a large number of irrelevant alerts - especially if the system's configuration is solely based on summaries of product characteristics (SPCs). If physicians are obliged to spend time and energy examining irrelevant alerts, the resulting "alert fatigue" may lead them to ignore relevant alerts generated by the CDSS [4-7].

It has been suggested that involving clinical pharmacists in the development and management of CDSSs interfaced with CPOE systems can help to limit "alert fatigue" and make the system more efficient [8]. Indeed, the clinical pharmacist's knowledge about optimal drug prescription can be used to guide the creation of rules and the analysis of alerts generated by CDSS before a pharmaceutical intervention (PI) is suggested to the prescribing physician [9-12]. The pharmacist's contribution to the CDSS could increase the physician's acceptance of PIs based on relevant alerts and could increase the quality of patient care [13;14]. Nevertheless, these previous studies don't develop practical methods necessary to initiate this activity on daily routine for clinical pharmacists, notably the protocol for evaluation alerts, the training and work organization of clinical pharmacists.

Aim of the study

The aim of the present study was to investigate the clinical pharmacist's role in enhancing the relevance of a CDSS by analyzing alerts generated before transmitting a PI to physicians. The numbers and reasons for technically valid and pharmaceutically relevant alerts analyzed by the clinical pharmacist, the number of PIs sent by physicians, and the proportion of PIs accepted has been described.

Ethics approval

In line with the French legislation on retrospective studies of clinical practice, the study protocol was approved by a hospital committee with competency for research not requiring approval by an institutional review board (reference: ID900).

Material and method

1. Study design

This retrospective, observational study was conducted in Lille University Hospital (Lille, France) between July 1st, 2019, and January 31st, 2020 - corresponding to the first seven months of use of the hospital's CDSS. Computerized data on 1,350 inpatient beds (located in 37 care services, such as pneumology, cardiology, geriatric, neurology, surgical and psychiatric wards) were obtained. The clinical pharmacy team comprised 19 senior clinical pharmacists and 8 pharmacy residents. Each of the 27 pharmacists was responsible for several wards with the same medical speciality, for which he/she analyzed prescriptions and suggested PIs. The pharmacists analyzed all the prescriptions entered in the CPOE system on weekdays (Monday to Friday).

2. Development and implementation of the CDSS

During the development of the CDSS (PharmaClass[®], KeenTurtle, Paris, France), the participating physicians and pharmacists interacted via a joint CPOE and electronic health record (EHR) software package (SILLAGE[®], SIB, Rennes, France). The pharmacists used this software to suggest PIs to the physicians, in addition to their routine prescription analysis activity. Indeed, the control of CDSS alerts by pharmacists is an integral part of their jobs and a new routine activity, which allows them to prioritize the orders to be analyzed in accordance with the iatrogenic risk (Figure 1). The development and implementation of the CDSS is part of the strategic direction for the teaching hospital, accepted by the medical committee and the hospital management. This project aimed to optimize the continuity of quality of care on routine activity with the management of CDSS by clinical pharmacist. Therefore, pharmacists can prioritize prescriptions based on the degree of iatrogenic risk, leading to suggest relevant PIs to physicians.

The CDSS was implemented in July 2019. From the outset, it was decided that the CDSS would be developed and operated by the pharmacy department. The data used in the CDSS (including laboratory results, drug prescriptions, and administrative data) were retrieved from local databases. The drug dosage was not available during the study period.

The rules implemented in the CDSS and used in daily practice were developed by a multidisciplinary working group of clinical pharmacists, pharmacologists specializing in drug-related events, medical biologists, and expert physicians. In accordance with national and international guidelines, the decision rules were based on SPCs, keywords, and Boolean operators (e.g. metformin AND estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m²). Next, the team developed a standardized PI for

each rule, in accordance with the guidelines and the members' expertise. The rules and the corresponding PIs were discussed and validated by clinical pharmacists before their final implementation for daily use in the CDSS.

During the study, a pharmacist from the multidisciplinary working group analyzed the PI data in order to improve the existing rules and (if required) create new rules. At the start of the study, CDSS contained 34 rules. As of January 2020, 14 new rules had been added (giving a total of 48), and 6 of the initial rules had been improved (Supplementary Data).

3. Use and evaluation of the rules implemented in the CDSS

In everyday practice, the CDSS ran the set of rules on all data available from the 1,350 inpatient beds every 20 minutes. If the conditions of a given rule were met, the software generated an alert and a standardized PI that could be suggested to the physician in charge of the patient. In order to homogenize the practices methods of evaluation alerts generated by CDSS, a training session is planned whenever necessary by a referent pharmacist for all the newcomers in the clinical pharmacist sector. Indeed, clinical pharmacists analyzed each alert generated by the CDSS in a standardized manner: (1) evaluation of the alert's technical validity; (2) evaluation of the alert's pharmaceutical relevance; (3) transmission of a PI to the physician in charge of the patient (Figure 2). In addition to orientation training, a meeting presenting PIs was organized regularly (twice a month on the hospital and once a month at the regional level) provides continuous training. Anytime, if there is any doubt about the rules and its evaluation, a referent pharmacist from the multidisciplinary working group is solicited.

During step 1, the clinical pharmacist checked that all the rule's criteria were met and chronologically valid in the patient's EHRs (i.e. the presence of the prescription and/or the laboratory results) and checked the patient's identity (e.g. name, age, sex, date of admission, date of discharge, and ward). If (for example) the alert "vitamin K antagonist (VKA) and "international normalized ratio (INR)>4" appeared for a discharged patient, then the alert was deemed to be technically invalid.

During step 2, the clinical pharmacist assessed the relevance of the technically valid alert, according to their own level of expertise and the available EHR data. If the alert was deemed not relevant, it was classified into three categories. The first category corresponded to a lack of specificity in the CDSS: all of the rule's criteria were met but another key criterion (not taken into account by the CDSS) was required for relevance. For example, the alert "sitagliptin and moderate renal impairment" can be irrelevant if the dose (not covered by the CDSS) is adjusted correctly. The second category corresponded to an alert that was irrelevant for a given ward, according to the physicians' prescribing habits. For example, the alert "switch from enoxaparin to tinzaparin" was irrelevant in wards in which the requirement for heparin is frequently reassessed. The third category corresponded to the need for the patient to be monitored by the clinical pharmacist: the rule's criteria did not generate an immediate PI for the physician. For example, a slight increase in the creatinine level led to a decrease in an eGFR that triggered the alert but not a dose adjustment.

During step 3, the clinical pharmacist sent a PI (if the alert in step 2 was considered to be pharmaceutically relevant) to the physician in charge of the patient. The method of communication depends on the severity of the iatrogenic risk of the relevant alert: the physician is contacted by phone call for alerts with a high iatrogenic risk and messaging on the computerized prescription with others alerts. If (for example) the

rule “VKA and INR>10” appeared, a PI (for withdrawal of VKA, prescription of a corrective treatment (e.g. vitamin K), and measurement of the INR) was sent to the physician. For each PI, the clinical pharmacist checked whether the PI had been accepted or refused (i.e. whether the prescription had been changed or not).

Step 1 could be performed by any of the clinical pharmacist in the pharmacy department. Step 2 was (if possible) performed by the clinical pharmacist in charge of the medical ward linked to the alert. Step 3 was carried out by the clinical pharmacist having performed step 2.

4. Data collection and analysis

Each pharmacist evaluated the alerts that appeared during his/her daily work. For each alert, we documented the triggering date, the verification date, the patient’s ward, and the type of rule. The cause of the technical invalidity (if applicable) in step 1 was recorded. The pharmaceutical irrelevance of the alert in step 2 was recorded and classified by the clinical pharmacist into the three categories described in the previous section. In step 3, each PI was codified with Act-IP® (Bilog, Versailles, France), a software tool for standardizing PIs according to the guidelines issued by the French College of Clinical Pharmacy (*Société Française de Pharmacie Clinique*) [15]. The criteria for each alert were collated in an Excel® 2013 (Microsoft Corporation, Redmond, WA, USA) spreadsheet.

Descriptive analyses were performed using R software (version 3.3.3) [16]. Quantitative variables were quoted as the mean, and qualitative variables were quoted as the frequency (percentage).

Results

1. Characteristic of the alerts analyzed by the clinical pharmacists

The CDSS generated a total of 1,430 alerts, concerning 1,175 patients (Figure 3). Overall, 1,077 alerts (75.3%) generated by the CDSS were invalid, according to the clinical pharmacist. The main reason for invalidity was pharmaceutical irrelevance. Hence, the clinical pharmacist's analysis prevented a large number of irrelevant alerts from being sent to physicians. The alerts judged to be pharmaceutically relevant by the clinical pharmacist generated 353 PIs. During the same period, 5,919 PIs were produced by the clinical pharmacist's routine activity (i.e. without using the CDSS). 5,019 (84.8%) of these 5,919 alerts were accepted.

2. Reasons for technical invalidity (step 1)

We found that 67.7% of the technically invalid alerts were due to an interface performance, with the lack of at least one triggering criteria (Table 1). Erroneous identification of the patient accounted for identity accounted for 25.3% of the technically invalid alerts.

3. Reasons for pharmaceutical irrelevance (step 2)

The clinical pharmacist deemed that 881 technically valid alerts were pharmaceutically irrelevant and classified them as lacking specificity (70.8%), being

irrelevant for a specific ward (15.6%), and requiring monitoring by the clinical pharmacist only (10.8%) (Table 2).

4. Accepted PIs (step 3)

Overall, only 353 (24.6%) alerts were valid according to the clinical pharmacist leading to suggest PIs to physician. In most cases, the accepted PI led to a medication switch (n=113; 32.0%), drug withdrawal (n=107; 30.3%) or a dose adjustment (n=82, 23.2%) (Table 3). Drug withdrawal and monitoring were the PIs most frequently accepted by physicians, whereas optimized administration was least frequently accepted.

Discussion

The objectives of the present study were to assess the value of involving clinical pharmacists in the development and maintenance of a CDSS's rules for generating alerts and PIs, and to describe the level of acceptance of these PIs by the physicians. We expected that involvement by a clinical pharmacist would make the CDSS more efficient and would limit the occurrence of "alert fatigue". Indeed, the initial literature results show that (i) alerts generated by a CDSS can reveal drug-related problems other than those detected in daily clinical practice, and (ii) the implementation of a CDSS by clinical pharmacists can help to select clinically relevant alerts and improve the prescribers' response rate [13-14; 17].

We found that thanks to the organizational set-up, the clinical pharmacist was an important checkpoint for invalid CDSS alerts. In the present study, 13.0% of the alerts were technically invalid, and 61.6% were pharmaceutically irrelevant. According to the clinical pharmacist, only 15.9% of the alerts were relevant to the prescriber. Previous studies with similar designs reported higher rates of clinically irrelevant alerts of 83.0% to 96.4% than in our study [14;18]. Another study performed by Claus and al. reported a very low rate of clinically irrelevant alerts (12.8%) but their rules were only focused dose adjustment of antibiotics according to clearance creatinine [19]. Moreover, the rate of pharmacist-recommended PIs accepted by physician is similar to the literature (64.5% versus 63%) [12]. On the other hand, comparing the number of alerts generated by or without CPOE/CDSS was little interest because PIs generated by the CPOE/CDSS targeted different alerts from those identified routinely [14]. Indeed, PIs suggested without the CDSS are performed by a pharmacist expert

on a care service with knowledge of prescribing habits and type of PIs usually accepted during routine activity on the ward.

The low proportion of relevant CDSS alerts after assessment by the clinical pharmacist is similar to that reported in the literature, which highlights the risk of “alert fatigue” when the physician alone analyzes alerts [12; 14]. Hence, the standardized analysis of alerts by a clinical pharmacist appears to be a good means of effectively developing and implementing a CDSS.

Firstly, the technical validity of alerts generated by the software was assessed in step 1; this is critical for determining the value of a CDSS. Over the first seven months of use, 87% of the alerts were technically valid. In our experience, this proportion is acceptable but our ultimate goal is to obtain a value of over 90%. The main reasons for technical invalidity were (i) the lack of at least one criterion of the rule and then (ii) patient identification errors. These aspects might be due to the complexity of developing rules within a newly formed working group and/or the limited number of source data interfaced with the new CDSS. To facilitate the development and implementation of a CDSS, clinical pharmacists should determine the causes of technical invalidity and then work with the software developer to optimize and update the system.

Secondly, the main reason of pharmaceutical irrelevancy was a lack of specificity in the CDSS. As mentioned above, the CDSS was not interfaced with all the hospital’s EHRs, and data on the drug dose was lacking. Our results emphasize the need to (i) interface the CDSS with all the relevant patient care data, and (ii) increase the specificity of the system’ rules. Even with these improvements, however, we consider that direct analysis by a clinical pharmacist is essential for optimizing the

pharmaceutical relevance of a non-negligible proportion of alerts (26.4% in the present study).

Lastly, nearly two-thirds of the suggested PIs were accepted by the physicians – highlighting the clinical pharmacist's role in the management of the CDSS. The development of a new CDSS in a university hospital provides access to a large quantity of computerized data on inpatients, and expert physicians and clinical pharmacist team. The feedback from a multidisciplinary working group is very important for reassessing rules based on guidelines from learned societies.

The present study had some limitations. Firstly, only one pharmacist per ward analyzed the CDSS alerts, which might have introduced interpretation bias. However, this approach reflects clinical reality: time is short, a large and growing number of prescriptions have to be analyzed, and prioritization rules are not always obvious. This new task for the clinical pharmacist included to review each alert, verify its technical validity, pharmaceutical relevance and to react if necessary. This task may be time-consuming and may negatively impact daily pharmaceutical activities. Secondly, most CDSS take into account medication dose, whereas our CDSS did not. This might limit the generalizability of our study and may have increased the proportion of technically invalid and pharmaceutically irrelevant alerts. "In our CDSS project, we have chosen to analyze alerts by pharmacists before intervening with the physicians, rather than intervening with the physicians at the time of the prescription. This choice may limit the effect of the intervention because physicians may be less likely to respond to and to agree to post-prescription requests for changes. However, the interruption of a task during the prescription by a CDSS can generate a fatigue alert among physicians [4-6]. On the other hand, a recent review of the literature

suggests that this approach is effective in preventing medication errors and optimizing pharmacotherapy [20].

Despite these limitations, our initial results were encouraging and are likely to improve over time as the CDSS and the rules are developed further.

Conclusion

The analysis of CDSS alerts by a clinical pharmacist will propose PIs to physicians of only relevant alerts, accepted in two third of the cases. The management by pharmacist limits “alert fatigue” and can improve clinical decision-making.

Determination of the reasons for irrelevant alerts helps to optimize the CDSS’s existing rules, create useful new rules, and facilitate the software development process. This activity constitutes one of the clinical pharmacist’s new missions in enhancing patient care, appraising the validity of CDSS alerts, and taking account of feedback from hospital wards.

2-4 bullets statements on 'what was already known on the topic'

- Clinical decision support systems can help to detect at-risk drug-related events.
- The system's effectiveness can be limited by "alert fatigue" among prescribers.

2-4 bullets statements on 'what this study added to our knowledge'

- Pharmacists can contribute to the development of clinical decision support systems.
- Pharmacists could be the first to assess the relevance of alerts.
- The screening of alerts increases the acceptance rate of pharmaceutical intervention.

Author contributions

EC analyzed and interpreted data and drafted the manuscript. LR and EM analyzed and interpreted data and helped to draft the manuscript. CR, RM, SG, PO, JBB and BD revised the manuscript for critical content. All authors read and approved the final manuscript.

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Statement on conflicts of interest

The authors declared no potential conflicts of interest related to this project.

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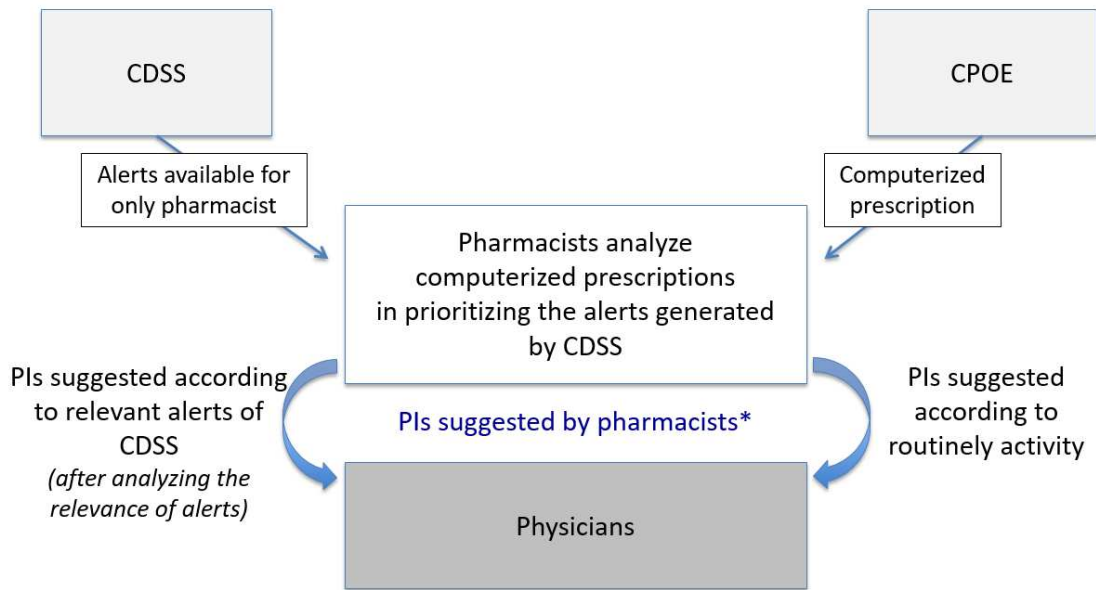


Figure 1: Representation of the work organisation of clinical pharmacists to analyze prescriptions. CPOE: computerized physician order entry; CDSS: Clinical decision support systems; PIs: Pharmaceutical interventions.

* The method of communication of relevant PIs depends of the iatrogenic risk (phone call or messaging).

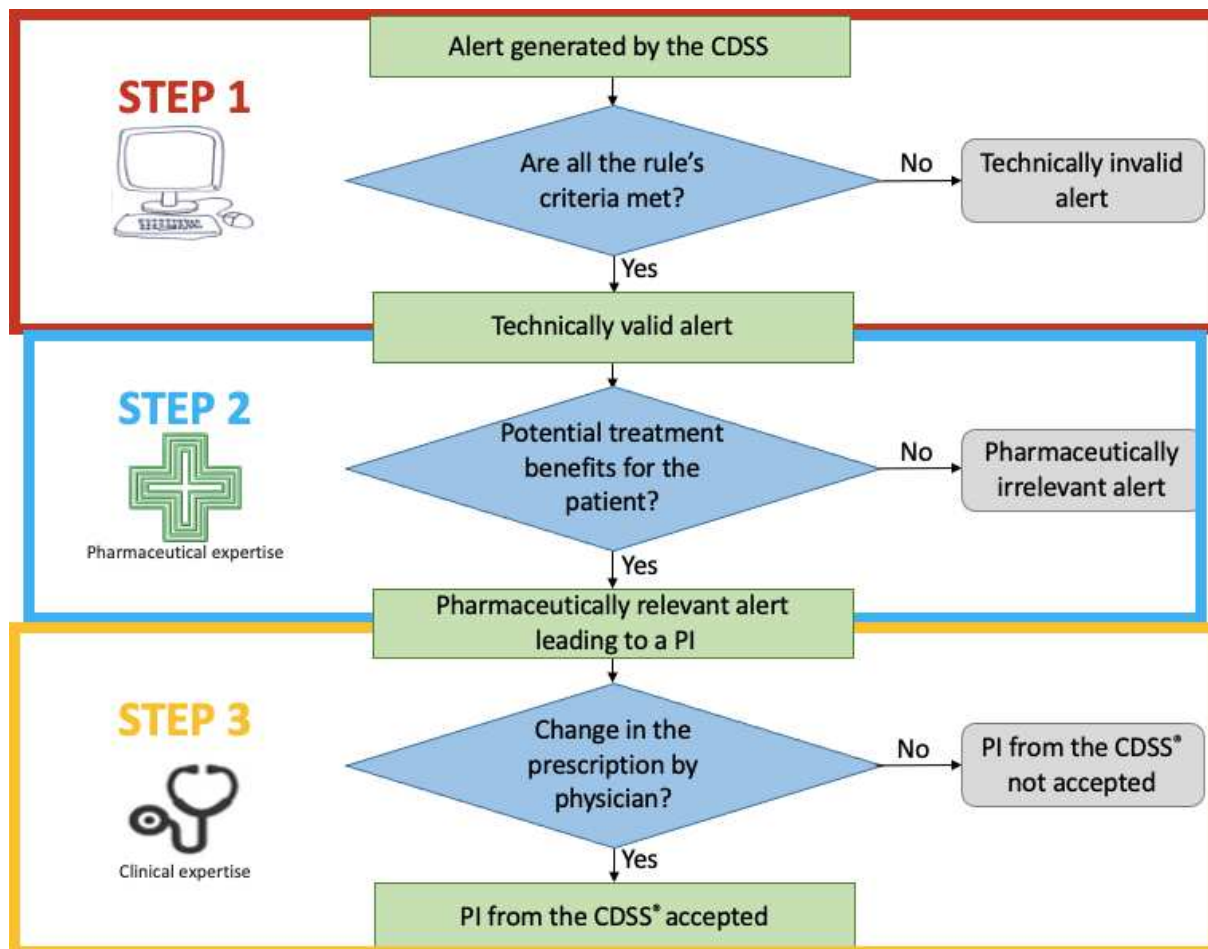


Figure 2: Flow chart for the CDSS, showing the three steps. CDSS: clinical decision support system; PI: pharmaceutical intervention

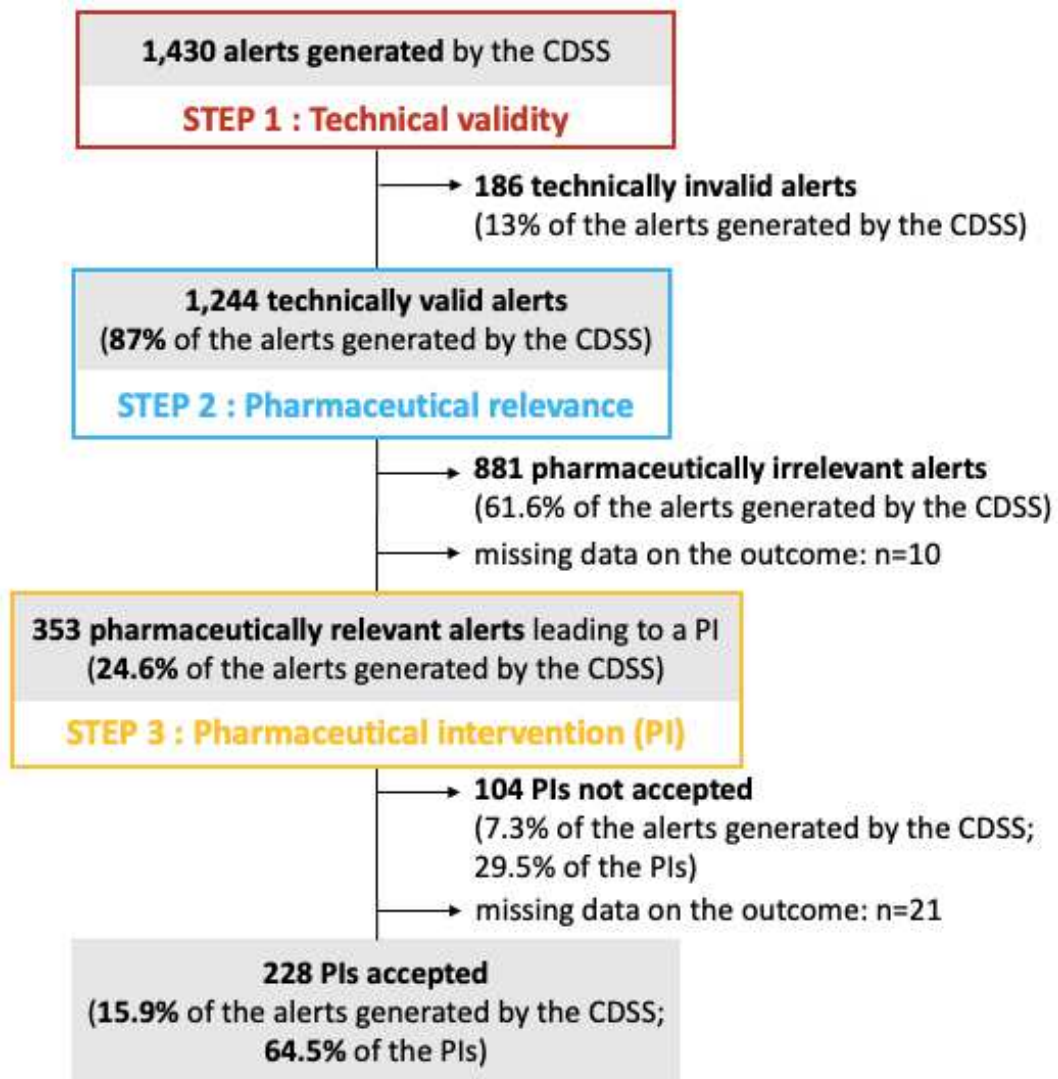


Figure 3: Flowchart for alerts analyzed by clinical pharmacists during the first 7 months of the CDSS's operation.
 CDSS: clinical decision support system; PI: pharmaceutical intervention

Table 1: Reasons for technical invalidity, according to the clinical pharmacist.

Reasons for technical invalidity	Proportion of total invalid alerts (n=186)
The lack of at least one of criterion for the rule	126 (67.7%)
- <i>Incorrect lab results</i>	14
- <i>Medication withdrawn temporarily</i>	60
- <i>Medication withdrawn permanently</i>	30
- <i>Medication error</i>	22
Patient's identity	47 (25.3%)
- <i>Patient deceased or discharged</i>	38
- <i>Incorrect ward</i>	9
Missing data	13 (7.0%)

Table 2: Reasons for pharmaceutical irrelevance, according to the clinical pharmacist.

Reasons for pharmaceutical irrelevance	Example	Proportion of total valid alerts (n=881)
Due to a lack of specificity in the CDSS		624 (70.8%)
Lack of specificity of the rule, relative to the actual data	For the rule " <i>Sitagliptin with chronic kidney disease</i> ", a dose of 50 mg/d is recommended (but the dose is not available in the CDSS)	429
Adjustment of the prescription not considered by the CDSS after the alert had been triggered	For the rule " <i>Hyperkalaemia and potassium intake</i> ", the single-dose treatment with ion exchange resin (the corrective treatment) could not be taken into account in the rule	94
Lab result not considered by the CDSS after the alert had been triggered	For the rule " <i>Hyperkalaemia and potassium intake</i> ", the kalaemia was normal after the alert had been triggered but this alert was not deactivated.	58
Redundancy of alerts when a criteria changed (not link to criterion of alert)	For the rule " <i>Metformin and eGFR between 30 and 45</i> ", the alert was irrelevant because the dosage was correct. But when another dosage of creatinine in the prescription was made, a new alert reappears.	43
Irrelevant alerts for a specific ward (known reject alert)		137 (15.6%)
PI not relevant for the ward's prescribing habits	For the rule " <i>Switch from enoxaparin to tinzaparin</i> ", the PI was always refused by surgery ward because the treatment was always rapidly re-evaluated.	109
PI already refused by prescribers (according to their own habits)	For the rule " <i>Hypoglycaemic sulfonamide in an elderly patient</i> ", the PI was always refused on non-diabetes wards (due to the prescribers' habits).	28

Patient monitoring by the clinical pharmacist		95 (10.8%)
Lab results close to the limit	For the rule “ <i>Calciparin in the absence of acute kidney injury</i> ”, the eGFR was nearly 30 ml/min/1.73m ² . The pharmacist must monitor changes in the eGFR before issuing a PI.	49
Patient monitoring	For the rule “ <i>Prevention of hyperkalaemia and potassium intake</i> ”, the dose of furosemide was increased. Hence, the potassium intake was not changed and the patient was monitored.	37
Irrelevant acute kidney injury (AKI) alert	For the rule “ <i>Presence of an acute kidney injury</i> ”, renal function was slightly impaired. The patient is monitored by a clinical pharmacist and the dose is adjusted if required.	9
Missing data		25 (2.8%)

Table 3: PIs suggested by the clinical pharmacists (according to the guidelines issues by the French College of Clinical Pharmacy) and the outcomes.

Suggested PI	N (%)*	Accepted by the physician**
Drug substitution	113 (32.0%)	59 (52.2%)
Drug withdrawal	107 (30.3%)	87 (81.3%)
Dose adjustment	82 (23.2%)	53 (64.6%)
Monitoring	18 (5.1%)	13 (72.2%)
Optimized administration	8 (2.3%)	3 (37.5%)
Addition of a drug	4 (1.1%)	2 (50.0%)
Missing data	21 (6.0%)	11 (52.4%)

* Percentage of the 353 pharmaceutically relevant alerts

** Percentage of the PIs of each type