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Bates, D. W.; Baysari, M. T. ; Dugas, M.; Haefeli, W. E.; Kushniruk, A. W. ; Lehmann, C. U.; Liu, J.; Mantas, J.; Margolis, A.; Miyo, K.; Nøhr, Christian; Peleg, M.; de Quirós, F. G. B.; Slight, S. P.; Starmer, J.; Takabayashi, K.; Westbrook, J. I.

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D. W. Bates[1]; M. T. Baysari[2,3]; M. Dugas[4]; W. E. Haefeli[5]; A. W. Kushniruk[6]; C. U. Lehmann[7]; J. Liu[8,9]; J. Mantas[10]; A. Margolis[11]; K. Miyo[12]; C. Nohr[13]; M. Peleg[14]; F. G. B. de Quirós[15]; S. P. Slight[1,16]; J. Starmer[7]; K. Takabayashi[17]; J. I. Westbrook[18]

[1]Centre for Patient Safety Research and Practice, Division of General Internal Medicine and Primary Care, Brigham and Women's Hospital, Boston, Massachusetts, USA;
[2]Australian Institute of Health Innovation, Faculty of Medicine, University of New South Wales, Sydney, Australia;
[3]Department of Clinical Pharmacology & Toxicology, St Vincent's Hospital, Sydney, Australia;
[4]Institute of Medical Informatics, University of Münster, Münster, Germany;
[5]Department of Clinical Pharmacology and Pharmacoepidemiology, University of Heidelberg, Heidelberg, Germany;
[6]School of Health Information Science, University of Victoria, Victoria, Canada;
[7]Department of Biomedical Informatics, Vanderbilt University, Nashville, TN, USA;
[8]Department of Medical Informatics, West China Hospital/West China Medical School, Sichuan University, Chengdu, China;
[9]Department of Otolaryngology, West China Hospital/West China Medical School, Sichuan University, Chengdu, China;
[10]Health Informatics Laboratory, University of Athens, Athens, Greece;
[11]Instituto de Computación, Facultad de Ingeniería, Universidad de la República, Montevideo, Uruguay;
[12]Department of Planning, Information and Management, The University of Tokyo Hospital, Tokyo, Japan;
[13]Danish Centre for Health Informatics, Department of Development and Planning, Aalborg University, Aalborg, Denmark;
[14]Department of Information Systems, University of Haifa, Haifa, Israel;
[15]Department of Health Informatics, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina;
[16]Division of Primary Care, The University of Nottingham, Nottingham, UK;
[17]Department of Medical Information and Management, Chiba University Hospital, Chiba, Japan;
[18]Centre for Health Systems and Safety Research, Australian Institute of Health Innovation, Faculty of Medicine, University of New South Wales, Sydney, Australia

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With these comments on the paper "Attitude of Physicians Towards Automatic Alerting in Computerized Physician Order Entry Systems", written by Martin Jung and co-authors, with Dr. Elske Ammenwerth as senior author [1], the journal wants to stimulate a broad discussion on computerized physician order entry systems. An international group of experts have been invited by the editor of *Methods* to comment on this paper. Each of the invited commentaries forms one section of this paper.

Correspondence to:
See list of authors´ adresses at the end of the article

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1. Comment by D. W. Bates and S. P. Slight

Jung et al. have performed the largest international survey of providers using computerized physician order entry (CPOE) applications which has been performed to date; it included nine countries from across Europe and had a substantial sample size.[1] Overall, attitudes were positive, though providers did not like getting too many alerts, and were understandably concerned about alert fatigue. The authors conclude that the use of less interruptive alerts is positive. While in general we agree with nearly all the conclusions of the paper, we disagree with this one – it is very important to have important alerts be interruptive, while unimportant ones can be suppressed or be made non-interruptive. We will present recent evidence regarding this. Also, there are major opportunities to improve the decision support that is delivered, and many such opportunities are likely internationally generalizable.

Overall, it is now clear that CPOE is highly beneficial for preventing medication errors [2, 3]. There is more controversy regarding the evidence with respect to preventing adverse drug events, but the vast preponderance of studies suggest that it is beneficial for this as well, though most studies that have been done have been under- powered [3]. While there is less evidence regarding this, CPOE may improve safety and efficiency in other ways as well

Regarding alerts, whether or not alerts are made interruptive are one of the most important factors affecting whether or not providers accept them. One study from our site illustrates this clearly [4]. In that study, at one site drug-drug interaction alerts were displayed in a tiered fashion; in the top tier, providers could not override, in the next they were warned but could override, and in the final the alerts were non-interruptive. At the other site, for technical

reasons, all the alerts were delivered as interruptive. At the first site, 100% of the most important alerts were followed, vs. only 34% at the non-tiered site. Moderately severe warnings were also much more likely to be accepted at the tiered site, 29% vs. 10%. Overall compliance at the tiered site was also much higher, 29% vs. 10%.

In addition, other factors have been correlated with higher levels of acceptance [5]. These included frequency of the alert, quality of display, textual information, and how the information was presented.

Yet another approach to improving the problem of alert fatigue is obtaining better consensus about which alerts to display. We were sponsored by the Office of the National Coordinator to identify a small set of drug-drug interactions which should never be overridden. We convened an international expert group to do this, and identified and published a list of 15 such interactions [6]. We also identified a much larger set of interactions which are of sufficiently low priority that they should not be delivered interruptively [7].

We suspect that most such issues could be addressed across national boundaries, and that all would be better off if this were done. Of course, drug availability and naming differs substantially among countries, but most of the adverse effects probably do not. We have argued that there would be major international benefits of doing this, and that this would take us a long way toward reducing alert fatigue [8, 9].

This work by Jung et al. is largely reassuring about the attitudes of providers towards computerized physician order entry. Providers clearly do not want to go back. But they are understandably and justifiably frustrated by alert fatigue. This is a problem that can and should be addressed by medical informatics, but if we care about patient safety and realizing the safety benefits of CPOE we should not do so by making important alerts non-interruptive.

2. Comment by M. T. Baysari and J. I. Westbrook

This study used a survey to examine physician attitudes towards computerised alerts in Computerized Physician Order Entry (CPOE) [1]. Although much research has explored user views of alerts, this is importantly the first international study to be conducted across multiple sites using various CPOE systems. The CPOE systems differed in the types and numbers of alerts they included, with for example, one hospital including only dosing guidance, and another including nine different alert types (dosing guidance, drug-drug interaction checking, drug-allergy checking, etc). Alerts also varied in their triggering strategy, with some presented automatically to prescribers, and other alerts being optional (i.e. presented on demand). Alerts could be interruptive or non-interruptive.

The study findings in several ways were not surprising. On the whole, most physicians viewed computerized alerts as useful and many felt that alerts could potentially prevent prescribing errors. At the same time, doctors were wary of being overalerted and expressed concern about the additional time alerts added to their work. These themes have emerged in many previous evaluations of computerised alerts, including our own [10], but what this current study demonstrates is that the same issues are faced by hospitals all over the world, regardless of system used. On inspecting Figure 1, remarkable consistency is apparent in many of the views expressed by participants from different sites, even those not using a CPOE.

The authors explain that their study was not designed to identify the factors that influence attitudes to alerts. This is perhaps a missed opportunity. The authors do briefly discuss some of the inter-site differences they observed and the implications of these (e.g. alerts should interrupt clinicians only to warn them about important and severe cases). But a detailed look at Figure 1 reveals some additional differences that are worthy of examination in more depth. For example, most physicians at most sites disagreed with the statement that alerts are essentially meaningless and a waste of time (item 3), but more than half the participants from Denain agreed with this statement. Those at Geneva and Rouen also appear less convinced than other sites. Why? When asked whether their CPOE generated too many alerts that were irrelevant for their patient (item 14), all participants from Galway disagreed with this statement, but the majority of physicians at Copenhagen and Denain agreed. How has Galway ensured that alerts are always relevant? Clinicians at different sites also had quite disparate views on whether alerts influenced their initial prescribing decisions (item 15). The extent to which these results reflect cultural differences or variations in the systems used is unknown, but clearly highlights the importance of understanding contextual environments. Linking the qualitative results to the characteristics of the CPOE systems would assist in understanding the relationship between specific design features and physicians' views of their value.

Jung et al. have confirmed what many of us knew to be the case within our own organisations: computerised alerts have great potential to prevent prescribing errors and improve patient safety, but alerts are useful only when well designed and clinically relevant. What is now needed is a shift away from identifying the problem to trialling potential solutions. How do we ensure that alerts are well designed and relevant? This is a highly complex and difficult question, with many factors to consider. For example, we recently discovered that suboptimal use of a CPOE resulted in the generation of 'technically preventable' alerts, a likely consequence of discordance between the prescribing task, as performed by prescribers, and the prescribing task envisioned by designers [11]. Although several strategies have been proposed to improve alert usefulness and usability – e.g. triggering alerts in certain clinical contexts (night shifts) but not others (ward rounds) [10], customizing alerts based on prescriber specialty [12], tiering alerts based on severity [4] – a need clearly exists for controlled and systematic studies of these potential approaches.

3. Comment by M. Dugas

Jung et al. [1] conducted a survey regarding the attitude of physicians towards alerting in CPOE systems in 11 hospitals (8 of 11 with CPOE systems) from 9 countries. 1018 of 2600 physicians responded to this survey and overall, indicated positive atti-

tudes towards CPOE and alerting. This is a multilingual, international survey covering a wide range of systems.

Electronic prescribing is a key module in CPOE. The benefits of ePrescribing have been demonstrated recently: a significant error reduction by ~ 60% [13]. However, the scientific debate about impact of eHealth on quality and safety of care is still controversial. A recent review [14] about this topic states "There is a large gap between the postulated and empirically demonstrated benefits of eHealth technologies" and summarizes with respect to electronic prescribing "weak-to-moderate evidence was indicated for improved practitioner performance due ... fewer medication errors".

If a new medication would reduce side effects by 60% with the same effectiveness like standard therapy, it would become the new standard on a global level. Apparently, this is not yet happening with CPOE solutions or eHealth systems in general. For example, it has been shown in a large randomized clinical trial (2506 patients) that electronic alerts linked to a CPOE system can reduce the risk of deep-vein thrombosis or pulmonary embolism by 41% [15]. Why are these systems not implemented on a global level?

The key challenge is missing interoperability: "Lack of semantic interoperability is the most important obstacle in clinical decision support system implementation" [16]. Due to incompatible information systems a global rollout of validated CPOE functionalities with CDS is currently not possible. A major roadblock are secret, heterogeneous and incompatible data models. Therefore we need to foster open data models in healthcare [17] to support standardization of data models and to facilitate rollout of CPOE and CDS. From a strategic point of view, more direct involvement of clinical opinion leaders in CPOE implementation is needed.

From my personal perspective, attitudes of physicians are important, but ultimately it is about the benefit for the patient. Even if physicians hated CPOE systems and electronic alerting: if patient outcomes are improved by CPOE systems and CDS, they must be implemented. Therefore future research should focus on these patient outcomes. All kinds of outcomes should be assessed: survival, physiological outcomes, but also quality of life, which can be measured by eHealth instruments [18]. Trials with high methodological standards are needed to provide bullet-proof evidence which kind of CPOE/CDS is effective in what kind of clinical setting.

4. Comment by W. E. Haefeli

It has become increasingly evident that computerized physician order entry (CPOE) is most useful if it is linked to a clinical decision support (CDS) system [19]. Equipped without CDS, a CPOE system may improve spelling and readability of orders but it will prevent only a small fraction of dosing errors, inappropriate drug administrations, or prescription of contraindicated drugs and never drug interactions. Hence, the most dangerous and frequent errors will not be intercepted. Conversely, while CDS systems may contain all the information needed for state-of-the-art decision making, their functionality and usefulness is limited if they are not integrated into the prescription process (on demand system) and not linked to anthropometric, demographic, clinical, and laboratory information of the particular patient that is relevant to separate patients at risk for adverse events or nonresponse from those benefiting from a particular medication.

The development of a CDS system forces developers to clearly define the rules guiding the decision to enable successful knowledge transfer into the world of computerized decision support. Obviously this can easiest be done if the decision process is well understood, unequivocal, and does not depend on context factors. However, only rarely context does not matter. As an example, users do not welcome pregnancy alerts in elderly people or prostate obstruction warnings in females indicating that even for very basic warnings context may be relevant. This is even truer for more sophisticated decision making.

In their multinational questionnaire survey Jung and co-workers [1] showed that the majority of physicians welcome automatic alerts issued by a CPOE-CDS system provided that these warnings are specific and sensitive. The survey also highlighted the need of sophisticated drug interaction warnings in order to make the CDS acceptable to the users.

4.1 Sophistication of Alerting

Options for sophistication of alerting with CDS systems are manifold and can nicely be illustrated using drug interaction alerts as an example. The success of a warning system depends on three fundamental areas each of which will modulate the impact and acceptance of the functionality and will require sophistication. First, CDS systems should be part of the prescription process, linked to the actual prescription (via CPOE), and enable access to relevant context information (technical integration) [19]. The depth of integration may be a decisive determinant of performance of a given CDS and thus of its transferability to other institutions and settings [20]. Second, the way how alerts are displayed to users may critically affect acceptance (human factors) [5], and, finally, alerts should be tailored to the individual patient, the system user, and the setting to issue only meaningful alerts (sophistication of content and reasoning).

Warnings in most but not all [21] interaction alert systems are only triggered by the combination of active ingredients. They will therefore also issue warnings if circumstances and context factors will preclude the manifestation of the interaction. As an example topically administered diclofenac, which does not become systemically available, will not interact with a systemic medicine [22] and ciprofloxacin will not build complexes in the stomach (e.g. with multivalent cations) and loose efficacy if it is given intravenously or administered several hours apart (spacing of doses [23]). Hence, if context factors are not appropriately considered by the CDS system over-alerting will result. A wealth of other options for sophistication is shown in ▶Table 1 and certainly several of them may concur and thus require comprehensive consideration. A pertinent example is the combination of lamotrigine with valproic acid or phenytoin increasing or de-

Situation	Interaction example	Required trigger beyond active ingredient	Reference
Only topical availability	Diclofenac and furosemide	Systemic availability	[22]
Galenic formulation	Slow release vs. instant release verapamil + dabigatran	Release characteristics	[31]
Physical encounter	Oral ciprofloxacin +calcium carbonate	Timing of administration	[32]
Route of administration	Clarithromycin + iv vs. oral digoxin	Route of administration	[33]
Dose dependency of perpetrator	Gemfibrozil + repaglinide	Administered dose of perpetrator	[34]
Dose dependency of victim	Simvastatin + amiodarone	Administered dose of victim	[35]
Time dependency (exposure to perpetrator)	Erythromycin + midazolam	Preceding duration of treatment	[36]
Time dependency (discontinuation of perpetrator)	St John's wort + ritonavir + midazolam	Timing of recent discontinuations	[37]
Triple combination	Lamotrigine + phenytoin + valproic acid	Combinations of more than pairs	[24]
Genotype	Voriconazole + ritonavir + CYP2C19 status	Genetic variants	[38]
Age	Rifampicin-induced enzyme induction	Age	[39]
Gender	Rifampicin-induced enzyme induction	Gender	[39]
Hepatic impairment	Fluvoxamine + theophylline or lidocain	Cirrhosis	[40]
Setting	Additive sedation of psychotropic drugs	Setting (e.g. ICU and mechanical ventilation)	

Table 1 Triggers for successful sophistication of drug interaction alerts

creasing lamotrigine but leaving lamotrigine dose requirements essentially unaffected when all three are combined [24]. Hence, in such instances the system should only issue a single integrated alert for each drug (quest for a one-alert strategy) and in this situation even suppress any alert as opposed to issuing two contradictory warnings for the management of lamotrigine. In addition to patient factors also the setting may influence the relevance of an alert. As an example, in mechanically ventilated patients additive sedation by an opioid and benzodiazepine may be irrelevant or even beneficial because the potential negative consequences do not matter in patients already mechanically ventilated.

Given the many options for improvement of current CDS systems it is not surprising that a majority of responders in the survey by Jung and co-workers [1] wished to get better tailored decision support. Indeed, such an approach would eliminate more than half of all statin alerts, if only the dose of the victim would be considered [25], and almost 4 in five of the top 100 alerts issued in a tertiary care hospital if laboratory information (potassium, kidney function, therapeutic drug monitoring, leukocytes, and INR) or detailed prescription information would be considered (in descending order) (Seidling and Haefeli, unpublished), highlighting the promise of this approach.

However, thus far CPOE-CDS systems rarely held their promises and very often only added little quality improvement [3, 19, 26,]. A major reason was that systems generally contained a rather basic set of rules addressing a particular error (e.g. inappropriate doses, drug interactions, elimination organ dysfunction, or age restrictions) and issued alerts whenever a rule applied irrespective of the individual context thus triggering alert fatigue. While such systems may be very efficient in performing a particular task, they usually fail if more than one rule applies. Therefore cofactors have to and should be considered before recommendations are issued in order to avoid revoking of warnings or triggering of new errors (quest for comprehensive assessment and a hierarchy of CDS modules and their alerts).

4.2 Patient Safety

Interestingly, among the top benefits of such CDS systems the physicians ranked increased patient safety. This is rather surprising because experimental evidence for such a benefit measured in clinical endpoints is rather limited. Thus far, many studies were not appropriately powered to detect changes in relevant clinical endpoints and rather assessed process changes (practitioner outcome) than patient outcome changes in clinical practice [19, 26]. However, process changes are non-validated surrogates such as medication errors or practitioner outcome and by far not all studies with a documented positive impact

on these markers also improved the clinical endpoints expected to be linked to it [26].

Studies addressing the impact of CPOE-CDS systems on adverse drug events are also rare and inconclusive because very often no change or only a trend towards a reduction of adverse events was observed [3] and for adverse events as a consequence of drug interactions only one study reported that the reduction of drug interactions with the help of a CDS also resulted in fewer adverse events [27].

Important reasons for the rather limited evidence for effectiveness of CDS systems lie in the challenge of performing a randomized controlled trial, the fact that blinding is difficult, and the uncertainty of the best practice standard. Moreover, because physicians typically treat clusters contamination, i.e. the spread of effect between groups, and correlation within clusters are relevant issues limiting validity and transferability of the results of such trials [28]. Moreover, setting effects may be substantial [20] and the often large disparity of features implemented in a local CPOE-CDS system [1] may preclude comprehensive checking from the start.

Another weakness of new decision support systems is that we do not know error rates in best case clinical settings and therefore do not exactly know when a CDS system provides added value. Indeed, while we may be well aware of a given error in our own environment we tend to believe that in best case scenarios such errors never occur. This may, however, be an error on its own because experts may also tend to express different views and even to disagree indicating that even in best case scenarios error rates may considerably deviate from zero [29]. Alternatively it might indicate that in certain cases (e.g. when patients with multiple morbidities are treated according to multiple guidelines [30]) there is not a single best decision and several options may apply. This is important information because it will define the target performance that should be achieved with a CDS system and that should guide its validation process.

In conclusion, the paper by Jung and co-workers [1] nicely shows that electronic decision support is welcomed by physicians but the way in which many alerts are generated today is suboptimal. The key weakness of current alert systems is the high frequency of inappropriate alerts due to a lack of tailoring to the specific situation and context.

These data therefore call for a major effort in the field of electronic decision support. Areas for improvement are the consequent consideration of relevant context factors and comprehensive simultaneous assessment of the whole group of modulators to avoid contradictory alerts and ultimately issue only one recommendation with integrated information from all knowledge bases (one-alert strategy). Therefore a clear hierarchy of electronic checking should be established that integrates drug interactions, elimination organ dysfunction, and laboratory monitoring information [21] and, in an ideal world, also considers all other modulators of potential interest and impact (e.g. setting, drug-disease interactions, guidelines, and patient abilities and preferences as well as training, experience, and educational status of the users). It might therefore even be better to use less complete but more sophisticated alerts than aiming for integration of all potential and conceivable risks in such a system.

5. Comment by A. W. Kushniruk

In their paper "Attitude of Physicians Towards Automatic Alerting in Computerized Physician Order Entry Systems" [1] Jung and colleagues describe the results of a broad international CPOE survey addressing physicians in a number of countries. The paper is very noteworthy in that it is the first such international survey addressing attitudes of physicians to alerting in CPOE systems and provides insights into both what are common issues internationally, as well as providing insights into differences across sites surveyed. In all the countries surveyed it was found that there was a generally positive attitude towards CPOE alerting and that the majority of physicians (both CPOE users and non-users) "appreciated" the benefits alerting in CPOE could offer. Other important findings include that despite general understanding of the potential benefits of CPOE alerting by most respondents, about half of the respondents saw possible alert overload as a major problem (with respondents coming from hospitals with more sophisticated and less interruptive alerting strategies showing better attitude scores). The key insights from the survey indicated that two factors have an important influence on the attitudes of physicians regarding CPOE alerting, namely: a) the chosen approach or strategy for displaying alerts, b) the clinical context in which they are triggered to appear.

The findings from Jung and colleague's paper are consistent with a growing body of international research that has indicated that physicians may experience alert fatigue, may find that alerts are not specific or relevant to their particular clinical situation and that they may at times interfere with normal workflow and activities [41–43]. It is hoped that the results of the international survey in conjunction with this growing and now extensive body of research will ultimately lead to more proactive approaches to designing and deploying CPOE alerts and clinical decision support in clinical settings. Along these lines the survey by Jung and colleagues confirms and extends results that have been increasingly discussed nationally and internationally regarding the need for improved consideration of human factors and human computer interaction in designing and implementing CPOE alerts. Such work will be needed in the customization of alerting to specific contexts and organizational settings where CPOE alerting is deployed. The finding that the chosen strategy for alerting is critical highlights the need for careful consideration of the mode of activation of alerts, how they are displayed on the computer screen, the selection and prioritization of alert content that will facilitate (and not hinder) complex healthcare work processes, as well as increased consideration of their overall usability. Furthermore, improved consideration of the context of triggering of alerts is critical and this finding is also consistent with a growing body of research from the area of human factors in healthcare, pointing to the need for local contextualization and optimization of CPOE alerting. This is discussed by Jung and colleagues in the con-

clusion of their paper where they aptly state that to achieve positive attitudes, "highly structured drug and patient case information is needed, as well as locally customizable CPOE systems which are capable of taking into account the clinical context and of differently presenting the alert information to the user".

It is clear from reading Jung's paper that in order to achieve improved user satisfaction, more work in applying methods from usability engineering and socio-technical design is needed, as well as more extensive conformance as well as local testing/customization of decision support. Work along these lines, focusing on how to assess and customize clinical decision support to more effectively fit local workflow has been reported by a number of authors. For example Li and colleagues [44] have conducted several layers of usability testing and clinical simulation to adjust and optimize both the content and triggering of vendor provided alerts and decision support prior to releasing these features within an electronic health record in a large healthcare institution. The results of this local optimization effort were a much improved uptake and adoption of the alerting and other decision support features by physicians. More work along these lines is needed as Jung's paper clearly points to. Given the key insights from Jung's paper, in particular the acknowledgement that the issues being reported span countries and continents, the time now appears ripe for extending and accelerating work on developing and applying methods for proactively improving the human factors involved in introducing CPOE alerting (and more generally clinical decision support) into complex healthcare work activities. Furthermore, such work is needed in order to ensure not only effective use and usability of alerting features and functions but also to ensure their safety and to mitigate any potential technology-induced error that their use might inadvertently introduce.

6. Comment by C. U. Lehmann and J. Starmer

Anaïs Nin, the French-Cuban author is credited with saying "We don't see things as they are; we see them as we are". This quote infers that our perception of reality is determined by our prior beliefs. Knowing that Jung et al. surveyed physicians, who as a group have a strong history of altruism [45], it is difficult to discern how much the answers in the survey were influenced by the perception of reality molded by the professional desire to do the best for the patients with the willingness to place the physician's own needs (efficient work environment) behind patient needs (additional safety).

Especially in commercial systems we have seen Clinical Decision Support (CDS) so granular in its alerting that its value is negligible and its power to interrupt extreme. The desire to be all-inclusive to reduce the risk of a malpractice suit causes vendors to routinely use the most stringent settings for their alert system, in order to deflect any accusation that their system should have provided an alert when it did not. A good example was the commercial drug-drug alert CDS implemented at the Johns Hopkins Hospital. A total of 15% of drug orders triggered alerts and the Medicine House staff overrode 97.4% of these alerts. Only 2.6% of drug-drug alerts resulted in order changes and disconcertedly two-thirds of substitutions were found to be inappropriate or dangerous. Examples included alerts for "heparin and coumadin", "clopidogrel and aspirin", and "spironolactone and potassium". Obviously, when a patient, who just underwent a cardiac catheterization, has her aspirin discontinued because an alert is fired reporting that the aspirin interacts with clopidogrel, harm may ensue. Worsening the situation is a lack of context including the inability to limit alerts based the administration route (Example: ophthalmic beta-blocker) and the extensive, often multiple page alert message that were too long to be reviewed by busy providers. In two months surveillance of the drug-drug alert, no discernible patient safety benefit was realized, however we can safely infer that the trust of providers into the system was ruined and the amount of alerts caused some building up of anger and frustration on the part of providers [46]. These issues are identified by clinicians responding to questions 4 and 5 of the survey by Jung et al.

In order to gain insights into key features that CPOE systems should support, we reviewed Jung et. al.'s results using a methodology based on a survey on the deontic terminology in guidelines by Shiffman and colleagues [47]. We analyzed the operative words "should, will, may, etc." in all questions and then divided the questions into two groups: One reflecting the current state of clinical decision support, and the other focusing on the beliefs of what clinical decision support should do in the future. We used the "level of obligation" of the operative word in each question as an indicator of certainty, or strength of the response. The two strongest negative beliefs in regards to the current state of clinical decision support were the perception that alerts will create too many irrelevant alerts and will cost too much time for providers. Among the strongest answers of the future state of clinical decision support were the notions that it should be filtered and be better at distinguishing important from less important alerts.

Clearly, the lack of efficiency expressed in the answers on current state is a function of the fact that informatics is in the early stages of developing decision support. As Jung et. al pointed out, providers would prefer context sensitive alerting that takes into account the type of patient, existing conditions, the provider's area of practice, etc. The context will provide the ability to reduce noise and to filter all potential alerts for those that may be clinically significant. As Jung et al. discuss, the alerting strategies chosen by the more successful hospitals had been targeted to provide some context information to reduce alert frequency. However, more can and should be done to reduce alert frequency and to render alerts more clinically useful. It is our belief that two important developments will need to occur to improve clinical alerts and decision support:

6.1 Leveraging Prior Knowledge

Any clinical system developer, who desires to experience the righteous wrath of clinicians, has do only one thing – alert a clinician multiple times on related events. An example would be alerting a clinician to an abnormal laboratory value like a high white blood cell count, if the same clinician had received the day prior an alert for an even higher value. We experienced this 'righteous wrath' effect when we created a laboratory result alerting system for the Newborn Intensive Care Unit in 2004 and can attest to the unpleasant encounters for developers as a result. Developing Clinical Decision Support that suppresses alerts taking into account the data a provider has seen, reviewed, or received alarms on will be critical to improve user satisfaction.

6.2 Presentation of Pre-coordinated Decision Support Content

An obvious but not realized concept in clinical decision support is the potential to help the provider make the right decision from the outset instead of admonishing the provider after the fact that his or her choice was incorrect and would lead to an error. An example would be pre-coordinated order entry content for a specific drug with different doses. A provider, who wants to order this drug for a child or a patient with renal compromise is offered only those choices on the order entry menu that would allow safe dosing. Any dose that would be too large based on the patient's weight or renal function would not be available on the menu, which is created "on the fly" based on all available menu items and patient characteristics. Similar, a patient with a drug that contraindicates the use of another drug, would only be able to see the drug in the menu 'greyed out' and would be unable to select it without supplying a reason for the override.

Preventing an error of commission by not allowing it, will reduce work since the provider does not have to back out of the ordering process and will improve satisfaction, however providers must have the option to overwrite the limited selection and be able to order items they deem needed.

These two proposed modifications address multiple concerns identified by the survey, including issues related to alert fatigue, taking too much time, being context sensitive, and being non-interruptive. This will require substantial design and development but it is critical that we start thinking not just about the patient and making care safer for the patient, but it is critical that we start taking care of our own and make care process easier on providers. More surveys of this nature, with attention to the words used to determine the strength of the response, would be quite helpful in gaining insights into how CDS systems can support better and more efficient decision making.

7. Comment by J. Liu

With the increased adoption of Computerized Physician Order Entry (CPOE) systems, it is important to recognize that CPOE use can be affected adversely due to design flaws. New types of iatrogenic medical errors, for example, can be the results of careless and unintended consequences arising from CPOE use. Survey is a commonly used methodology and an efficient way to obtain a firsthand understanding of what and how physicians work habits are or can be affected by the introduction and adoption of CPOE systems and Clinical Decision Support Systems (CDSS).

M. Jung, et al. surveyed the attitude of physicians towards automatic alerting in CPOE systems under various settings [1]. Their work provides a more in-depth understanding of physician attitudes towards having automated alert feature designed into a CPOE. Jung and colleagues have contributed a thoughtful study on CPOE and CDSS. Clearly, there is a need for more empirical work and sharing of findings, lessons, and best practices on how to best design and implement CPOE and CDSS so as to improve health care and reduce medical errors. Their work makes us rethink on how to define the attitude more objectively, understanding the use of CPOE, CDSS as well as the impact of particular alert design feature, more specifically, alert fatigue.

7.1 Physician Attitudes towards CPOE/CDSS

In the paper, the authors measured the attitude towards automatic alerting in CPOE systems in various settings. Physician attitude is a pre-requisite to drive CPOE adoption in hospitals. Attitude is key in the formation of intention and behavior. Attitude is typically viewed as a latent or underlying variable that is assumed to guide or influence behavior. Attitude is associated with behaviour, and precedes it [49]. However, physician attitude towards CPOE is difficult to measure because it is quite challenging to identify objective criteria to evaluate a subjective theme. There is no gold standard for measuring physician attitude towards CPOE as the tools used and specifications of thresholds for physician attitude levels can be somewhat different in the design of each study.

Attitude is multifactorial, making it a very challenging variable to operationalize and measure. In general, attitudes are action tendencies and as such they can facilitate or hinder actions at different as well as all levels, specifically, individual, group, community, state, and national level. Meanwhile, attitude may influence behaviour and in turn be influenced by it. Among the major factors influencing physician attitude towards CPOE and CDSS include:

- The individual physician characteristics and socio-technical factors
  Age; Gender; Clinical specialty; Education; Computer literacy; Physician need; Physician knowledge, and Previous experience, etc.
- The contextual factors
  Management support (e.g., ongoing service and support, clinical leadership, workflow impact, technical support, expert support); Physician involvement in system selection; Training (e.g., supportive material, learning to use, learning curves and learning styles); Physician autonomy; Additional work load for physicians; User behavioral; Characteristics of study hospital (e.g., for-profit hospitals and non-profit hospitals, teaching hospital and non-teaching hospital, urban hospital and suburban hos-

pital); Feedback acquisition; Cost, and other factors.
- The technical issues
  User/system interactions (e.g., accessibility, flexibility, ease of use, efficiency, functionality); System's basic characteristics (e.g., speed, reliability, accuracy, capabilities, point-of-care entry and viewing of documentation, usability, usefulness); and Screen design.

Together, these various factors should be taken into account carefully when evaluating physician attitude towards CPOE and CDSS. They are important in the design, acceptance and implementation of the system. Understanding what factors affect attitude could lead to significant changes in designing future CPOE systems and CDSS. We need and want to know how physician attitude affects their acceptance or non-acceptance the system prior to its implementation.

7.2 Standards

The definitions of CPOE systems and CDSS are critical for comparing measures of the physician attitudes towards CPOE and CDSS meaningfully across different hospitals or healthcare organizations that adopt these tools. If we use different definitions of these systems, we will get different results. Unfortunately, both of these clinical tools are frequently applied in different settings with resulting variations of meaning in terms of how the systems are accepted or adopted by physician users depending on the context of use. Each study and each professional organization reviewed had a different definition of CPOE and CDSS. Most studies clearly indicate that their results are not generalizable owing to the uniqueness of the health IT systems being studied.

Guidelines and key information on relevant standards activity for various health IT tools and technologies exist at the national level, such as the National Library of Medicine as provided on the government websites, at the level of standards organizations such as HL-7, and at the level of professional organizations, such as AMIA and HIMSS as provided on their respective websites.

7.3 Alert Fatigue

Clinicians are often exposed to too many CDSS alerts that they may eventually stop responding to them, thereby decreasing the overall effectiveness of the system and such designed feature. This phenomenon is often called alert fatigue [50, 51]. Alert fatigue is often caused by poor signal-to-noise ratio in alerts (non-serious, irrelevant, repeated, low credibility, trivial medical concerns, less useful information, etc.). Alert fatigue can also drain on one's emotion (consuming time, mental energy, etc.), which can further caused life-threatening alerts to be ignored along with unimportant ones. Some studies showed that most of the alerts (from 55% to 91.2%) were ignored by the physicians [52–55]. Physicians wish that alerts should be less interruptive in their workflow and if possible, could be avoided altogether. They have little tolerance for processes they perceive which could hinder their clinical workflow. Alert filter is one possible approach to reducing alert fatigue. Through alert filter, we can avoid irrelevant and non-serious alerts, and tailor the alerts according to physician needs and contexts of the clinical situation. The systems should be designed to create a clear and concise alert that displays sufficient information so that the clinician understands the rationale for the interruption, as well as makes it easy for the physician user to take a more appropriate action [56].

Different specialties have different needs from CDSS. They need substantial different information and knowledge based on uniqueness and varying characteristics of clinical decisions. Meanwhile, CDSS should accommodate appropriate clinical practice variations. Locally customizable CDSS can make use of the clinical context and present the alert information to the user differently. Furthermore, alerting should be better adapted to the clinical context and make use of more sophisticated ways to present alert information. CDSS needs continuous improvement to be accurate, and up-to-date. Redesigning the system is effective in reducing unnecessary alerts while supporting clinician overrides.

In summary, CPOE and CDSS can be good tools to improve patient safety and medical quality but these tools, if poorly designed and used inappropriately, can also hamper patient safety. CPOE and CDSS can reduce certain types of errors but may also often slow clinicians while simultaneously increasing other types of errors. CPOE is not simply a technology, rather it is a design (or redesign) of clinical processes that integrates technology to optimize physician ordering of medications, laboratory tests, and other workflow processes. There are clear benefits if we are able to design them correctly. Indeed, CPOE could foster rather than reduce errors if we cannot do it right. Technology is only part of the solution, and socio-technical issues are at least as important. Taking care of these technical issues and clinical work flow challenges will eliminate most barriers to using the system. Physician attitude towards CPOE and CDSS should be carefully considered. From my own experience, physicians are not opposed to CPOE, but they are opposed to CPOE that is badly designed such as the inability for physicians to override alerts. Physicians should not be forced to change how they practice medicine to accommodate the design of these software tools; conversely, the software tools should be designed to support good physician work habits. Further research should also involve partnering CPOE developers and vendors in order to exchange thoughts on how to successfully integrate these socio-technical and contextual factors into the next generation of context-aware CPOE systems and CDSS.

8. Comment by J. Mantas

The paper presented in *Methods* regarding the survey of CPOE systems across a large number of European sites and the attitudes of the physicians to them, is an important research work that exemplifies the dynamic outcome that such international cooperation research works may provide, especially when funded out of European Commission research programs.

The authors realise the diversity of CPOE systems and medical cultures implemented in a variety of health care systems

in Europe and try to work on the common denominator issues focused mainly on the physicians attitudes disregarding the other healthcare professionals such as nurses where they may play an important regulated role in certain healthcare systems but not in all countries of Europe.

The data of such surveys are usually based on subjective information collected by questionnaires that are filled in on a volunteer basis. The percentage of returns of the questionnaires varies greatly from location to location, however, the overall percentage is reasonable compared to similar studies but there is no explanation of the differences, the reasons of rejection, and the possible influence on the final outcome. It should be stressed what the authors said that the overall sample due to the limitations is not representative of the overall physicians population in Europe, therefore the results should not be generalised. However, useful results are drawn that may be used in CPOE implementations.

It is well known from the literature that for a successful CPOE implementation there are many factors such as motivation of implementation, cost-benefit issues, value to healthcare users, vision and leadership of key stakeholders, technical considerations, sophistication of the application, strategic management, training and support, and continuous evaluation and improvement. The authors understand the limitations of the survey by not considering all the other factors and focusing only to the attitudes of the physicians towards CPOE and alerting.

On this particular issue the outcome is very important as it provides to the developers of CPOE systems information that the physicians require alert designs which distinguish between the severity levels, a result that concurs with other works by other researchers.

Financial issues should be discussed when dealing with CPOE systems. We have the cost of implementation which may vary if for example other legacy existed before CPOE system is implemented and need to be integrated or new CPOE system is designed and implemented from the beginning. In dealing with evaluation of CPOE systems the financial benefits need also to be estimated.

The authors should be commended for their modesty as they realise that the result out of this work that hospitals with a sophisticated alerting strategy with less interruptive alerts tend towards more positive attitudes require further investigation by saying that this should be further investigated by experiment in future studies, probably including even more hospitals. In this future study financial issues (costs and benefits) should be investigated as well.

9. Comment by A. Margolis

Health care organizations are classified as "professional bureaucracies" by Mintzberg [57]. As such, they traditionally have a large percentage of their knowledge and power in their front line: this means that the chief of a clinical unit has more knowledge and experience about a certain clinical domain and about the patients being cared by the unit than the top managers of the health care organization. The so-called "technostructure" or brain of the organization, which includes information systems, has therefore been usually small.

The epidemiological changes resulting in a growing burden of chronic conditions and the mediocre results in the management of patients with these conditions [58] has triggered a change of paradigm in health, with more emphasis on team-based care, patient empowerment, prevention and integration across levels of care. Moreover, after the Institute of Medicine's report "To Err is Human", there has been a greater awareness regarding the need for safer health care systems and the use of information technology for that purpose. Therefore, clinical information systems are a centerpiece to allow and support the changing paradigm in these organizations, being crucial from direct patient care to managerial decision making.

In order to improve quality, safety and efficiency, CPOE is an important part of the meaningful use of information systems in health care. As such, it was catalogued as "core measure 1" in the USA [59].

There have been attempts to view clinical systems implementation from an economic perspective [60–63]. In [60], it was stated that "all cost-benefit analyses predicted substantial savings from electronic health record (and health care information exchange and interoperability) implementation: The quantifiable benefits are projected to outweigh the investment costs. However, the predicted time needed to break even varied from three to as many as 13 years". In [61], the greatest savings from a CPOE already in place in a major academic hospital were nursing time utilization, drug guidance and adverse drug event prevention. In general, CPOE may impact costs through error prevention and resource utilization (for example, detection of duplicate orders, use of generics rather than brand drugs, less space allocated for paper records, and so on).

In our perspective, it would be a mistake to analyze the use of CPOE primarily on the basis of return on investment (ROI), because:

- Clinical information is a strategic asset, as explained before: information is crucial for the governance of the system under this new paradigm.
- Many of the costs are upfront and tangible, while many of the benefits are long term and intangible. For instance, to implement a clinical system with CPOE in an organization, there needs to be an initial investment in hardware, software, connectivity, training, change management, and so on; while there could be some initial benefits in efficiency mentioned above, most benefits take several years to happen and are not easily measured (integration of clinical information across levels of care, error prevention, clinical and cost analysis of available information, proactive chronic disease management, and so on).

In any case, a possible misalignment of economic incentives for CPOE adoption across the health care system should be addressed. For example, care should be taken to ensure that practicing physicians do not have the highest burden and the least benefits of CPOE implementation. Moreover, securing funds for the initial investment and for increased annual ongoing costs in health care organizations could be challenging for already tight budgets, unless government is willing to invest in seed funds to accelerate the process, while at the same

time requiring organizations to comply with new information system capabilities.

As stated in [64], "given the strong arguments in favor of adopting clinical information systems, perhaps it is time to put aside the ROI arguments and focus instead on ensuring that all implementations are successful." In this regard, the paper published in *Methods* [1] points in the right direction, since organizational culture, change management and usability testing during CPOE implementation are paramount to success. And CPOE in turn covers an important set of functionalities within clinical information systems. Therefore, the success (or failure) of a clinical informatics project relies to a significant degree in the success of CPOE implementation.

In conclusion, we believe the discussion should focus on *how* to implement CPOE, and how to secure funding and align incentives, rather than *if* implement CPOE or not.

10. Comment by K. Miyo

In an inter-institutional study, Jung et al. reported that physicians' attitudes toward the alerting systems of computerized physician order entry (CPOE) systems were generally positive [1]. In addition to this important result, they provided information regarding the types of alerting systems and CPOEs ordinarily used in European regions. This comment focuses on both clinical decision support (CDS) systems, which include alerting systems, and CPOE systems. A historic overview is briefly provided, and current developments, and future diffusions are discussed.

10.1 CPOEs and CDSs

CPOEs, CDSs, and the relationship between them are first introduced because the subject of the research of Jung et al. is about alerting systems in CPOEs.

The major purposes of implementation of CPOEs are improvement of hospital business processes, facilitation of communication and collaboration among professionals, and enhancement of the quality of patient care. For physicians involved in clinical care daily, the third purpose is particularly important in terms of preventing medical errors.

Some medical errors can be prevented by implementing CPOEs [65, 66]. Printed prescriptions generated by CPOEs offer higher legibility than handwritten ones. Prescription orders created using controlled vocabularies or code systems enable rigorous communication with pharmacists and nurses. Completion of an order inputting form comprising required elements then fulfills the prescription requirements. However, advanced alerting functions, such as dose or drug-drug interaction alerting, require implementation of CDSs equipped with knowledge bases.

The development of CDSs has a long history [67]. From the 1970s to the 1990s, some remarkable expert systems, such as MYCIN [68], INTERNIST-1 [69], and DXplain [70], were developed. These were independent of CPOEs because the latter were under development and their use was not widespread at that time. The user was required to input all parameters manually. Furthermore, their adoption for all patients in daily clinical practice would likely have been problematic.

On the other hand, most recent CDSs involve use of a CPOE. They extract various patient parameters from the database of the CPOE, reducing the time and labor associated with data input. In addition, this consolidation establishes a systematic medical-error-checking process. Although alerting systems used in the hospitals that participated in the research of Jung et al. vary from simple to advanced in terms of their adopted techniques, all of them are the type of the CDS that works as part of a CPOE.

10.2 Sophisticated Alerting against Alert Fatigue

Use of alerting systems in clinical practice has also created some problems. Figure 3 in the report by Jung et al. indicates these problems clearly. However, not all are serious. For example, "time consumption" seems to be the greatest problem for physicians. This is inevitable because addition of some processes to physicians' workflow is unavoidable. However, although a time cost is associated with the alerting system, physicians may not regard this as a total waste because the "waste of time" problem in the center of Figure 3 is small. This opinion is supported by the responses to Question 4 (Figure 1).

Instead, alert overload and the succeeding alert fatigue, which are second and third in Figure 3, are larger problems in terms of physicians' workload and patient safety. How to resist alert fatigue has been a major topic of study in this field [6, 7, 71–75]. One key measure is use of non-interruptive alerts [7]. This technique is partially performed in Buenos Aires, Galway, and Thun hospitals [1]. This increases the usefulness of automatic alerts, as shown by the fact that these hospitals have the three highest scores (Figure 2).

Another key measure is adoption of a sophisticated alerting system. A possible method is for CDSs to offer alert indication that varies according to clinical importance [6, 7]. For example it offers a "hard stop" window for lethal issues and shows only an exclamation mark for less important issues. This is one of the responses to Questions 6 and 11 in Figure 1. An effort to identify a set of high-severity and clinically significant drug-drug interactions for use in the electronic health record (EHR) is underway [6]. Existing patient-specific alerting techniques are mentioned in relation to Question 5 of Figure 1. Alerting systems using a combination of prescribed drugs and laboratory examination results [71, 72] and those using a combination of drugs and patient diagnosis [71, 73] have been developed and used. Moreover, development of a context model for medication alerts in CPOEs has been attempted [74]. In addition, an empirical alerting method (e.g., a dose alert or prescription recommendation based on the statistical information extracted from the huge prescription dataset stored in a CPOE) has been proposed [75].

For effective implementation of sophisticated alerting system, patient information stored in a CPOE must be machine-readable. The use of controlled vocabulary or a code system is required. Furthermore, CPOEs should adopt international standardized codes such as ICD-10 or LOINC, and applicability of various CDS resources

is desirable. The issue of language to describe clinical knowledge is also important. Patient-specific, sophisticated alerting systems require use of language that can describe the detailed decision rules and criteria, and represent complex patient statuses. One of the resources currently used for this purpose is the Arden Syntax compiler and its knowledge repository [76, 77]. When an alerting system involves laboratory tests, careful handling of the results is required. Individual test results provide information regarding only an extremely narrow time window. Thus, the continuous status of patients must be reconstructed using this limited information. Temporal reasoning methods such as temporal abstraction [78] is one possible solution to this issue.

10.3 Diffusion of Alerting Systems on CPOEs

Jung et al. showed that the general attitudes of physicians are positive. It is particularly important and novel that non-CPOE system users obtained the same results as CPOE users. The positive attitude of physicians regarding the alerting systems of CPOEs is likely an important factor in their diffusion. Figure 3 reflects physicians' mood for automatic alerting. The placed comments in Figure 3 may be used as a compass showing what functions should be developed and what issues must be improved.

The results of Jung et al. were obtained from the alerting systems in European and South American hospitals. Considering the universality of physicians' business processes, professional authority, and responsibility, I suggest that their results could be applied to systems in other areas, such as Asia, Oceania, and North America, in which CPOEs have been spreading rapidly, similar to Europe.

Finally, costs and benefits must be discussed. Alerting systems potentially reduce medical error. Reducing the risk of medical error not only increases patient safety, but decreases related costs. Some systems can provide direct financial benefits. For example, an alerting system that uses a combination of prescribed drugs and patient diagnosis not only avoids prescription error, but also prevents omission of inputting the diagnosis into the EHR [73]. Because of the decreasing number of cases in which health insurance organizations refuse to pay the treatment fee, the system cost is recovered within several months [79]. Obtaining information regarding physicians' expectations and system costs and benefits would increase the use of alerting systems.

10.4 Conclusion

Jung et al. showed that the general attitude of physicians was positive, regardless of their background or setting. As shown in other related studies, physicians consider the benefits of automatic alerts to be patient safety and prevention of medical error, and the problems to be alert overload or alert fatigue. Specific methods of overcoming these problems and related studies were introduced in this comment. However, many issues remain in this field. Further studies are expected to give the power to diffusion of useful alerting systems and, as a result, to advance patient safety.

11. Comment by C. Nøhr

The study by M. Jung et.al gives some very important insight for the design and implementation of automatic alerting in CPOE systems.

The study was not designed to identify and quantify factors that influence the CPOE attitudes of physicians, but from the numerous free text statements a number of significant benefits and problems were identified by the physicians. And in an area which, at this point in time, is not developed to a very high and sophisticated technological level it makes a lot of sense to focus on these qualitative results. The quantitative data are more difficult to analyze because of the differing influence from a) structure of health care system, b) professional specialty, c) local work culture, and d) personal experience with CPOE – differences that have not been taken into account in the analysis.

In relation to a) it is well known that in some countries pharmacists are more closely involved in the medication process than in other countries. This involvement makes the need for decision support and alerting play a different role as in countries where the physician and the nurse are responsible for the whole medication process. b) The different professional specialties will have different use of the different functionalities in CDSS e.g. in internal medicine the medication process is often closely connected to the diagnostic procedure, whereas in e.g. orthopedic surgery medication is usually simpler. c) The local work culture has a determining effect on who and how the individual physician asks for advice – how the professional network structure is organized and how the communities of practice is established. d) More experienced users will have less need for some of the trivial alerts than new users. Furthermore physicians tend to make more errors towards the end of their shift than in the beginning.

I assume that these differences also account for the author's conclusion that the CPOE systems should be "locally customizable" and "capable of taking into account the clinical context and of differently presenting the alert information to the user".

One aspect of contextualization as mentioned above is the presentation of the alert in the HCI of the CPOE. Another aspect is the content of the alert or decision support, and on what grounds are the alert fired.

During the PSIP project [80] that developed prototype CDSSs to enhance patient safety in drug prescribing in hospitals, we learned a lot about the design of alerts. In the prototypes the alerts were triggered by decision rules derived from the results of data and semantic mining of local data. The rules were validated by confronting them with the existing clinical and pharmacological knowledge available in the scientific literature. The alerts were contextualized according to the frequency and prevalence of adverse drug events in specific countries, hospitals and medical units.

The physicians testing the prototypes on full scale simulated patient cases were very comfortable with the alerts and the support they could get from the rules, especially because they were grounded in local data. The outcomes were not quantified, but we observed a trend that the senior physicians were more hesitant to trust the rules than

the younger physicians. The younger physicians were more familiar with their dealings with information generated by observational study of data as opposed to the senior physicians who called for decision support based on meta analysis or randomized controlled trials [81].

This observation can initiate a discussion on the level of evidence-based alerts in CDSS. According to evidence based medicine (EBM) [82] the most highly prized form of evidence comes from randomized controlled trials (RCT) and meta analysis of RCTs. Observational studies appear at lower levels in the evidence hierarchy but are better suited for local customization of the alerts in CDSS.

The paradigm behind RCT is a hypothetical-deductive approach where diseases and treatment are studied by testable hypothesis, but massive advances in computer power and information science are now challenging the dominance of this approach. The empirically driven inductive approach is the logic behind data and semantic mining, but also the use of Internet search engines such as Yahoo! Bing and Google, which are likewise familiar to all physicians. I will not argue that these search engines can generate scientifically sound results, but in many cases observational studies based on induction will generate a sufficiently sound result to justify an alert or a specific action.

Consequently an inductive approach can be appropriate for designing sustainable and context sensitive CDSS, or more specifically: customizing the presentation as well as the content grounding of the decision support in CPOE systems that will take into account the clinical context of differently presenting the alert information to the user – as requested by M. Jung et al. in their conclusion.

12. Comment by M. Peleg

The paper by Jung and coauthors reports on an international survey conducted to assess the attitudes of physicians towards automatic alerting in Computerized Physician Order Entry (CPOE) systems. What are the attitudes of physicians towards CPOE alerting? Do the attitudes vary between different countries, organizational and technical settings? Are the attitudes of physicians who are already using CPOE systems different than those of physicians who are not currently using CPOE systems? The results are encouraging and in agreement with previous studies that assessed attitudes towards alerting in CPOE systems for single healthcare institutions: physicians see the great benefit that alerts provide for identifying potential errors in prescribing medications. They do not think that reacting to alerts costs them too much time. Although certainly a single hospital is not representative of all hospitals in a country, it is striking to see that the pattern of answering 15 different questions that assessed different aspects of physicians' attitudes towards CPOE alerting is very similar in all 11 hospitals, regardless of the difference in country, in setting, and in experience of using CPOE.

Alerting takes account of a vast amount of detailed facts, such as contra-indications and drug interactions, which need to be considered during prescribing and calculations of dosage; these fit precisely with tasks that computers are better at than human beings. In different hospitals worldwide, CPOE alerting have capabilities such as support of dosage calculation, consideration of drug-drug interactions, duplicate therapies, drug allergies, drugs preferred by the hospital's health plan, drug-disease contra-indications, and some can provide guidance for medication-related laboratory testing. The positive attitudes are present despite the fact that physicians recognize possible alert overload as a major problem. Hence, it seems that they are willing to accept alert overload realizing the importance of patient safety. The positive attitudes are also indicative of the success of CPOE systems. Much work has been done to address barriers to successful use of CPOE systems, in particular specificity of alerts to patients data and to healthcare professional's specialty, addressing workflow issues and timing of alerts, their relevance, and seriousness (i.e., whether ignoring an alert could be fatal), as well as limiting the amount of work that needs to be done to work with the CPOE system when accepting or overriding an alert [41].

12.1 Opportunities for Biomedical and Health Informatics Research Related to CPOE Alerting

So, given these positive attitudes, is work for researchers in this field done? Although I am not an expert on CPOE systems, I see opportunity for research in several directions.

The first direction includes evaluation studies that evaluate together effectiveness of CPOE reminders on reduction of prescribing errors with physician attitudes. Such studies could try to compare the impact of cultural differences between countries, organizational setting (e.g., hospital or medical group), technical setting, and physicians' personal experience with CPOE systems, as done in this study. Furthermore, the studies can address specific capabilities of the CPOE alerting system, such as drug-diseases contra-indications, in conjunction with differences in organizational, technical, or cultural settings. CPOE alerting systems have added benefits when the patient's problem list is complete, which may be true in the setting of primary-care clinics but not at the setting of a general hospital. In the survey described in the paper, only one hospital supported drug-disease contra-indication checking. The fact that this functionality was not available in the other seven hospitals with CPOE systems assessed, might be because the hospital managers realized that contra-indication alerts will not be generated when medical records do not contain enough information about patients' medical problems and allergies, or when this information is not structured but is documented in free text, which is hard to process. Moreover, if physicians receive some alerts for contraindications they may incorrectly assume that when the system does not generate a contra-indication alert this means that their other prescriptions are free of contra-indication errors. Hence, their interpretation of the system's lack of alert (error of omission) may cause a false-negative error, prescribing a drug (error of commission) that is contra-indicated while not realizing the problem of incomplete medical records. Problems may also occur with medical records that are not kept up-to-date. Such records may indicate that the

patient is taking medications that he stopped taking. In this case, the system may generate false-positive alerts. Additionally, if the system contains outdated record of the patient's weight, errors (of commission) in drug dosage recommendations may result. Errors of CPOE alerts (false negatives or false positives) could result in physicians not trusting the system and ignoring its recommendations.

The second direction of research lies in learning from non-clinical domains in which alerting is successfully used. One such domain is IT security, for example, the generation of alerts of potential security breach by Internet browsers or anti-virus software. Browsers contain default security settings that can be set up by the user's organization to different levels of security. Setup options include optional warnings when a site tries to install add-ons. Reported attack sites and web forgeries could be blocked and specific web sites could be added to a list of sites allowed to install add-ons. A user can override the organizational security setting and change the level of security, for example, when he receives an alert about a particular site trying to install an add-on, he can allow this site single access or access for a limited duration of time. If too many alerts are generated for a site that he trusts, he may add this site to the list of allowed sites, and decide to turn off the alerting system. Of course, such risky behavior prevents the system from functioning correctly and is especially problematic when patient safety is concerned.

An interesting line of research is in the study of physician user behavior. Such research in the non-healthcare setting, tries to understand users' security-related behavior and to predict how system features will affect user actions. This line of research has theoretic contributions from fields such as psychology, human-factors engineering, economics and decision making. Based on a conceptual model that draws from all of these disciplines, Ben-Asher and coauthors [83] developed a controlled research environment to study users' tendency to take precautionary actions as a function of the tradeoff between a system's usability and the level of security the system provides. The environment consists of a modified version of a "Tetris" game and includes an alert system that warns about possible virus attacks, which, if not prevented, can cause losses of monetary earnings. Users could alter the threshold settings of the security system. The system allows us to manipulate the usability cost of using a security feature, the severity of the consequences of an attack, the likelihood that a threat will occur, and the statistical properties of the security system. Preliminary results demonstrated that when attacks were more likely, participants selected more cautious thresholds, and tended to respond more to security system alerts. It is interesting to apply such research methods to the medical domain and to study how the likelihood of certain types of medication errors affects user attitudes towards CPOE alerting.

From the paper by Jung et al., we learn that different healthcare organizations use different options for controlling the tradeoff between usability and safety in CPOE alerting. These include the following properties of alerts: automatic, optional, and interruptive. These options allow the organization to impose safe behavior by physicians during order entry. However, organizations are aware of incompleteness of the alerting rules and of the fact that physicians can get annoyed from systems that produce too many false positive alerts. Therefore, as is done in IT security where users can allow exceptions for some sites to install add-ons, some CPOE systems allow entering exceptions or mitigating circumstances that make it easy to influence the number and accuracy of future alerts [41]. To prevent annoying repetition, users that perform well can be allowed to turn off alerting for certain periods of time. At the same time, alternative actions are presented and reasons for non-compliance are requested. Research could address the design of pre-enumerated justification options or automatic processing of natural language justification. It would also be interesting to use probabilistic approaches to infer from users' requests to override system alerts, which alerts are problematic and should be changed.

It is interesting to note that the three hospitals with the highest scores used more sophisticated alerting strategies which only interrupt users for the more important and severe warnings while the three hospitals with the lowest scores only offer automatic and interruptive alerts. These findings support the need for research on sophisticated alerting strategies that make alerts more sophisticated and specific, in order to decrease the number of false-positive alerts and increase their relevance while maintaining patient safety. An example for this kind of research is shown in the paper by Riedmann and other colleagues from the University for Health Sciences, Medical Informatics and Technology, Hall in Tirol, Austria, who also led the study reported in this paper (Jung, Hackl, Ammenwerth) [74]. The authors have used a combination of literature searches and expert interviews to identify and validate the possible context factors of an alert. Their context model contains twenty factors, which they grouped into three categories: characteristics of the patient or case (e.g., clinical status of the patient); characteristics of the organizational unit or user (e.g., professional experience of the user); and alert characteristics (e.g., severity of the effect).

Another line of research would be to use machine-learning methods to learn which alerts should be modified and in which ways. Such learning could use information regarding compliance or non-compliance to alerts, alternative actions used, and justifications for deviation provided. In addition, learning should also use contextual information about the alert and patient outcomes to learn about effective deviations from alert recommendations that for particular alert context led to better outcomes. This approach is similar to that used by Soffer, Ghattas, and Peleg [84] for learning how to improve business processes and healthcare processes based on context and outcome.

Using knowledge-based decision-support with CPOE system to generate context-specific recommendations while employing sophisticated strategies could also benefit from the rich literature on computer-interpretable clinical guidelines [85–87]. Works in this field address challenges such as sharing of executable clinical knowledge by different implementation sites, ontological approaches for semantic integration of formalized medical knowledge with electronic health records [88]

and hospital information systems, models for decision-making, including argumentation-based logic [89] and probabilistic decision-theoretic models, and temporal abstraction and reasoning [90].

13. Comment by F. G. B. de Quirós

The healthcare system manages information gathered from the patient and the evidence in order to help providers and patients to make informed decisions that will be transformed into actions (preventive, diagnostic and therapeutic). The primary objective of implementing Computerized Provider Order Entry (CPOE) systems with clinical decision support (CDS) functionalities is to improve a fundamental component of this workflow by helping clinicians' (and sometime patients) decision making based on scientifically valid evidence, adjusted to individual patient context and without unintended consequences [91]. To achieve better clinical outcomes and cost improvement there is also a need of patient engagement in this process. There is increasing recognition that the availability of information alone is insufficient and a growing body of research distinguishes between the 'mere transmission of information to patients' and the 'development of skills and confidence to make choices' [92].

For a significant impact of CDSS in clinical outcomes, a number of steps should occur: 1) Clear definition of the patient's information and context in a controlled environment understandable by a computer, 2) Definition of the decision process being undertaken by the provider (preventive care, diagnostic or therapeutic) and make it understandable for the computer. 3) Scientifically valid knowledge about the process under analysis. 4) Presentation of information in a simple, concise, accurate, contextualize and timely way to the provider. 5) When the context is complex and there is no specific evidence available for this complexity, the information should be interpreted and prioritized in the same way as the provider, so that he or she will agree and will not override the recommendation. 6) Recommendation should be transmitted from the provider to the patient so that he/she can understand what to do and the reason to do it. 7) The patient needs to have a positive attitude and willingness to stay healthy (and if necessary to pay the copayment) at the time the information is provided and accepts the recommendation. 8) The recommendation has to match with the patient's culture. 9) For chronic conditions, the patient needs to maintain the recommendation over long periods of time, and 10) Once the decisions were made and implemented, „the effect" of the intervention has to have similar and not lower results than the trial in which was based (by chance or some other "cause").

We could group these 10 steps in three groups; steps 1 to 5 are related to information system characteristics and how professional interact and agree with them. This study done by Jung at col. primarily focuses on some aspects of this first group of variables [1]. Steps 6 to 9 are mainly related to patients and healthcare professionals' variables and especially the relationship and empathy between them. Finally step 10 depends on decision and scientific variables, in particular, the quality of the evidence and its interpretation, the biology of the disease and chance.

So far there has been published a large number of experiences showing improvement in health care process indicators with the use of CDSS, like providers compliance with preventive practices in different clinical settings and by different users [93]. They also can positively impact healthcare providers' performance with drug ordering and preventive care reminder systems [94]. However, all the steps mentioned before are needed for the translation from de correct decision to the clinical outcome.

Regarding group one variables, others studies measured physicians' attitude towards CPOE systems [95] , but in their paper, Jung et col. made it with a different approach. They used a mix of quantitative and qualitative methods and included hospitals from different countries and with different CPOE systems, including three without CPOE in use. The results show positive attitude in general and specially with the reminders related to severe errors in drug prescriptions. The authors also found that physicians would prefer less interruptive alerts to avoid possible overloads of not important alerts that could lead to override recommendations and alert fatigue.

As it was shown in other studies [96], Jung and colleagues showed that hospitals with more sophisticated systems had higher attitudes scores in general to the alerts.

One of the strengths of the study is that the assessment was done in healthcare institution from different countries, mostly Europe, and for the first time a Hospital from South America was included. Attitude of physicians towards CPOE systems was comparable and independent of the country, and with no differences between continents.

As authors stated, the study has some limitations, in particular the use of a convenience sample of hospitals and, furthermore, potential recruitment biases due the convenience sampling of doctors.

Another level of complexity not addressed in this study and not thoroughly studied in the literature is that CDSS do not usually take into account the full context of the setting where decisions are made [74]. There is a need for better tools to help systems to make this context more accurate and of higher quality. As Jung et al. have shown, the patient variables adjustment is critical and will impact in the level of acceptance or recommendation overridden by providers. However, few CDSS projects consider the context of the provider, for example: profession (nurse or physician), specialty, setting where he or she works, years from graduation, the continuing education process of the provider, history of the behavior related to received previous recommendation and whether this recommendation is about his own field of knowledge, among others. Probably as patient's context is important to optimize the usefulness of the CDSS, this kind of provider context variables will modify the usefulness of the CDSS as well.

The work of Jung et al. is a valuable contribution to understand the variables that determine the level of CDSS acceptance from clinicians. To move from process to clinical outcomes improvement, CDSS still needs to evolve conceptually in order to integrate all the components of the health-

care workflow process, the role that provider and patient's have in decision making and its consequences for clinical outcomes.

14. Comment by K. Takabayashi

As Jung et al. concluded [1], the majority of physicians appreciate the benefits of an automatic alerting system in a computerized physician order entry (CPOE) system. Automatic alerts contribute to the safety of the prescription process by reducing prescribing errors, thereby improving patient safety. Most physicians report that they do not find the alerting systems too time-consuming, yet there have been some complaints that using an alerting system takes too much time or effort.

The attitudes of physicians toward CPOE systems and electric medical records (EMR) systems have not been shown to differ significantly, not only in the Western countries described in this paper [1], but also worldwide. The prescription formats in CPOE systems are not the same around the world, but the algorithm or process to complete prescriptions is nearly the same the world over, and physicians' needs are the same globally.

In this paper, there is no description of CPOE systems in Asian countries although such systems are common, especially in major hospitals. I would therefore like to introduce Japanese CPOE systems and provide some comments. The use of CPOE systems in Japan began around 1990. By 2009, CPOE and EMR systems had been installed in 24.2% and 12.5% of the total number of Japan's hospitals, respectively. In the major hospitals (> 400 beds), these figures were 71.0% and 41.6%. Thus tens of thousands of physicians in Japan have been using CPOE daily for more than 10 years. The prescription-process error rate decreased after the implementation of CPOE systems to an average rate of between 1% and 2%.

The currently used automatic alerting systems concern mainly the drug dosage, administration route, overlapped with other prescriptions, and contraindications for drug co-administration. At the present time there is no doubt that automatic alerting is essential to reduce human errors in the process. Every physician seems to agree on the safety standards of alert systems. Practically, however, it is important to not take too much time to validate prescriptions. In the early days of CPOE, the addition of various alerting functions to the CPOE increased the time required to validate prescriptions, which was a troublesome overload for physicians. After a period of trial and error, the CPOE systems used today in Japan seem to be better balanced with the hardware. I believe the problem of time consumption depends on the degree of evolution that a particular CPOE system has experienced.

It is natural to expect the continued implementation of new functions such as automatic alerts in a CPOE system, since the order entry system is not just a word processor and the purpose of a CPOE system is to enable and improve the safe and timely ordering. It appears that physicians who have not yet used a CPOE system have high expectations for CPOE, and this may account for their positive attitude toward the inclusion of an automatic alerting function.

One key point is the types of item to be checked in alerts. No physician is a specialist when it comes to all of the thousands of drugs used today, and physicians are generally not acquainted with medicines outside their specialty. The verification of the maximum dose of all drugs is essential and is acceptable to all physicians. It is also fundamental to check the potential interaction of two or more drugs – a phenomenon that continues to increase in frequency and complexity – as well as the limits of the daily and total dosages. Alerts regarding contraindications specific for patients (such as allergies) are also crucial. Some CPOE systems have expanded the alert process by comparing the current prescription with former prescriptions (e.g., the patient's last warfarin dosage) or with laboratory data (e.g., digitalis and renal function data), or the drug concentration. In addition to automatic alerts, assisting systems that deal with drug co-administration have also been implemented. In countries where drug usage is indicated only for specific medical conditions and is strictly controlled, it is vital to verify the relationship between medical conditions and medication, but this is often a taxing issue. For example, Tokyo University Hospital applied such an alerting system with 188 drugs, and an alert arose in 3.9% in the related prescriptions, 80% of which were corrected accordingly [75].

Adequate instructiveness is essential to avoid disrupting physicians who must use a CPOE system. For convenience, as an alternative to automatic alerts, some CPOE systems allow a physician to choose a set of prescriptions or a regime for chemotherapy that was prepared earlier, though in some cases more patient data (e.g., body weight) is necessary for calculating individual dosages. Checking systems during dispensation are also useful, and this does not lengthen the prescription response time when patients receive medication in the hospital. Kinoshita et al. demonstrated that of 377,525 prescriptions, 999 (0.25%) were checked and 524 of these cases (0.12%) were corrected [97].

Alert systems are obviously aimed to reduce errors during the prescription process, but close attention must be paid to the errors produced by the system itself. Advanced alert systems have improved the quality of prescription checks, but if the data are incorrect, a critical error might be produced by the system. Ironically, the more that medical staff rely on CPOE and EMR systems, the more errors may increase because of the system. For example, a drug allergy alert is made possible by connecting the alerting system to the basic patient data recorded by medical staff. However, when a new drug is administered and its information is not yet connected to the alert system as a contraindication because of patient allergy, an accident may occur because no alert is issued by the system. Additional problems concern drugs such as phenobarbiturates, which are used not only alone but also in medical compounds that might not be connected to the alert system, and drugs such as penicillin which may trigger an allergy unless all relevant drugs are listed.

Since it is not possible for an individual physician to name all potential drug combinations and interactions that may affect each patient, a complete database of related drugs is desirable for physicians to check.

When we think of these problems in terms of drug information, we come to the conclusion that a standard national (or greater) database of drug information that can interface with CPOE systems in all hospitals is needed. The maintenance of a drug information database including contraindications for co-administration is too large a job for one medical facility or network, and thus a standard database maintained and delivered periodically by a government entity would be desirable.

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Addresses of the Authors

David W. Bates
Brigham and Women's Hospital
Division of General Internal Medicine and Primary Care
Center for Patient Safety Research
1620 Tremont Street, 3rd floor
Boston, Massachusetts 02120
USA
E-mail: DBATES@PARTNERS.ORG

Melissa T. Baysari
Department of Clinical Pharmacology and Toxicology
Therapeutics Centre
Level 2 Xavier Building
St. Vincent´s Hospital
Darlinghurst NSW 2010
Australia
E-mail: m.baysari@unsw.edu.au

Martin Dugas
University of Münster
Institute of Medical Informatics
Albert-Schweitzer-Campus 1
Gebäude A11
48149 Münster
Germany
E-mail: dugas@uni-muenster.de

Walter E. Haefeli, MD
University of Heidelberg
Department of Clinical Pharmacology and Pharmacoepidemiology
Im Neuenheimer Feld 410
69120 Heidelberg
Germany
E-mail:
walter.emil.haefeli@med.uni-heidelberg.de

Andre W. Kushniruk
University of Victoria
School of Health Information Science
Human & Social Development Building A202
3800 Finnerty Road (Ring Road)
Victoria, BC V8P 5C2
Canada
E-mail: andrek@uvic.ca

Christoph U. Lehmann
Vanderbilt University
Department of Biomedical Informatics
2200 Children's Way
Vanderbilt, TN 37232
USA
E-mail: chris.lehmann@vanderbilt.edu

Jialin Liu
Sichuan University
West China Hospital/West China Medical School
Department of Medical Informatics
Chengdu
China
E-mail: DLJL8@163.com

John Mantas
University of Athens
Health Informatics Laboratory
Papadiamantopoulou 123 Goudi
Athens 11527
Greece
E-mail: jmantas@nurs.uoa.gr

Alvaro Margolis
Universidad de la República
Facultad de Ingeniería
Instituto de Computación
Julio Herrera y Reissig 565
CP 11300, Montevideo
Uruguay
E-mail: margolis@fing.edu.uy

Kengo Miyo
The University of Tokyo Hospital
Department of Planning, Information and Management
7-3-1, Hongo, Bunkyo-ku
Tokyo 113-8655
Japan
E-mail: miyo-sup@h.u-tokyo.ac.jp

Fernán Gónzalez Bernaldo de Quirós
Hospital Italiano de Buenos Aires
Department of Health Informatics
Peron 4190
(1199) Ciudad Autonoma de Buenos Aires
Argentina
E-mail:
fernan.quiros@hospitalitaliano.org.ar

Katsuhiko Takabayashi
Chiba University Hospital
Dept. of Medical Information and Management
Inohana 1-8-1
Chiba, 260-8677
Japan
E-mail: takaba@ho.chiba-u.ac.jp

Christian Nøhr
Aalborg University
Department of Development and Planning
Danish Centre for Health Informatics
Vestre Havnepromenade 5
9000 Aalborg
Denmark
E-mail: cn@plan.aau.dk

Sarah P. Slight
Brigham and Women's Hospital
Division of General Internal Medicine and Primary Care
Center for Patient Safety Research
1620 Tremont Street, 3rd floor
Boston, Massachusetts 02120
USA
E-mail: SSLIGHT@PARTNERS.ORG

Johanna I. Westbrook
University of New South Wales
Faculty of Medicine
Australian Institute of Health Innovation
Level 1 AGSM Building (G27)
Gate 11, Botany St
Wales, Sydney NSW 2052
Australia
E-mail: j.westbrook@unsw.edu.au

Mor Peleg
University of Haifa
Department of Information Systems
Rabin Building, room 7047
Haifa, 31905
Israel
E-mail: peleg.mor@gmail.com

Jack Starmer
Vanderbilt University
432 Eskind Biomedical Library
2209 Garland Avenue
Nashville, TN 37232
USA
E-mail: jack.starmer@vanderbilt.edu