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ESTONIAN FAMILY PHYSICIANS USAGE AND SATISFACTION WITH DRUG-DRUG INTERACTION ALERT SYSTEM

Master's thesis

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RAVIMITE KOOSMÕJU HOIATUSSÜSTEEMI KASUTUSE JA RAHULOLU ANALÜÜS EESTI PEREARSTIDE SEAS

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Author’s declaration of originality

I hereby certify that I am the sole author of this thesis. All the used materials, references to the literature and the work of others have been referred to. This thesis has not been presented for examination anywhere else.

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Abstract

The aim of the thesis was to analyse the effect of computerized Drug – Drug Interaction alert system to Estonian family physicians prescribing habits of clinically significant drug-drug interactions and investigate their satisfaction with the solution.

Two researches were conducted. For quantitative results regarding amount of interactions, data from e-prescription centre was obtained and for qualitative data regarding satisfaction a questionnaire for family physicians was developed. The results were later presented to two experts in the field to ask their input for possible reasons and insights.

Results from prescription centre´s data show that the number of clinically significant interacting drugs prescribed by family physicians is staying at a relatively same level throughout the study period. The most often issued interacting drugs during the study period have also stayed relatively the same with a few exceptions. On average, family physicians issue 7-8 prescriptions with clinically significant interactions per patient with older patients (over 50 years old) being more at risk of getting prescriptions with drug interactions than younger ones.

Results from the questionnaire show that the respondents are overall satisfied with the system but would like some improvements made to the system regarding correct dosages, possibility to cancel interaction alerts for patients who are no longer taking some medications, change the level of alerts for topical drugs and receive alternative drug recommendations from the system to the interacting drugs.

This thesis is written in English and is 55 pages long, including 3 chapters, 7 figures and 13 tables.

Annotatsioon

Ravimite koostoimete hoiatussüsteemi kasutuse ja rahulolu analüüs Eesti perearstide seas

Käesoleva töö eesmärgiks oli analüüsida ravimite koostimete hoiatussüsteemi kasutust ja rahulolu Eesti perearstide seas.

Töös viidi läbi kaks uurimust. Kvantitatiiseks analüüsiks hoiatuste ja retseptide arvu kohta saadi andmed retseptikeskuselt ja kvalitatiivse analüüsi jaoks koostati veebipõhine küsimustik, mis saadeti Eesti Perearstide Seltsi e-maili listi kaudu perearstidele. Töö tulemused esitati tõlgendamise õigususe suurendamiseks ja võimalike põhjuste väljaselgitamiseks kahele eriala eksperdile.

Retseptikeskuselt saadud andmed näitavad, et kliiniliselt oluliste koostoimetega retseptide arv uurimisperioodil ei ole oluliselt muutunud. Kõige tihedamalt välja kirjutatud koostoimetega ravimite paarid top kümnes on jäänud mõningate eranditega samuti küllatki samaks. Perearstid kirjutavad keskmiselt patsiendi kohta välja 7-8 ravimit, mis omavat kliiniliselt olulist koosmõju mõne teise patsiendi ravimiga. Vanematele kui 50-aastastele patsienditele kirjutatakse koostoimetega ravimeid välja tihedamini kui noorematele.

Küsimustiku vastustest selgub, et vastanute rahulolu ravimite koostoimete kuvamise süsteemiga on küllaltki kõrge, kuid soovitakse siiski mõningaid täiendusi. Tihedamini mainitud muudatustest võib välja tuua doseerimissoovituste lisamist, patsiendi poolt enam mitte tarvitatavate ravimite hoiatuste eemaldamise võimalust, välispidiselt kasutatavate ravimite erineva mõju arvestamist hoiatuste tasemete kuvamisel ja alternatiivsete ravimite soovituste kuvamist süsteemi poolt.

Lõputöö on kirjutatud inglise keeles ning sisaldab teksti 55 leheküljel, 3 peatükki, 7 joonist ja 13 tabelit.

List of abbreviations and terms

ADE	Adverse drug event
ADR	Adverse drug reaction
CDSS	Clinical decision support system
DDI	Drug - drug interaction
NSAID	Non - steroidal anti-inflammatory drugs
UCD	User - centred design
GP	General Practitioner

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1 Introduction

Drug-drug interactions (DDIs) are a special category of adverse drug reactions (ADRs) where the effects of one drug alter the effects of the other. Although it is expected that drugs have a synergistic action between them, it may result in toxicity or adverse events instead. This may range from diminished therapeutic effect to increased morbidity and mortality of patients (Roblek et al., 2015).

The number of new drugs launched to the market and new indications approved for already marketed drugs create a situation for health care professionals where the recognition of the occurrence of DDIs is becoming more and more difficult (Roblek et al., 2015).

There are many discrepancies in studies regarding the amount of potential DDIs in medical prescriptions. According to studies the rate of potential DDIs range from 5,4–63 % out of all prescriptions issued and most of them are not considering whether they lead to actual adverse clinical consequences. All these differences can be accounted mostly to the differences in methods for classifying drug interactions, different study periods and target populations (Mannheimer et al., 2008).

Based on community practises the Morera et alles suggest that the prevalence rate in potential drug interactions is 4-6%. This rate increases depending on the number of drugs prescribed, number of doctors prescribing per patient, the co-existent presence of several pathologies and patient age. The amount of clinically significant adverse drug effects is estimated to be 10-15% of potential interactions which sometimes are of sufficient severity to account for 3-7% of medical hospital admissions (Morera et al., 2004).

Out of all factors patient age seems to be a very important indicator where to turn the focus when studying DDI-s. Polypharmacy is especially common and often adopted as a strategy to alleviate symptoms, reduce disease-related problems and improve quality of life of older adults (Ghibelli et al., 2013). Prescribing drugs with adverse drug reactions

are highly prevalent in older people resulting in some form of health resource utilisation or even acute hospitalization (Ghibelli et al., 2013).

It is difficult to estimate the cost related to adverse drug effects but different studies have found that all drug-related morbidity and mortality caused an economic burden to an estimate of 177,4 billion dollars per year in the United States and 434 million euros per year in Germany (Moura et al., 2012). More recent data has estimated the annual cost in US to be 528,4 billion dollars, equivalent to 16% of total US health care expenditures in 2016 (Watanabe et al 2018). The estimations are made on the basis that ADEs significantly increase the cost of treatment, prolong the length of hospital stay and elevate the risk of death (Moura et al., 2012). In the case of Germany, it has been calculated that out of all the cases regarding adverse drug reactions 20,1 % would have been preventable saving a potential of 87 million euros per year (Rottenkolber et al., 2011).

In order to reduce human errors in drug prescriptions multiple clinical decision support tools - databases and screening programs have been implemented (Roblek et al., 2015). A nationwide clinical decision support system (CDSS) for all Estonian physicians has been available since June 2016. The usage of this system and whether physicians´ prescribing habits have changed since the introduction of the CDSS are investigated in this master's thesis. Out of all possible physicians and specialities this study is focusing on family physicians since according to data from Estonian prescription centre most prescriptions (69,7% of all prescriptions issued) in 2017 were issued by family physicians. The number of registered and therefore affected family physicians in Estonia in 2018 was 763 (Terviseameti registrid, 2018). This research is made also in the interest of the Estonian Health Insurance Fund who were contacted and interviewed regarding the topic of this paper.

1.1 Literature review.

There are multiple DDI alert systems available worldwide that are helping physicians make better informed drug-drug interaction related decisions. Based on literature review we highlight some of the main outcomes and issues that these systems may have. This section also includes ideas from previous studies regarding what have been some of the key factors in improving the systems.

1.1.1 Main outcomes and drawbacks

By conducting a literature review, Eslami et alles found that the main outcomes of DDI systems can be categorized into six main groups: adherence to guidelines; medication safety; cost and (organizational) efficiency; alerts and appropriateness of alerts; time; and satisfaction, usage and usability (Eslami et al., 2008). This could be one way to evaluate the usability of a DDI alert system.

A review done by Roblek et alles finds it more important to focus on the prevalence of potential DDIs. In their research they evaluated the usability and appropriateness of commercially available electronic databases which assess the prevalence of potential DDIs. They found that the most commonly used software in the included studies (Micromedex® Drug-Reax) was the most reliable due to highest sensitivity. It provided information about clinical consequences of DDIs, classified underlying mechanism and onset of the adverse outcomes (either rapid, or delayed) as well as severity (such as minor, moderate, or major), and provided the level of evidence which supports this information (Roblek et al., 2015).

Roblek et alles also found that only a small number of studies compared number and relevance of DDIs displayed by the electronic database with clinicians´ assessment of the situation. Based on the studies, there seemed to be a large discrepancy in what is clinically relevant versus the amount of all displayed alerts. The overlap was in some cases as low as 11 %. Their study concluded that the deficiency of clinical relevance of detected DDIs should be addressed in the upcoming research as it would provide more relevant information to the prescribers' in clinical practice (Roblek et al., 2015).

Moura et alles point out in their article that one of the key issues is the fact that physicians override 89,4 % of drug interaction alerts. Thus, creating a system that only triggers clinically important drug interaction alerts or that differentiates them by level of severity has been recognized as an effective method to reduce alert fatigue (Moura et al., 2012).

The basic criteria to identify whether a drug interaction is clinically important are described by Phansalkar et alles and are displayed in Table 1.

Table 1. Criteria for identifying clinically important drug-drug interactions for clinical decision support in electronic health records.

Criteria	Description of the criteria and key sub-criteria that emerged from the literature review and expert panel discussion
1. Severity of interaction	■ Clinical Importance: Hansten et alles in their ORCA classification identify clinical importance as a function of both the inherent danger of the drug combination and the extent to which the presence of risk factors predisposes the patient to the interaction. Also, consideration of potential severity of the adverse outcome (Hansten, et al, 2004)
	■ Likelihood of Mortality
	■ Likelihood of Morbidity
	■ Likelihood of Intervention: The probability of the suggested intervention being able to prevent harm caused by the interaction.
2. Probability of interaction	■ Likelihood of the Adverse Reaction
	■ Timing of Administration
	■ Consideration of the pharmacokinetic properties of the interaction
	■ Dose and Duration of Therapy
	■ Route of Administration
	■ Sequence of Administration
	■ Monitoring planned for the patient
	■ Therapeutic window of the object drug
	■ Combination of drugs commonly used for therapeutic reasons
3. Clinical implications	■ Management burden: defined as the course of action a clinician may have to take for each potential drug interaction
	■ Monitoring planned for the interaction
	■ Awareness of the intervention: Likelihood that providers may be aware of the ability to intervene in order to prevent harm caused by an interaction.

Criteria	Description of the criteria and key sub-criteria that emerged from the literature review and expert panel discussion
4. Patient characteristics	■ Considering alcohol, diet, smoking and drug use which might alter the characteristics of the drug in consideration resulting in possible DDIs.
	■ Importance of age
	■ Importance of gender
	■ Concurrent diseases
	■ Other active medications on the patient's profile
5. Evidence supporting interaction	■ Quantity of evidence: Adequacy of documentation in the literature
	■ Quality of evidence: Association of the evidence with the study design and source of evidence. For example, randomized trials can be rated as providing high quality evidence and observational studies or case reports as low-quality evidence.
	■ Biological plausibility: Causal association as supported by medical evidence

(Phansalkar et al., 2013)

The number of alerts that are overridden in family medicine seems to be a widespread issue and there are many researches done investigating this. For example, Magnus et alles conducted a study among general practitioners in UK to assess GPs views on the relevance of information provided by their drug interaction alerts systems and to determine the proportion of GPs that admit to frequently overriding the alerts without properly checking them. They also explored factors that might be associated with a tendency to override alerts (Magnus et al., 2002).

They found out that 22% of the respondents admitted to frequently or very frequently overriding drug interaction alerts without properly checking them. The main reason for this was the perception that the alerts were irrelevant. It was also highlighted that all alerts were too easy to override and it should not be so for most significant interactions. Out of all respondents, 90% agreed that it should be more difficult to override potentially lethal

drug combinations alerts. The study also found that the computer system used by GPs may play a role in whether they override alerts (Magnus et al., 2002).

The high level of overrides is also supported by research conducted in a medical centre in Boston by Weingart et alles who found that primary care physicians overrode 91,2% of drug allergy alerts and 89,4% of high-severity drug interaction alerts. They found that the alerts were less likely to be overridden if the prescriber was a house officer (a doctor in the first two years after qualification) and if the patient had many drug allergies. The overrides were also more likely if it was a renewal prescription compared to a new prescription. Physician reviewers also similarly to Magnus et alles´ research judged 36,5 % of the alerts to be inappropriate. The actual amount of adverse drug effects was very low and non-significant which led the authors to conclude that the threshold of the alerting was set too low and the alerts for renewals of medication combinations that the patients currently tolerated should be supressed (Weingart et al., 2003).

In order to examine the overrides more thoroughly Slight et alles conducted a cross-sectional, observational study of DDI alerts generated over a three-year period between January 1st, 2009, and December 31st, 2011 in primary care practices affiliated with two Harvard teaching hospitals. They found that overall 68,2% of the DDI alert overrides were considered appropriate. Among inappropriate overrides, the therapeutic combinations put patients at increased risk of several specific conditions including: serotonin syndrome (21,5%, n=34), cardiotoxicity (16,5%, n=26), or sharp falls in blood pressure or significant hypotension (28,5%, n=45). In addition, they found that out of the 121 appropriate alert overrides where the provider indicated they would "monitor as recommended" only 35,5% (n=43) actually did. Also, providers sometimes reported that patients had already taken interacting medications together (15,7%, n=78), despite no evidence to confirm this. All in all, Slight et alles found that even when relatively few false positive alerts are displayed, providers continue to override important and useful alerts that are likely to cause serious patient injuries (Slight et al., 2013).

The number of overrides and their reasons have also been studied in Taipei by Yeh et alles. They found in their research that most (91,5%) of the alerts were overridden and that out of all specialities, physicians of family medicine and gynecology-obstetrics were more willing to accept the alerts than other physicians. They conclude that although the override rate is high, the reasons why physicians may override DDI alerts were well

analysed and most DDI were recognized by physicians and the trend for total overrides was in decline (Yeh et al., 2013).

In addition to alert fatigue from excessive alerts due to low clinical significance Luna et alles found in their research multiple other drawbacks that these systems have highlighting more problem areas including rudimentary interfaces that lack intuitive design and workflow integration, low monitoring levels that hinder continual improvement processes and lack of standards even for the same vendor (Luna et al., 2017)

1.1.2 Improvement factors

From improvement ideas to the systems pharmacists' interventions have shown good results. A study conducted by Moura et alles showed that the implementation of drug–drug interaction screening software (IM-Pharma) integrated with active pharmacist intervention decreases the co-dispensing of interacting drugs. A decrease of approximately 50 % was observed in the average number of DDIs per patient and in the DDI rate after IM-Pharma implementation. A remarkable risk reduction of 83 % was noted for high-severity drug–drug interactions in the intervention period (Moura et al., 2012).

Pharmacists´ help has also been used to help identify the significance of alerts for specific patients. Heringa et alles studied with the help of Netherlands pharmacists' how to improve DDI systems focusing on the number of alerts displayed. They investigated which events require (re)assessment of a drug interaction and whether using these events as triggers in clinical decision support systems (CDSSs) would affect the alert rate. A panel of community pharmacists analysed top 10 of the most frequently generated drug interactions. After reaching a consensus which events should trigger an alert a simulation was run to see how many alerts less were displayed. The simulation showed a reduction of the alert rate of 93,0% for the ten selected drug interactions corresponding with a 28.3% decrease of the overall drug interaction alert rate. Their study highlighted that a consensus-based better specification of the events that trigger drug interaction would reduce the alerts significantly (Heringa et al., 2018).

From the perspective of improving user interface for the DDI system, Luna et alles conducted a research to see whether a user-centred design improves the usability of drug-drug interaction alerts. Their research used the Hospital Italiano de Buenos Aires in

Argentina´s electronic health record system with drug-drug interaction alerts for their experiment. Despite enhancing the drug-drug interaction knowledge database, the alert override rate of this system was very high. The researchers redesigned the alert system using user-centred design (UCD) and participatory design techniques to enhance the drug-drug interaction alert interface. They used a crossover method with realistic, clinical vignettes to compare usability of the standard and new software versions in terms of efficiency, effectiveness, and user satisfaction. Luna et alles´ study showed that, compared to the traditional alert system, the UCD alert system was more efficient (alerts faster resolution), more effective (tasks completed with fewer errors), and more satisfying. These results indicate that UCD techniques that follow ISO 9241-210 can generate more usable alerts than traditional design (Luna et alles 2017).

According to Herniga et alles when concentrating on primary care some special improvement strategies (compared to hospital settings) need to be considered. For example, most of prescriptions in primary care are related to chronic medications. The systems often trigger the same alerts regardless of whether it is a repeat or first-time prescription but are relevant to only at the start of the therapy. This contributes to alert fatigue. Therefore, the need for alert for first time and repeat prescription should be different. In addition, alerts should be triggered only when re-assessment of the drug interaction is actually needed (e.g. change of daily dose) (Heringa et al., 2018).

Another difference from hospital settings according to Heringa et alles is that patients are not closely monitored after administration of drugs. Since the patients are responsible for their drug administration’s themselves they need to be instructed on correct use and monitoring. After instructions patients need to be followed up whether they have understood the instructions correctly. This option should be supported by the physicians CDSS alert system (Heringa et al., 2018).

1.2 Estonian DDI software overview

A nationwide drug-drug interaction software to check for ADR-s has been available since June 2016 for all Estonian physicians. The system uses SFINX-PHARAO database to check for interactions and displays notifications regarding the interactions (Ilves, 2016). The database has been created in collaboration with Clinical pharmacologists from Karolinska Institute in Sweden and Turu University central hospital in Finland. PHARAO

database has been in use in both countries for over 10 years. The web-based application contains profiles for 1300 drugs with 9 clinically significant adverse drug effects: anticholinergic effect, constipation, risk of bleeding, orthostatism, sedation, risk of seizures, serotonergic effect, QT-prolongation, renal toxicity. The database is updated 4 times a year. The representor of SPINX-PHARAO in Estonia is OÜ Celsius Data and it is funded by Estonian Health Insurance Fund (Ilves, 2016).

The PHARAO decision support system has been previously tested for functionality and acceptance in a clinical setting by Böttiger et alles. Their study found that during a 4-month test period the database worked as intended and was appreciated by the users. From improvement factors they pointed out that the integration aspects should be improved to minimize unnecessary signalling. Furthermore, the system does not include information about doses. Therefore, the end user will not get a signal for an unnecessarily high dose of a single substance (Böttinger et al., 2017).

The effects of the integrating the SFINX database into primary health care records have been previously studied by Andersson et alles in the Swedish health care system. In their study they investigated whether the use of the database decreased the amount of prescriptions of potentially serious drug-drug interactions in primary health care. They conducted a controlled before and after study at 15 primary healthcare centres who had implemented the SFINX database compared to 5 centres who had not. The data was collected from the Swedish prescribed drug register for September - December 2006 (pre-intervention) and September - December 2007 (post-intervention). The results showed that the use of SFINX was associated with a 17% decrease of D level (highest severity) interactions per prescribed drug-drug pair concerning potentially serious drug-drug interactions. No significant effect was observed in the control group. Therefore, they concluded that the integration of the drug-drug interactions database SFINX significantly reduced the amount of prescriptions with potentially serious drug-drug interactions (Andersson et al., 2013).

When issuing a prescription in the system in Estonia, the physician must first select the type of treatment. Different types can be either a fixed period, permanent treatment or special schemas in the form of free text. In the case of fixed schema, the period of the treatment is fixed and taken into account while displaying DDI alerts. In the case of permanent treatment, the default setting for length of alerts is 90 days. This may also be

shorter and varies between different drugs. If the treatment dosages changes after some time the total period of treatment is entered into the system with the dosage of the first week into the dosage fields. More detailed instructions are written into the free text field. This info can also be seen by the pharmacist to help explain the proper method to the patient again when they are purchasing the drugs. The approximate amount of prescriptions where the dosages are needed to be written in free text filed is around 10% of all cases. (Ilves, 2016)

The alerts for different DDI-s in SFINX are divided into 4 categories – A, B, C and D. Category D and C, and their subcategories (D4 D3, D2, D1, D0, C4, C3, C2, C1, C0) are considered as clinically significant interactions and are automatically displayed. The severity levels are explained in Table 2.

Table 2. Classification of significance.

A	Minor interaction of no clinical relevance.
B	Clinical outcome of the interaction is uncertain and/or may vary.
C	Clinically relevant interaction that can be handled e.g. by dose adjustments.
D	Clinically relevant interaction. The combination is best avoided.
0	Data derived from extrapolation on the basis of studies with similar drugs.
1	Data derived from incomplete case reports and/or *in vitro* studies.
2	Data derived from well-documented case reports
3	Data derived from studies among healthy volunteers and/or pilot studies among patients.
4	Data derived from controlled studies in relevant patient populations

(Böttiger et al., 2009)

Alerts are displayed as pairs of the interacting drugs with additional information regarding the severity category and the interacting substances´ names. D category interactions are displayed with red background and C level category with yellow background (Figure 1). Automatic information is also displayed when there are no interactions saying, "No significant interactions found" (*Ravimite koostoimete e-teenus*).

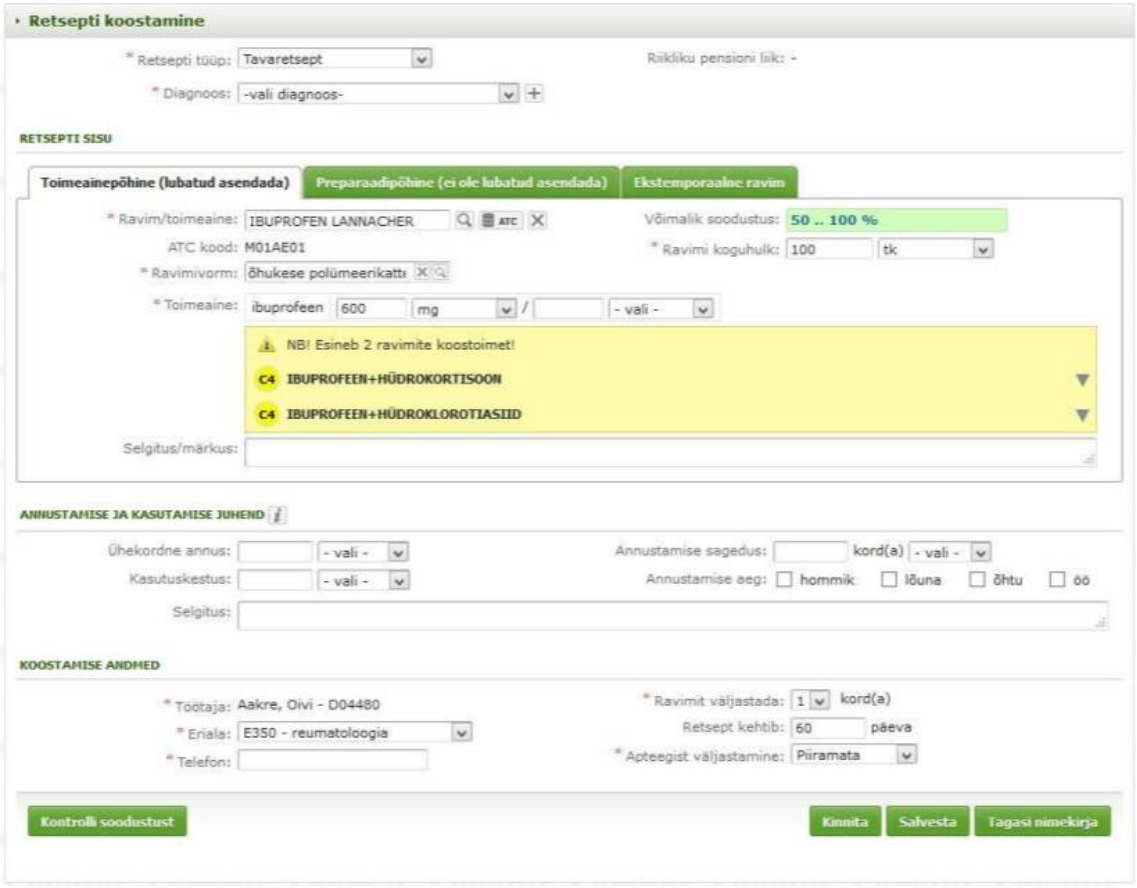

Figure 1. DDI interaction alert in the prescription module.

If needed, the user can open additional information provided with the alert to display more specific information regarding the interaction (Figure 2). The additional field offers information regarding the interacting substances names in Estonian, clinical significance classification of the interaction (form D to A), documentation classificatory (0-4), text regarding the consequences, text regarding recommendations and a link providing more thorough description of the interaction (*Ravimite koostoimete e-teenus*).

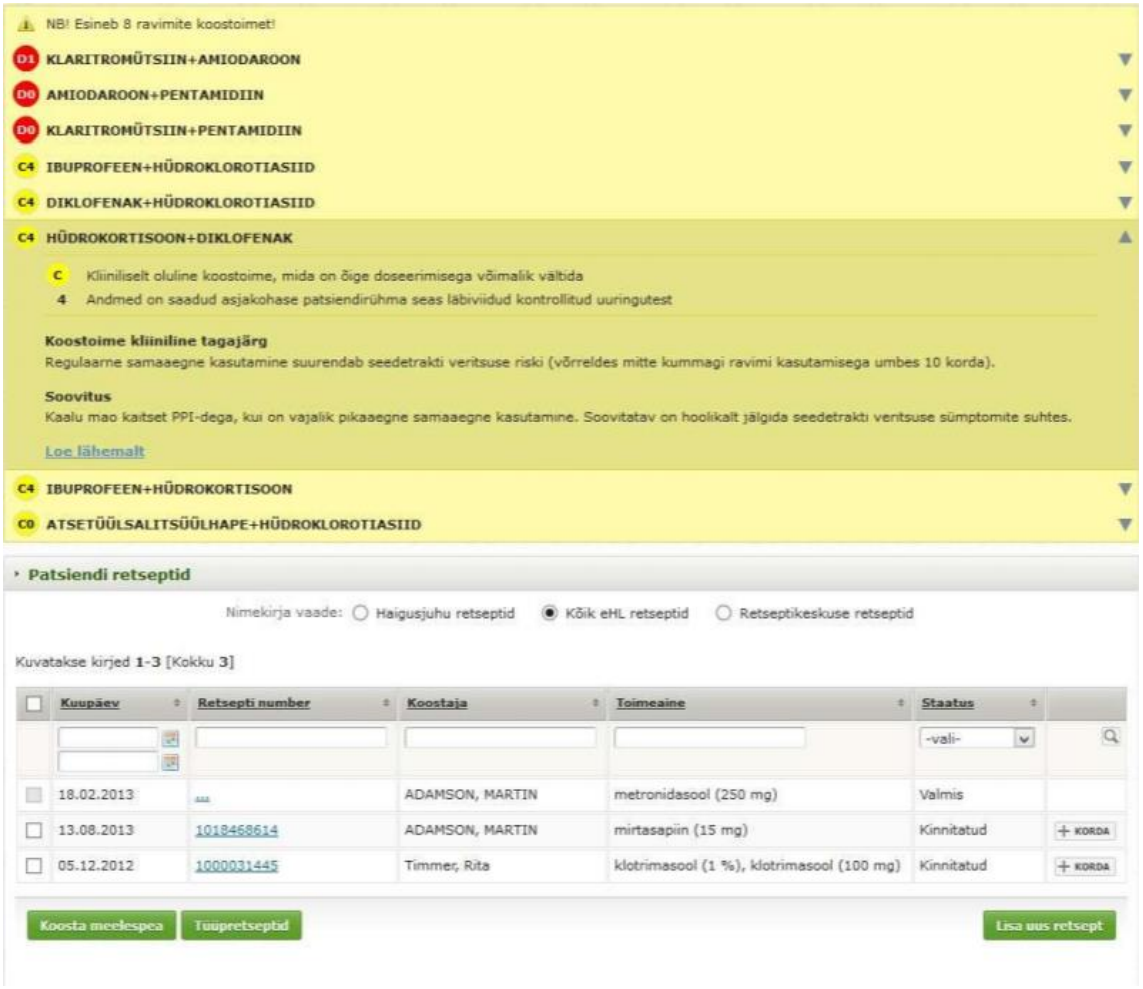

Figure 2. Additional information field in the prescription module.

The user can choose if they wish to see alerts about all interactions of drugs prescribed or only regarding a new drug being prescribed (*Ravimite koostoimete e-teenus*).

If the interaction is regarding clinically significant interactions (C or D) the user must confirm being aware of the interaction by clicking a button seeing notification with text: “I am aware of the interaction or I confirm the prescription being aware of the interaction” (*Ravimite koostoimete e-teenus*).

1.3 Aim of the research

The aim of the current research is to analyse the effect of computerized DDI alert system to Estonian family physicians prescribing habits of clinically significant drug-drug interactions and investigate their satisfaction with the solution.

1.4 Hypotheses

1. Estonian primary care physicians´ prescribing habits have not significantly changed since the introduction of the DDI alert system regarding prescriptions with clinically significant drug interactions.

2. Estonian Family Physicians are overall not satisfied with the current solution.

2 Method and materials

Two researches were conducted to test these hypotheses. For quantitative results regarding amount of interactions data from e-prescription centre was obtained and for qualitative data regarding satisfaction a questionnaire for family physicians was developed. The results were later shown to two experts in the field to ask their input for possible reasons and insights regarding the topic.

2.1 E-prescription data

For quantitative results data was acquired from the prescription centre. Comparisons of data from the first month of usage for all physicians (June 2016), and 3 more months with half a year intervals (January 2017, June 2017 and January 2018) were made. Since literature review shows that older patients tend to have more potential drug-drug interactions the analysis also included comparisons considering patient age (Morera et al., 2004).

Based on the data available from prescriptions centre, a comparative analysis regarding these periods was conducted for the following:

- How many prescriptions with drug interactions do family physicians issue?
- Number of drug interactions per family physician – change in top 10 during these study periods.
- What are the top 10 DDI interacting drug pairs during these study periods regarding D4, D and C category interactions?
- Number of drug interactions per patient with comparison of results dependent on patient age.
- How many times the prescriptions have been cancelled due the reason "unwanted DDI or side effect"?
- How many prescriptions do family physicians issue compared to other professions?

After data analysis the results were presented to two experts in the field to receive comments regarding the drug interactions and their possible reasons.

2.2 Web-based questionnaire

In order to measure Estonian family physicians' satisfaction and usage of the drug-drug interaction alert system a web-based questionnaire in Estonian was constructed in Google Forms. It was accessible via link sent to family physicians via e-mail. The e-mails were sent by a family physician to Estonian Family Physicians´ Society´s e-mail list containing 822 recipients. After 1 week a reminder was sent to encourage more physicians to fill in the questionnaire. The final questionnaire contained 23 items and is added in Estonian in appendix 1.

The questionnaire was constructed mostly based on research by Eslami et alles on main outcomes of drug-drug interaction alert systems including questions regarding medication safety, efficiency in time savings, level of actual usage, usability, and overall satisfaction (Eslami et al 2008).

The questionnaire also includes subjects from research of Luna et alles investigating the main drawbacks of the systems. These include the number of alerts, satisfaction with the interface and trustworthiness of alerts. (Luna et al., 2017)

From previous literature reviews questions were added to specify whether the family physicians actually follow up their patients after interacting drugs have been changed and how much alerts do they read thoroughly. Questions about possible add-ons and changes to the system were also included that were highlighted in the interview with the prescription centre and from the feedback of family physicians to the first draft of the questionnaire.

There is also a survey instrument for assessing prescribers' perception of computerized drug–drug interaction alerts developed by Zheng et alles that was considered for use when constructing the questionnaire. (Zheng et al 2011). The questionnaire in its original form is added in Appendix 3. On closer inspection, some of the questions from this instrument were used but most were disregarded since it was as a whole not compliant with this current study. For example, we have pre-existing knowledge about the Estonian system what makes some questions not necessary to be asked, includes fields not addressed in

this current study (e.g. social acceptance), asks many different aspects of the same category (E.g. safety) making the survey really long snd increasing the risk of the recipients not finishing the survey. In addition, most of the items were created as positive sentences towards the system creating a possible response bias.

In the construction of the final questionnaire essential elements of questionnaire design and development were also followed as described by Rattray et alles (Rattray et al., 2007). The questionnaire was kept as short as possible including only questions to increase the likelihood of more responses. This meant removing questions that measured the same category or questions that were not in the focus of this study. Since the questionnaire investigates attitudes, the answers to main part were displayed mostly in a 5-point Likert-type scale from "strongly agree" to "strongly disagree". Exceptions were 3 free text questions regarding which system was in use to check for ADI-s before the current system, question regarding the most common reason for ignoring the alerts and estimated percentage of repetitive prescriptions. The main part consisted of an equal mix of negative and positive sentences towards the system to avoid creating response bias.

After initial questionnaire was completed, it was sent for review to a small sample (6) of family physicians´ and to the Estonian prescription centre for review. Changes were implemented based on their feedback. The wording was improved, negative statements (hard to answer a mix of "I do" or "I do not" questions) removed, dropdown option added and an open question added to the end for any additional feedback not covered by the questionnaire.

In order to raise the likelihood of filling in the questionnaire by more family physicians and therefore being able to make more conclusive results help from Prescription centre and Estonian family physicians society was requested in distributing the questionnaire.

The final questionnaire added in Estonian (appendix 1) and English (appendix 2) consists of 3 sections. The first asks the respondents' demographic information regarding their gender, age, years of work experience, county in which they practise and vendor name of their system service provider. The second or the main part measures the attitudes of family physicians towards the system. Most of the questions (11/14) were answerable in 5-point Likert-type scale from "totally agree" to "disagree". The third and final part asks optional

additional questions concerning add-ons; additions and changes to the system; and offers an open comment possibility.

2.3. Results

The data from prescription centre was received via e-mail in excel format and analysed in MS Excel. During the analysis, multiple additional data was required which was also provided by the prescription centre. Together, 3 datasets with additional explanatory texts were received.

Regarding the questionnaire, since this was the first-time usage of this user developed version, in addition to the field validation by family physicians the reliability of the questionnaire was calculated. The results were analysed using the Statistical Package for Social Sciences (version 16.0) and MS Excel. The reversed negative questions were re-coded in opposite order to run the calculations.

2.3.1 Results from E-prescription database

Data included is a comparison of prescriptions from June 2016, January 2017, June 2017 and January 2018 based on their date of issue.

Firstly, to have an overview of the overall amounts, we start by looking at the total number of prescriptions with interactions (level C and D) compared to all prescriptions issued in family medicine. As seen on table 3, the amount of prescriptions with interactions is not drastically changing being the lowest the first month of usage and then staying at around 35%

Table 3. Prescriptions with issued in family medicine.

Family medicine	**Jun-16**	**Jan-17**	**Jun-17**	**Jan-18**
Total prescriptions	660 548	743 956	697 451	777 224
All interactions	179 617	268 592	262 344	253 768
All prescriptions with interactions	27%	36%	38%	33%

On a little more detailed approach we look whether there is a change in top 10 family physicians with the most amount DDI-s on their prescriptions (severity levels D4-C0). Figure 3 displays the percentages of prescriptions with interactions compared to all prescriptions issued by that family physician. The top is comprised of physicians

prescribing the most number of drugs with interactions during the displayed periods and are not identified as the same physician for any of the months. As can be seen the amount in the top 10 has risen and family physicians are issuing more prescriptions with interacting drugs than before. The average percentage of prescriptions with interactions among the top 10 has risen from 36% in June 2016 to 54% in January 2018.

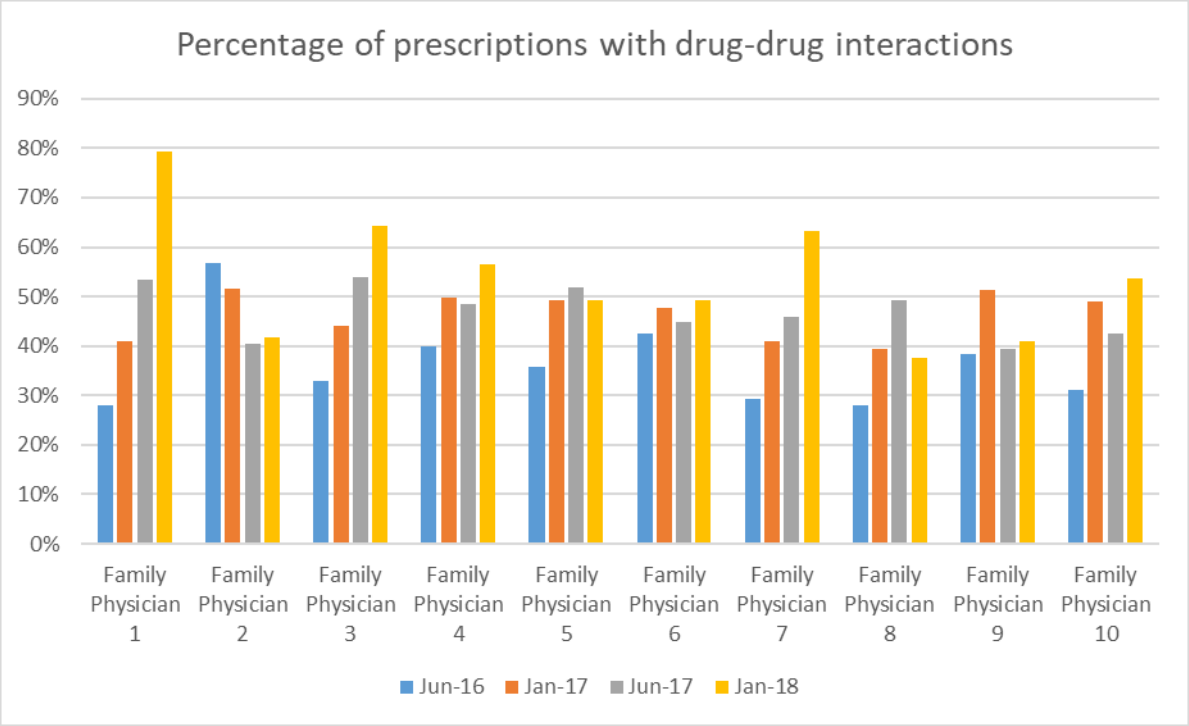

Figure 3. Top 10 family physicians with the most amount of displayed DDI-s.

The top 10 issue around 8 interacting prescriptions per patient which is consistent throughout all viewed months. The average number of prescriptions with interactions per patient among all family physicians in around 7. Therefore, we could say that there are not significant differences between family physicians prescribing habits regarding prescriptions with interactions meaning that there are no family physicians who prescribe much more interacting drugs than the others.

To go more into detail, table 4 shows the total number of clinically significant (level D and C) interactions on prescriptions that family physicians have issued (prescription status issued or purchased). It can be seen that prescriptions with level C nor D interactions is decreasing. The number of clinically significant interactions compared to

all prescriptions issued was 23% in June 2016 and afterwards rises to 30% in January 2018.

Table 4. Clinically significant interactions in family medicine.

Interaction level	June 2016	January 2017	June 2017	January 2018
C	135 801	198 317	187 841	220 410
D	14 584	24 132	22 376	25 918
Total C and D	150 385	222 449	210 217	246 328
Total all prescriptions	660 548	743 956	697 451	777 224
C and D level compared to all prescriptions issued	23%	30%	30%	32%

Next, we look at changes of drug pairs with significance level D4 (table 6), D (table 7) and C (table 8) interactions. Prescription statuses chosen from the system were "prescribed" or "purchased" (excluding cancelled). Data was filtered by profession: Family medicine. As can be seen from the results, the top 10 drug pairs stay relatively the same for all the viewed months and severity levels. According to an expert interview regarding these results the interactions presented in this paper could be grouped into categories by the related diseases they are used to treat. The categories are presented in table 5.

Table 5. Categories on diseases regarding interacting drug pairs.

Category	Explanation
I	Anticoagulants and NSAID (Non-steroidal anti-inflammatory drugs)
II	Congestive heart failure and Antihypertensive drugs
III	Medications related to Psychiatric diseases
IV	Drug for nervous system and cardiovascular diseases
V	Pain relief and Nervous system diseases
VI	Cardiovascular diseases
VII	Cardiovascular diseases and anticoagulants
VIII	Digestive system diseases and Thyroid hormone

The highest severity level (D4) drug pairs issue during the study periods are presented in table 6. It can be seen that most of the drug pairs are not decreasing in the amounts they have been prescribed. The 3 exceptions are: Diclofenac and Warfarin with decrease of 44% in June 2017 (compared to January 2017) and decreases by 16 % more half a year later in January 2018; Meloxicam and Warfarin with decrease of 24% in June 2017

compared to January 2017 (stays at the same level half a year later); Ibuprofen and Warfarin with a decrease of 4% in June 2017 and 9% more decrease in January 2018 (compared to June 2017). It should be also mentioned that all of the drug pairs were prescribed less in the first month of usage (June 2016) than half a year later.

Table 6.Top 10 interactions in severity level D4.

Drug pair	Related disease category	June 2016	January 2017	June 2017	January 2018	Total
Diclofenac & Warfarin	I	1 100	1 270	709	596	3 675
Verapamil & Digoxin	II	377	536	576	581	2 070
Meloxicam & Warfarin	I	351	385	291	291	1 318
Naproxen+Esomeprazole & Warfarin	I	233	290	258	341	1 122
Ibuprofen & Warfarin	I	189	261	251	229	930
Carbamazepine & Quetiapine	III	136	243	254	282	915
Ketoprofen & Warfarin	I	158	159	158	221	696
Diltiazem & Metoprolol	II	48	89	118	120	375
Aceclofenac & Warfarin	I	30	67	68	83	248
Carbamazepine & Risperidone	III	45	65		138	248

For overall level D interactions (Table 7) in addition to the previously mentioned Diclofenac and Warfarin, there can also be seen a slight decrease in the drug pair Tramadol and Warfarin with 6% drop in June 2017 and 8% more in January 2018 (compared to June 2017). The rest of the prescribed interacting drug pairs have increased. Carbamazepine and Amlodipine can also be singled out with no prescriptions in the first month of usage, then prescribed half a year later, decrease of 17% half a year later and then having a large increase of 47% in January 2018 (compared to June 2017). Again, we can see that the during the first month of system usage the drug pairs were prescribed less than half a year later.

Table 7. Top 10 interactions in significance level D.

Level	Drug pair	Related disease category	June 2016	January 2017	June 2017	January 2018	Total
D3	Metoprolol & Propafenone	II	3 237	5 638	5 798	6 217	20 890
D3	Metoprolol & Verapamil	II	992	1 426	1 515	1 574	5 507
D4	Diclofenac & Warfarin	I	1 100	1 270	709	596	3 675
D2	Tramadol & Warfarin	I	565	696	657	605	2 523
D0	Diazepam & Carbamazepine	III	544	692	568	647	2 451
D4	Verapamil & Digoxin	II	565	536	576	581	2 258
D0	Rivaroxaban & Warfarin	I	283	587	546	599	2 015
D0	Apixaban & Warfarin	I	166	370	553	703	1 792
D0	Carbamazepine & Amlodipine	IV	-	573	476	701	1 750
D0	Tramadol & Duloxetine	V	323	311	431	433	1 498

When looking at table 8 regarding the amount of drug pairs of significance level C the same pattern occurs as with D level drug pairs. The first month of use shows smaller prescribed interacting pairs than half a year later. After that, Metoprolol & Propafenone decrease of 32% in June 2017 and 8% more in January 2018 (compared to June 2017). The other decrease is with Diclofenac & Perindopril + Indapamide combination with decrease of 23% in June 2017 and 3% more in January 2018 (compared to June 2017). The rest of the pairs did not make a significant change in June 2017 (average 3% difference) and had an increase in January 2018 of an average 29% (ranging between 15 - 41%) compared to June 2017.

Table 8. Top 10 interactions in significance level C.

Level	Drug pair	Related disease category	June 2016	January 2017	June 2017	January 2018	Total
C0	Diclofenac & Metoprolol	I	7 989	9 644	6 540	6 043	30 216
C2	Torasemide & Warfarin	VII	2 341	3 667	3 806	4 580	14 394
C0	Meloxicam & Metoprolol	I	2 490	3 354	3 461	3 992	13 297
C0	Diclofenac & Perindopril + Indapamide	I	3 076	3 832	2 964	2 866	12 738
C4	Metoprolol & Amiodarone	VI	2 110	3 249	3 031	4 030	12 420
C4	Spironolactone & Ramipril	VI	1 780	3 237	3 054	4 267	12 338
C3	Omeprazole & Levothyroxine sodium	VIII	-	3 469	3 399	4 803	11 671
C0	Naproxen + Esomepras & Metoprolol	I	2 244	2 681	2 860	3 458	11 243
C3	Spironolactone & Digoxin	VI	1 803	2 708	2 877	3 587	10 975
C0	Diclofenac & Ramipril	I	2 383	3 089	1 876	2 062	9 410

To check whether older patients´ are more at risk than younger ones, figure 4 shows the percentage of prescriptions with C and D level interactions compared to all prescriptions issued within that age group. The patients have been divided into 5-year age groups. As can be seen from the figure, older patients are more at risk of getting a prescription with a clinically significant interaction.

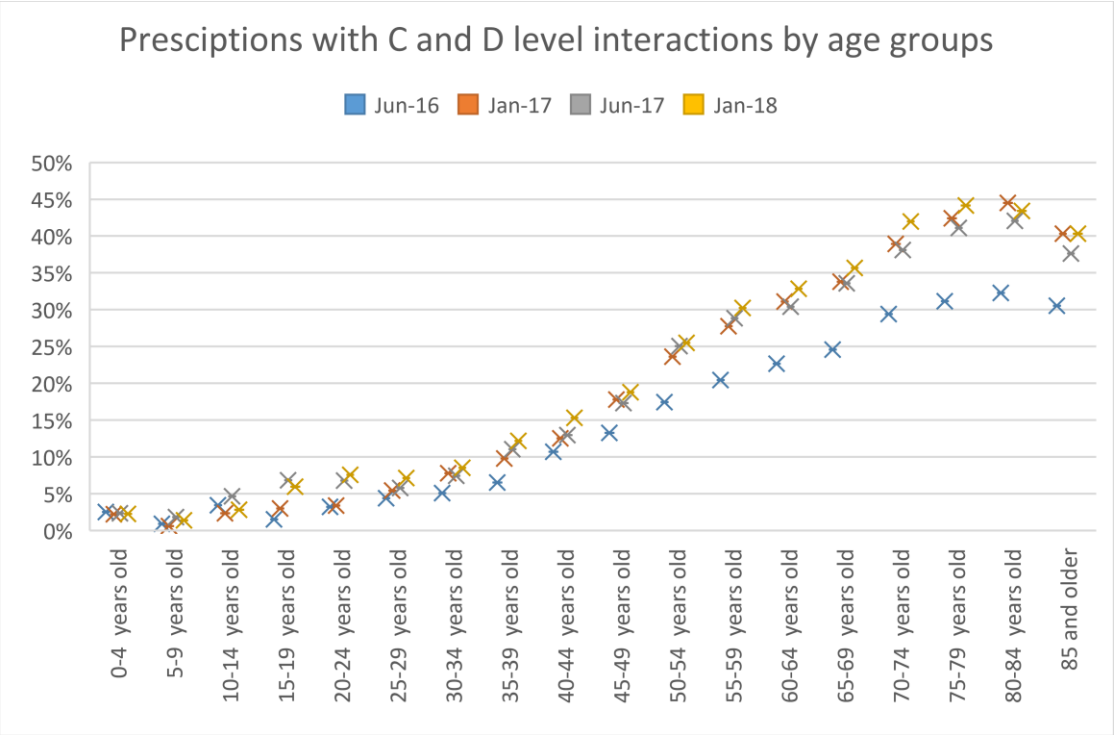

Figure 4. Prescriptions with level C & D interactions by patients´ age group

In additions data was also collected for prescription cancellation reason "Unwanted side effect or interaction". This was the only reason for cancellations that could associated with prescription change due to an interaction. Table 9 shows the amount of all prescriptions cancelled (all professions) with comparison of cancelled prescriptions with selected reason: AN01 "Unwanted side effect or interaction". It must be emphasized that this reason can mean also a side effect and therefore is not necessarily an indicator showing the amount of cancelled prescriptions regarding interactions. As can be seen in the table this reason for cancellation has been chosen very rarely averaging below 1%.

Table 9. Cancelled prescriptions vs selected reason: AN01 "Unwanted side effect or interaction"

Criteria	**June 2016**	**January 2017**	**January 2018**	**June 2017**
Unwanted side effect or interaction	455	423	252	296
All cancelled prescriptions	176 167	124 123	22 454	119 978
	0.3%	0.3%	1.1%	0.2%

Lastly, we can see in table 10 how many of C and D significance level alerts have family physicians seen on prescriptions they have issued (prescription statuses: issued, purchased or cancelled) compared to all other professions. As can be seen from the table

family physicians issue at an average 76% of all prescriptions with C and D level alerts in Estonia making them the profession who would benefit from improvements to the system the most.

Table 10. Amount of C and D significance level alerts.

Month	All professions	Family physicians	Family physicians/ All professions
June 2016	195 022	150 385	77%
January 2017	290 448	222 449	77%
June 2017	277 231	210 217	76%
January 2018	332 161	246 328	74%

2.3.2 Web questionnaire results

Firstly, to look into the reliability of the questionnaire, Cronbach's alpha was calculated at 0,84 which is sufficient for even more established questionnaires (Rattray et al., 2007). Therefore, the questionnaire items should all be measuring the same thing – which in this research is the family physicians' satisfaction with the drug-drug interaction alert system.

Correlations between items revealed that most of the items had the needed correlations between 0,3 and 0,7. Therefore most of the questions should measure the same concept – in this research the satisfaction level of family physicians. The only exceptions were question regarding the ease of finding alternatives and question regarding following up patients. Both these items had correlations even below 0,2 with other items in the questionnaire. These questions seem not to be good indicators to measure satisfaction with the system. None of the questions had too high correlations (all stayed below 0,8). Therefor none of the items should be duplicates of the same question.

To check the validity of the questionnaire meaning whether the test measures what it is supposed to measure the first step was collecting expert opinions of family physicians to the initial questionnaire (face validity). Factor analysis was also run on the results to test for the validity. The results show that the same as previously mentioned that all of the questions should be measuring same thing except for the alternatives question and question regarding follow- ups.

Previous literature suggests that there should also be differences in work experience on the level of thoroughness in checking the alerts. Therefore, the effects of work experience on the results of the question regarding thoroughness were checked. The respondents were divided into 5- year groups and the means of their results were compared by an analysis of variance (ANOVA), with significance level set at $p<0.05$.) The results show that there were no significant differences ($p=0,520$) between the groups. Therefore, according to the questionnaire results, the number of work experience years should not play a role in the thorughness of checking the interaction alerts.

The final number of respondents to the questionnaire was 88 which is 11,5 % of all registered family physicians in Estonia. Number of female respondents was 85 (96,6%) and 3 (3,4%) were male. The average age of the respondents was 49 years. Average work experience of the respondents was 22,4 years. Most used family physicians´ software was Perearst 2 (84,1%). Usage of Watson was at 11,4 %, Medicum family physicians´ software at 3,4 % and Arstiportaal + at 1,1 %. The highest number of respondents were from Harju county (42 %). More precise figure with all the respondents´ county of practise can be seen on figure 5.

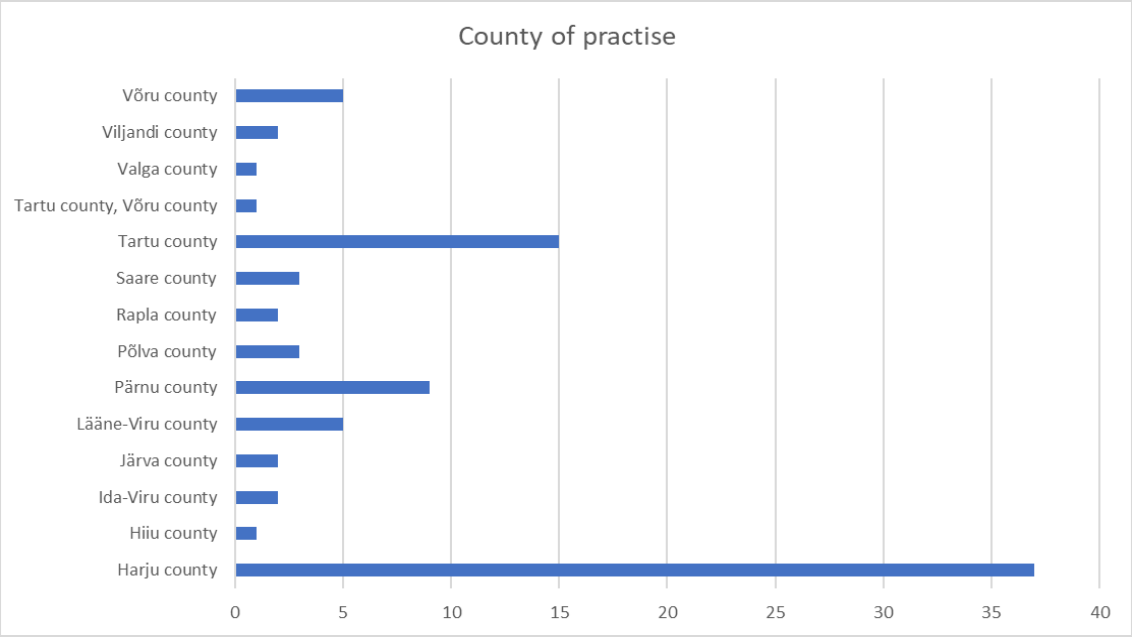

Figure 5. County of practise of the respondents.

When looking at the results of the main part of the questionnaire the overall satisfaction with the drug-drug alert system among Estonian family physicians seems to be high.

Respondents mostly agreed on the interaction alerts systems benefits when it comes to results regarding main outcomes of drug-drug interaction alert systems as described by Eslami et alles. The aspect of increased medication safety with rating “agree” or “totally agree” was 83% of all respondents, increased efficiency in time savings was felt by 82,9%, actual usage while creating treatment plans (adherence to guidelines) was expressed by 69,4%, mostly easy to use system reported by 78,4%, of all respondents. Overall satisfied with the system by reporting that the alerts are an appropriate tool for their everyday work was expressed by 85,2%.

When looking at possible drawbacks of the system described by Luna et alles regarding number of alerts, satisfaction with the interface, monitoring level (follow -ups of patients) and trustworthiness of alerts it seems that respondents did not consider them to be relevant enough to compromise their satisfaction. The results are as follows: Too many number of alerts were recognised (“agree” or “totally agree”) by 22,7%, user interface not satisfying agreed by 9%, alerts being not trustworthy by 13,7 % of all respondents.

13,6% of the family physicians admitted not following up on their patients after they had switched their interacting medication. It should be pointed out that this does not provide any information on the systems options but rather on the family physicians personal approach.

Results to the additional question regarding whether it is hard to find alternatives results are show in figure 6. It could be said that respondents do sometimes struggle with this but there is a quite even mix of those who do and those who do not.

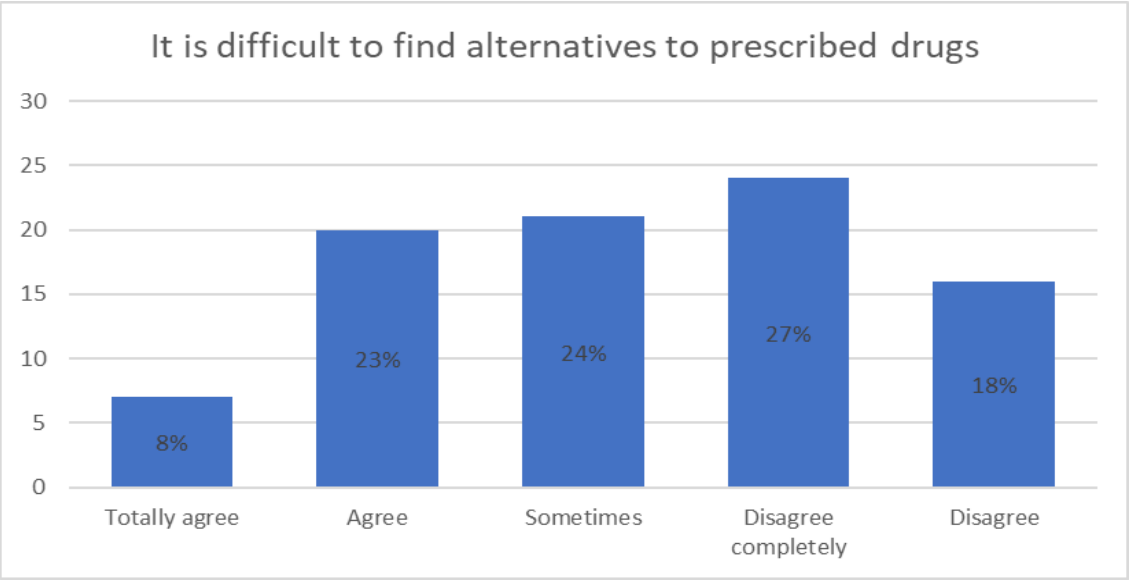

Figure 6. Finding alternatives.

The second additional question regarding thoroughness shows that most respondents (64,8%) replayed that they mostly check the displayed alerts thoroughly.

To analyse the open question regarding most common reasons for ignoring the alerts the drawbacks start to emerge even though they were mostly disregarded in the previous questions. To have a better overview the answers were grouped together on the basis of their content with the help of an expert in the field. Most common reasons for ignoring an alert by respondents was the fact that the system keeps showing interaction alerts even though the patient is no longer taking one of the drugs and that there are no suitable alternatives to the current drug pair. Also, a common reason was reportedly the lack of time. It was also often stated that patient has been taking this drug combination previously with no side-effects. Furthermore, there were also frequent statements saying that the benefits of the drugs outweigh the risk these interactions could have and that the system gives alerts for topical and systemic use of the drug with the same severity level but the physician did not consider this equal or worth paying attention to. All of the grouped results can be seen in table 11.

Table 11. Reasons for ignoring alerts.

Reason	**Total**
Drugs simultaneously not in use	**14**
No alternative	**14**
Lack of time	**13**
No problems so far	**8**
Benefits overweight risks	**5**
Topical drug	**5**
Alerts are not correct	3
Needed interaction	2
Repetitive alert	2
Risk low	2
Short term treatment	2
Special patient	2
Specialist set drug schema	2
High number of alerts	1
Do not notice alerts	1
NSAID + AKE	1
Patient wants to use the drug	1
Pragmatism	1
Treatment plan instructions	1

The answer to the question what system did the physicians use before the automatic alert system answers could be grouped into 4 main categories: Free online databases, Drug information sheet (or online version), memory/previous experience and book version of drug interactions (Pharmaca Estica mentioned in most cases). All the results are displayed in table 12.

Table 12. Previous source of drug-drug interactions.

Source of information	**Total**
Free online database	34
Drug info sheet/online	26
Memory/previous experience	18
Pharmaca (book)	7
Mobile application	1
Pharmacists’´ solution	1

Out of all prescriptions the respondents estimated an average of 67% of their prescriptions to be refills of previously issued drug. All the results are displayed on figure 7. As can be seen from the figure, most of the respondents (61/88) tend to say that most of their prescriptions (over 70%) are refills of a previously issued drug.

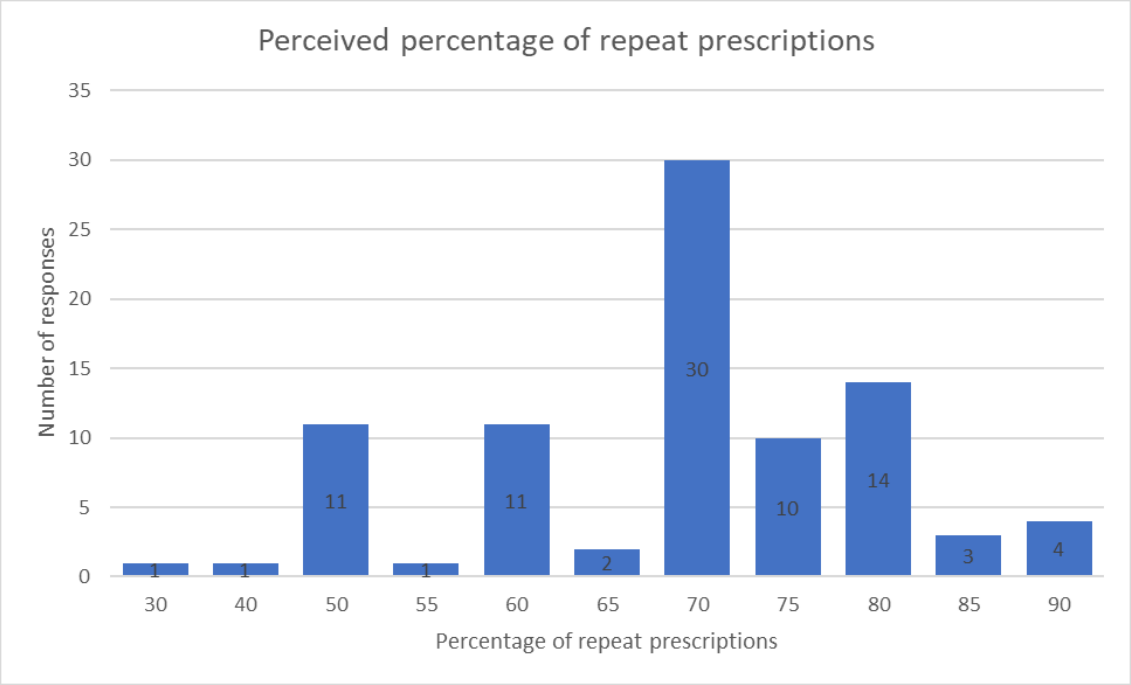

Figure 7. Percentage of perceived prescription refills.

From the section regarding improvements to the current system most of the respondents (over 93% for all three options) would like to see add-ons to the system proposed. Open question regarding what other add-ons would family physicians like to see are displayed in table 13. Many respondents found this question to be basically the same as the last proposed add-ons question or had nothing to add in addition to the already proposed ones. However, out of the proposed changes most dominant change request included the request for a possibility to change or refresh prescription status meaning that when a patient is no longer taking the drug its alerts could be removed or turned inactive in the system. The results for this question go hand in hand with the question regarding reasons for ignoring alerts. It was again highlighted that the type of treatment should be considered when displaying the effect (topical vs systemic drug).

Table 13. Proposed changes.

Proposed changes	Total
Option to stop a non-active prescription	10
Type of treatment (topical vs systemic)	6
Better structure	2
High level alerts info opens immediately	1
More concrete info	1
Needs to have not so strict rules	1
Option not to use the system at all	1
Should offer alternatives considering all prescribed drugs	1

Most users did not use the additional comment section. The 5 added comments were: "Trust the doctors, they don´t need it", "Missing interactions with over the counter medicines like Aspirin", "Alerts displayed regarding drugs the patient is no longer using", "Good idea but could use additional pharmacist's advice" and "Heading in the right direction but the system is still a bit clumsy".

2.4 Discussion

Based on the results, the number of prescriptions with clinically significant drug-drug interactions issued by family physicians is not decreasing staying overall at around 35% out of all prescriptions issued. However, the data does not show how many alerts did the physician see before they finalized a prescription and how much changes or considerations to alternatives were made before the prescriptions were issued.

It is good to state that there does not seem to be family physicians who prescribe significantly more interacting prescriptions to their patients than all the others. The average amount of interacting drugs per patient stays relatively the same at 7-8 per patient. Since this a calculation done by average means, more detailed analysis should be conducted in the future regarding the impact of DDIs on patients who are most exposed to a large number of drug interactions.

When looking at the top 10 of clinically significant interactions issued during the study periods it can be seen that most of the drug pairs in the top stay relatively the same with a few exceptions. According to expert interviews the combinations of Rivaroxaban & Warfarin and Apixaban & Warfarin with their increases show that there is a tendency to go from using Warfarin to more modern medicines with less side effects: Rivaroxaban

and Apixaban. It can be that the system displays old prescriptions (already purchased or not cancelled in the system) together with the new ones. This is also what multiple respondents mentioned in the questionnaire answers.

Moreover, the presence of the Warfarin is most often seen in both level D4 and overall D level interactions tables. According to the expert interview, the usage for it compared to the alternatives can be the fact that it is cheaper (more discount from prescription centre) and its usage is not so strictly regulated than the newer drugs. Yet again, while being a highly necessary drug (anticoagulant) for people with cardiovascular diseases, Warfarin causes a wide range of side effects and choosing the correct dosages together with constant adjustments is very complicated. Warfarin has a wide range of interactions with many drugs and even with foods and food supplements *(Ravimiomaduste kokkuvõte)*.

According to the expert interview the decreasing use of Diclofenac may be caused by the new drug safety announcement in 2013 that is starting to show results. The safety announcement states that with careful consideration whether the outcomes overweight the risks, Diclofenac should not be used with patients with cardiovascular problems (*Ohutusalane teave*). More detailed analysis by clinicians regarding the most issued drug pairs and their alternatives should be conducted.

In line with findings of previous studies, probability of patients becoming exposed to and affected by clinically significant DDIs increases substantially with age. As we can see from the quantitative analysis these results are further corroborated by most frequent DDI pairs. Most of these pairings fall into categories that could be intuitively considered to be prescribed mostly with patients of older cohorts. Since more interacting drugs are being prescribed to the elderly (over 50 years old) the risks involved and how to avoid them should be closely studied in the future.

When comparing key factors from to previous literature to the results of this study, the drug-drug interaction system among Estonian family physicians seems to be well implemented. Most positive outcomes including adherence to guidelines, medication safety, efficiency in time savings, appropriateness of alerts, usage and usability of the system have been successfully achieved. As a result, the family physicians who participated in this study seems to be overall satisfied with the system.

According to the answers to the questionnaire, the main reason for overriding the alerts is not the overall dissatisfaction with the system. Instead, family physicians point out that the main reasons for overrides are that the system shows alerts with prescriptions the patient is no longer taking. They also highlight that there is no possibility to stop the system from displaying alerts for patients that already have been taking the drug combinations without any side effects and therefore in their opinion should be ignored. These results are in line with previous studies claiming that many overrides can be appropriate.

Since most of the questionnaire respondents rated a very large number of their prescriptions to be refills of a previously issued drug, we could create a hypothesis that many family physicians do not pay enough attention to the alerts when writing a repeat prescription. This is also supported by the questionnaire answers reporting that the patients have not had any problems so far so therefore they ignore the alert. This hypothesis is worth looking into in the future to find out if it is true and how to improve this situation.

Furthermore, the majority of respondents agree that their system could be more helpful by offering correct dosages for children, patients with declined renal or liver functions and whether the drug is suitable for patients who are pregnant or breastfeeding. It was also highlighted that the system should offer alternatives to the interacting drug pairs to make the alerts more valuable and that topical drugs should not give the same level of alerts as systemic ones. All this information should be valuable to the system developers by adding these new possibilities for all physicians.

The reason of overrides due to lack of time should be studied further since the number of alerts was not reported to be too high. It was estimated that the system actually saves the physicians´ time. Therefore, this reason seems to be in contradictory and would require more research.

This study did not focus on the number of overrides compared to all alerts displayed since this this data was not available from the prescription centre. Since this was a key issue in previous literature a method to investigate it in Estonian context would be a good subject for research. This this study the subject was addressed on the level of subjective feedback from family physicians. It can be hypothesized that since the percentage of interactions

compared to prescriptions issued has stayed relatively the same, the number of overrides can be high. Further research proving or disproving this should be conducted in the future.

As suggested by expert in the field, the study periods for comparing drug interactions in the future could be viewed in 2-3 months together (instead of monthly data) as this is the average time drugs are issued for. It would also provide valuable information to do precise cost calculations regarding the economic burden of drug-drug interactions´ consequences to the Estonian healthcare system.

The results of this research bring out the most commonly issued interacting drugs by family physicians as well as some of the main drawbacks of the system. This kind of research should be repeated in the future to keep improving the software. It would also benefit further researches if the information system providing the drug pairs would give this kind of analysis (top 10 interacting drug pairs) automatically. Currently it provides the interacting drugs in separate columns and in mixed order. The development would be useful to track changes faster and take actions if needed.

Finally, it is good to note that the advancement of technology creates more and more opportunities for personalised medicine and possibilities for physicians to keep up to date with recent developments. The users´ satisfaction with the solutions in Estonian drug-drug system among family physicians seems to be relatively high helping physicians make safer and better-informed decisions for their patients. In addition, the system creates valuable data to be analysed in order to highlight and improve problem areas in the field. Thus, the findings of the study reinforce the case for development and implementation of evidence-based clinical decision support systems in Estonia. These kinds of software developments would assist physician make better informed decisions in all care settings and improve efficiency and quality of treatments and care.

3 Summary

The aim of this research was to analyse the effect of computerized DDI alert system on Estonian family physicians prescribing habits of clinically significant drug-drug interactions and investigate their satisfaction with the solution.

Two researches were conducted. For quantitative results regarding amount of interactions data from e-prescription centre was obtained and for qualitative data a questionnaire for family physicians was developed. Interviews with experts in the field were conducted regarding the results.

Results from prescription centres data show that the number of clinically significant interacting drugs prescribed by family in not decreasing. More research regarding the possible reasons is required. The most often issued interacting drugs during the study period have also stayed relatively the same with a few exceptions. On average, family physicians issue 7-8 prescriptions with clinically significant interactions per patient with older patients (over 50 years old) having prescribed more interacting drugs than younger ones.

Results from the questionnaire show that the respondents are overall satisfied with the system but would need some improvements to be made to the system regarding correct dosages, possibility to cancel interaction alerts for patients who are no longer taking some medications, change the level of alerts for topical drugs and provide alternative drug suggestions to the interacting drugs.

This research provides valuable insights to the Estonian drug-drug interaction systems´ usage among family physicians. The results of this research will be shared with Estonian prescription centre and family physicians' society.

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Appendix 1 – Questionnaire in Estonian

Uuring perearstidele: Rahulolu automaatse ravimite koostoimete kuvamise infosüsteemiga

Järgnevate küsimuste vastuseid kasutatakse Tallinna Tehnikaülikooli Tervishoiutehnoloogia õppekava magistritöös, mille eesmärgiks on selgitada välja Eesti arstide rahulolu ravimite koostoime kuvamise infosüsteemiga.

Küsimustikule vastamine on anonüümne.
* Kohustuslik

1. Sugu: *
.
Mees
Naine

2. Vanus (aastat): *

3. Tööstaaž (aastat): *

4. Kasutusel oleva perearsti tarkvara: *
(valida 1 variant)
Perearst 2
Watson
Medicumi perearstiprogramm
Arstiportaal +
Muu

5. Praktiseerimise maakond: *
(võib valida mitu varianti)

Harju maakond
Tartu maakond
Ida-Viru maakond
Pärnu maakond
Lääne-Viru maakond
Viljandi maakond
Rapla maakond
Võru maakond
Saare maakond
Jõgeva maakond
Järva maakond
Valga maakond
Põlva maakond
Lääne maakond
Hiiu maakond

Palun valige vastuste hulgast kuivõrd nõustute järgnevate väidetega:

6. Ravimite koostoimete kuvamine on muutnud ravimite väljakirjutamise ohutumaks. *

Nõustun täielikult 1 2 3 4 5 Ei nõustu

7. Ravimite koostoimete kontrollimise süsteemi on keeruline kasutada. *

Nõustun täielikult 1 2 3 4 5 Ei nõustu

8. Koostoimete kuvamise süsteem säästab mu aega ravimite koostoimete kontrollimise arvelt. *

Nõustun täielikult 1 2 3 4 5 Ei nõustu

9. Süsteem kuvab koostoimete kohta liiga palju teateid. *

Nõustun täielikult 1 2 3 4 5 Ei nõustu

10. Olen rahul koostoimete esitlusviisiga ekraanil. *

Nõustun täielikult 1 2 3 4 5 Ei nõustu

11. Süsteemi soovitused on ebausaldusväärsed. *

Nõustun täielikult 1 2 3 4 5 Ei nõustu

12. Koostoimete hoiatused on mu töös kasulikuks abivahendiks. *

Nõustun täielikult 1 2 3 4 5 Ei nõustu

13. Alternatiive väljakirjutatavatele ravimitele on raske leida. *

Nõustun täielikult 1 2 3 4 5 Ei nõustu

14. Arvestan raviplaani koostamisel süsteemi hoiatustega. *

Nõustun täielikult 1 2 3 4 5 Ei nõustu

15. Jälgin oma patsientide tervisenäitajate muutumist pärast koostoimetega ravimite väljavahetamist. *

Nõustun täielikult 1 2 3 4 5 Ei nõustu

16. Süvenen harva koostoimete hoiatustesse põhjalikult. *

Nõustun täielikult 1 2 3 4 5 Ei nõustu

17. Süsteemi hoiatuse ignoreerimise kõige sagedamateks põhjusteks on:

18. Millist meetodit kasutasite koostoimete kontrollimiseks enne automaatset süsteemi?

19. Hinnanguliselt mitu protsenti väljakirjutavatest retseptidest on korduvretseptid? *

Olemasoleva süsteemi täiendused:

Vastamine pole kohustuslik, kuid aitaks panustada olemasoleva süsteemi parendamisse.

20. Kas oleksite huvitatud süsteemi lisast, mis aitaks:
(Võimalik on valida mitu varianti)

Määrata korrektseid ravimite doose (nt patsiendi vähenenud neeru- või maksafunktsiooni korral, laste puhul)

Kontrollida ravimite sobivust rasedate või imetavate patsientide puhul

Leida väljakirjutatavatele ravimitele alternatiive

21. Milliseid lisasid Te süsteemile veel sooviksite (kuni 3 peamist)?

22. Loetlege kuni 3 peamist muudatust, mis tuleks olemasolevale süsteemile teha:

23. Soovi korral võite lisada veel kommentaare ravimite koostoimete süsteemi kohta, mida antud küsimustikus pole käsitletud:

Appendix 2 - Questionnaire in English

Questionnaire for family physicians: Satisfaction with drug-drug interaction system

The following questionnaire is used in the master´s thesis for Healthcare Technology curriculum in Tallinn University of Technology . The purpose of this study is to study Estonian family physicians´ satisfaction with their drug-drug interaction alert system.

The questionnaire is anonymous.
* Required

1. Gender: *

Male
Female

2. Age (years): *

3. Work experience (years): *

4. Family physcians software in use: *
(Choose 1)
Perearst 2
Watson
Medicum family physicians software
Arstiportaal +
Muu

5. County of practise: *
(multiple choice option)

Harju county
Tartu county
Ida-Viru county
Pärnu county
Lääne-Viru county
Viljandi county
Rapla county
Võru county
Saare county
Jõgeva county
Järva county
Valga county
Põlva county
Lääne county
Hiiu county

Please choose in which degree do you agree with the following statements:

6. Drug -drug interaction alert system has made prescribing process safer. *

Agree completely 1 2 3 4 5 Disagree

7. Drug - drug interaction system is difficult to use. *

Agree completely 1 2 3 4 5 Disagree

8. Drug - drug interaction system saves my time on checking for interactions. *

Agree completely 1 2 3 4 5 Disagree

9. System displays too many alerts. *

Agree completely 1 2 3 4 5 Disagree

10. I am satisfied how interactions are displayed on my screen. *

Agree completely 1 2 3 4 5 Disagree

11. Alerts of the system are trustworthy. *

Agree completely 1 2 3 4 5 Disagree

12. Interaction alert system is a useful tool in my work. *

Agree completely 1 2 3 4 5 Disagree

13. It is difficult to find alternatives to prescribed drugs. *

Agree completely 1 2 3 4 5 Disagree

14. I take the interaction alerts into account when creating my patients´ treatment plan. *

Agree completely 1 2 3 4 5 Disagree

15. I follow up on my patients´ symptoms after replacing interacting drugs. *

Agree completely 1 2 3 4 5 Disagree

16. I rarely check the displayed alerts thoroughly. *

Agree completely 1 2 3 4 5 Disagree

17. Most frequent reasons for ignoring an alert are:

18. What method did you use before the automatic system to check for interactions?

19. Approximately how many percentage of precriptions are refills? *

Improvements to the system:

Answers are not required but would help to contribute to improving the current system.

20. Would you be interested in add-on to the sytem that helps:
(Multiple choice option)

Set correct dosages (e.g. For patients with declining renal or liver functions, for children).

Check medications adherence for patients who are pregnant or breastfeeding.

Find alternatives to prescribed drugs.

21. What other add-ons would like to see made to the system (up to 3 main ones)?

22. Please list up to 3 main changes that should be made to the system:

23. Please provide any additional comments regarding drug-drug interaction system not covered in this questionnaire that you would like to add:

Appendix 3 – Survey instrument

Preamble

PRE.1 A. Please estimate, during an average week of your practice, how many *Drug–Drug Interaction* alerts you receive from [*name of CPOE*]? _____ (Please provide a numeric estimate)

PRE.2 B. Please estimate, of the *Drug–Drug Interaction* alerts you receive, what per cent do you read thoroughly? _____ %

PRE.3 C. Please estimate, of the *Drug–Drug Interaction* alerts you read, what per cent do you find relevant? _____ %

PRE.4 D. Please estimate, of the *Drug–Drug Interaction* alerts you find relevant, what per cent change your prescribing decisions? _____ %

- Section 1 of 5
- Please respond to the following statements based on your experience using [*name of CPOE*] at [*name of institution*]
- (Scale: Strongly Disagree, Disagree, Agree, Strongly Agree, and Does not apply)

PE.1 1. *Drug–Drug Interaction* (DDI) alerts are useful in helping me care for my patients.

PE.2 2. DDI alerts are relevant to the individual patients for which they appear.

PE.3 3. DDI alerts capture all drug interaction instances for my patients.

PE.4 4. DDI alerts I receive are clinically important.

PE.5 5. DDI alerts help me better understand which drugs should not be used at the same time.

PE.6 6. DDI alerts help me improve the monitoring for and management of DDIs for my patients.

PE.7 7. DDI alerts help me reduce professional risk by preventing potential adverse events in my patients.

Section 2 of 5

EE.1/EU1* 8. I find *Drug–Drug Interaction* (DDI) alerts easy to understand.

EE.2/EU2* 9. The system makes it easy to respond to DDI alerts.

EE.3 10. Reading and responding to DDI alerts takes too much time.

EE.4 11. I repeatedly receive DDI alerts to which I have already responded.

EE.5 12. Reading and responding to DDI alerts interferes with my workflow.

SI.1 13. I read and respond to *Drug–Drug Interaction* (DDI) alerts because my colleagues read and respond to them.

SI.2 14. My supervisor (eg, attending physicians, nurse managers) encourages me to read and respond to DDI alerts.

SI.3 15. Reading and responding to DDI alerts helps to improve my professional image.

Section 3 of 5

FC.1 16. I received adequate training on how to read and respond to *Drug–Drug Interaction* (DDI) alerts.

FC.2 17. I have adequate clinical knowledge to understand DDI alerts.

FC.3 18. The system provides adequate explanations of clinical relevance for DDI alerts.

FC.4 19. The system provides adequate management alternatives for DDI alerts.

FC.5 20. If I have questions about DDI alerts, I always have someone to consult with.

Section 4 of 5

PF 21. During order entry, I receive too many *Drug–Drug Interaction* (DDI) alerts that I must read and respond to.

- Section 5 of 5
- Please respond to the following statements based on your experience using [*name of CPOE*] at [*name of institution*]
- (Scale: Never, Rarely, Less than half the time, About half the time, More than half the time, Always, and Does not apply)

UB.1 22. I thoroughly read the *Drug–Drug Interaction* (DDI) alerts that I receive.

UB.2 23. I provide reasons for DDI alerts that I decide to override.

UB.3 24. DDI alerts presented to me during order entry change my prescribing decisions.

Open-ended closing

Please provide any additional comments you have regarding *Drug–Drug Interaction* alerts you receive from [*name of CPOE*]. Thank you for your time.