The effect of computerised decision support alerts tailored to intensive care on the administration of high-risk drug combinations, and their monitoring: a cluster randomised stepped-wedge trial

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Summary

Background **Drug–drug interactions (DDIs) can harm patients admitted to the intensive care unit (ICU). Yet, clinical decision support systems (CDSSs) aimed at helping physicians prevent DDIs are plagued by low-yield alerts, causing alert fatigue and compromising patient safety. The aim of this multicentre study was to evaluate the effect of tailoring potential DDI alerts to the ICU setting on the frequency of administered high-risk drug combinations.**

Methods **We implemented a cluster randomised stepped-wedge trial in nine ICUs in the Netherlands. Five ICUs already used potential DDI alerts. Patients aged 18 years or older admitted to the ICU with at least two drugs administered were included. Our intervention was an adapted CDSS, only providing alerts for potential DDIs considered as high risk. The intervention was delivered at the ICU level and targeted physicians. We hypothesised that showing only relevant alerts would improve CDSS effectiveness and lead to a decreased number of administered high-risk drug combinations. The order in which the intervention was implemented in the ICUs was randomised by an independent researcher. The primary outcome was the number of administered high-risk drug combinations per 1000 drug administrations per patient and was assessed in all included patients. This trial was registered in the Netherlands Trial Register (identifier NL6762) on Nov 26, 2018, and is now closed.**

Findings **In total, 10 423 patients admitted to the ICU between Sept 1, 2018, and Sept 1, 2019, were assessed and 9887 patients were included. The mean number of administered high-risk drug combinations per 1000 drug administrations per patient was 26·2 (SD 53·4) in the intervention group (n=5534), compared with 35·6 (65·0) in the control group (n=4353). Tailoring potential DDI alerts to the ICU led to a 12% decrease (95% CI 5–18%; p=0·0008) in the number of administered high-risk drug combinations per 1000 drug administrations per patient, after adjusting for clustering and prognostic factors.**

Interpretation **This cluster randomised stepped-wedge trial showed that tailoring potential DDI alerts to the ICU setting significantly reduced the number of administered high-risk drug combinations. Our list of high-risk drug combinations can be used in other ICUs, and our strategy of tailoring alerts based on clinical relevance could be applied to other clinical settings.**

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Introduction

Drug–drug interactions (DDIs) are an important cause of patient harm.[1] Patient harm occurs when two drugs known to interact are co-administered and subsequently their effect is increased or decreased, causing drug toxicity or therapy failure.[2] Patients admitted to the intensive care unit (ICU) are more prone to adverse drug events compared with patients on non-ICU wards.[3] The observed rate of adverse drug events was 11·5 per 1000 patient-days in general wards compared with 19·4 in the ICU in the USA in 1995.[4] Approximately 16% of all adverse drug events in the ICU are caused by DDIs.[5–7]

A potential DDI refers to the administration of two drugs known to interact. The term potential implies uncertainty regarding whether the exposure will lead to an actual DDI, harming the patient. The occurrence of an interaction depends on factors such as the patient's renal and liver function, and the dose and duration of the co-administration. For potential DDIs that are considered clinically relevant in the ICU, the term high-risk drug combination is used, indicating exposure to a combination that might result in an actual DDI with clinically relevant consequences harming the patient.

Several studies have shown that clinical decision support systems (CDSSs) help to prevent DDIs and

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Research in context

Evidence before this study

Drug–drug interactions (DDIs) are a notable cause of patient harm. Patients admitted to the intensive care unit (ICU) are more prone to adverse drug events compared with patients on non-ICU wards. We searched MEDLINE for studies in English published from Jan 1, 2010, to April 13, 2017, on information technology-based interventions to improve DDI outcomes. We subsequently conducted an update of this search for studies published in the period April 13, 2017, to Oct 9, 2019. We used the search terms "drug interaction", "medication interaction", "decision support system", "expert system", and "prescribing system". We excluded studies that focused on the feasibility, validity, acceptability, or description of information technology-based applications. We found that clinical decision support systems (CDSSs) are plagued by an overload of low-yield potential DDI alerts. Producing many low-yield alerts desensitises clinicians and leads to alert fatigue, high over-ride rates, and the risk of missing relevant alerts, thereby compromising patient safety. In the ICU, approximately 90% of the potential DDI alerts are over-ridden, and 84% of these over-rides appear justified because of the perceived low yield of the potential DDI alerts. Furthermore, we found no studies that evaluated the effect of tailoring potential DDI alerts to the ICU setting on high-risk drug combination frequency, patient monitoring, or ICU length of stay.

Added value of this study

This cluster randomised stepped-wedge trial showed that tailoring potential DDI alerts to the ICU setting, by only producing alerts that are clinically relevant in this setting, improved CDSS effectiveness and led to a 12% decrease in the number of administered high-risk drug combinations (95% CI 5–18%; p=0·0008). Additionally, patient monitoring for potential consequences of DDIs improved by 9% (6–11%; p<0·0001), and the length of stay in the ICU was reduced by 6% (2–10%; p=0·0021). These findings contribute to the goal of intensivists to avoid high-risk drug combinations if possible and, if not possible, to prescribe them while being aware of and adequately monitoring the potential consequences.

Implications of all the available evidence

Tailoring potential DDI alerts to a specific setting can reduce the administration of high-risk drug combinations and length of stay in the ICU, and improve patient monitoring for the potential consequences of DDIs. Our results are relevant to clinicians, hospital pharmacists, CDSS developers, managers, quality-of-care officers, and researchers in the ICU setting. Other ICUs could use our list of high-risk drug combinations to tailor their potential DDI alerts and improve CDSS effectiveness. Additionally, our results might encourage other medical practitioners to establish a set of high-risk drug combinations for patients in other specific settings, such as in neonatology, paediatrics, or oncology.

See Online for appendix

thereby adverse drug events.[8,9] CDSSs support clinicians in safe prescribing by showing potential DDI alerts during drug order entry.[8] The main follow-up actions after an alert are either stopping the interacting drugs, or continuing and monitoring the patient.

However, current CDSSs are plagued by an overload of low-yield potential DDI alerts (ie, those of a low relevance).[10] When CDSSs produce numerous low-yield alerts, this desensitises clinicians and leads to alert fatigue, high over-ride rates, and the risk of missing relevant alerts, which compromises patient safety.[10–12]

In the ICU, approximately 90% of the potential DDI alerts are overridden, and 84% of these over-rides seem appropriate because the alert is low yield.[13,14] Additionally, the critical condition of patients in the ICU might require the administration of drugs known to interact, despite the risk of harm. Moreover, patients in the ICU are extensively and continuously monitored. Although not fail-proof, this monitoring facilitates the early detection of adverse consequences of DDIs, allowing for timely appropriate actions to prevent further harm. Therefore, it is important to consider the setting in which the potential DDI alerts operate.

We hypothesised that tailoring potential DDI alerts to the ICU setting, by only showing alerts that are clinically relevant in the ICU setting, would increase attention towards these alerts and, in turn, would improve CDSS effectiveness and lead to a decreased number of high-risk drug combinations being administered (appendix p 2).[12] When the administration of a high-risk drug combination cannot be avoided, patient monitoring for potential consequences of such combinations might prevent or ameliorate patient harm. Monitoring might include monitoring laboratory values, reviewing electrocardiograms (ECGs), and therapeutic drug monitoring. Recommended monitoring actions are shown in the alerts. Hence, in addition to evaluating the frequency of high-risk drug combinations, it is important to evaluate whether potential DDIs were monitored appropriately.

Therefore, the aim of this multicentre study was to evaluate the effect of tailoring potential DDI alerts to the ICU setting on the frequency of administered high-risk drug combinations, proportion of appropriately monitored high-risk drug combinations, and length of stay in the ICU.

Methods

Study design

To evaluate the effect of tailoring potential DDI alerts, we implemented a cluster randomised stepped-wedge trial. The study period was from Sept 1, 2018, to Sept 1, 2019. The intervention was rolled out sequentially to nine ICUs, with the intervention staggered by 1 month between each ICU (figure 1). During the first 2 months, all ICUs were in

the control group. By the last month, all ICUs were in the intervention group. To analyse the intervention's effectiveness, data in the control section of the wedge were compared with data in the intervention section (figure 1). This study was conducted in nine mixed medical and surgical closed format ICUs in the Netherlands.

We chose the stepped-wedge design because, when compared with a parallel cluster randomised controlled trial, it is more powerful with a small number of clusters but a large number of patients per cluster, which aligns with our situation.[17] We designed the intervention at the ICU level, because of the expected contamination (ie, the effects of the CDSS spreading to the control group) at the patient or ICU physician level.

This study is reported according to the Consolidated Standards of Reporting Trials 2010 extension for stepped-wedge cluster randomised trials, and the reporting of studies conducted using observational routinely collected health data statement for pharmacoepidemiology (appendix p 7). The study protocol was reviewed by the Medical Ethics Committee of the Amsterdam University Medical Centers (the Netherlands) and has been published previously.[12] This committee provided a waiver from formal approval (W16_391 number 17·001) and informed

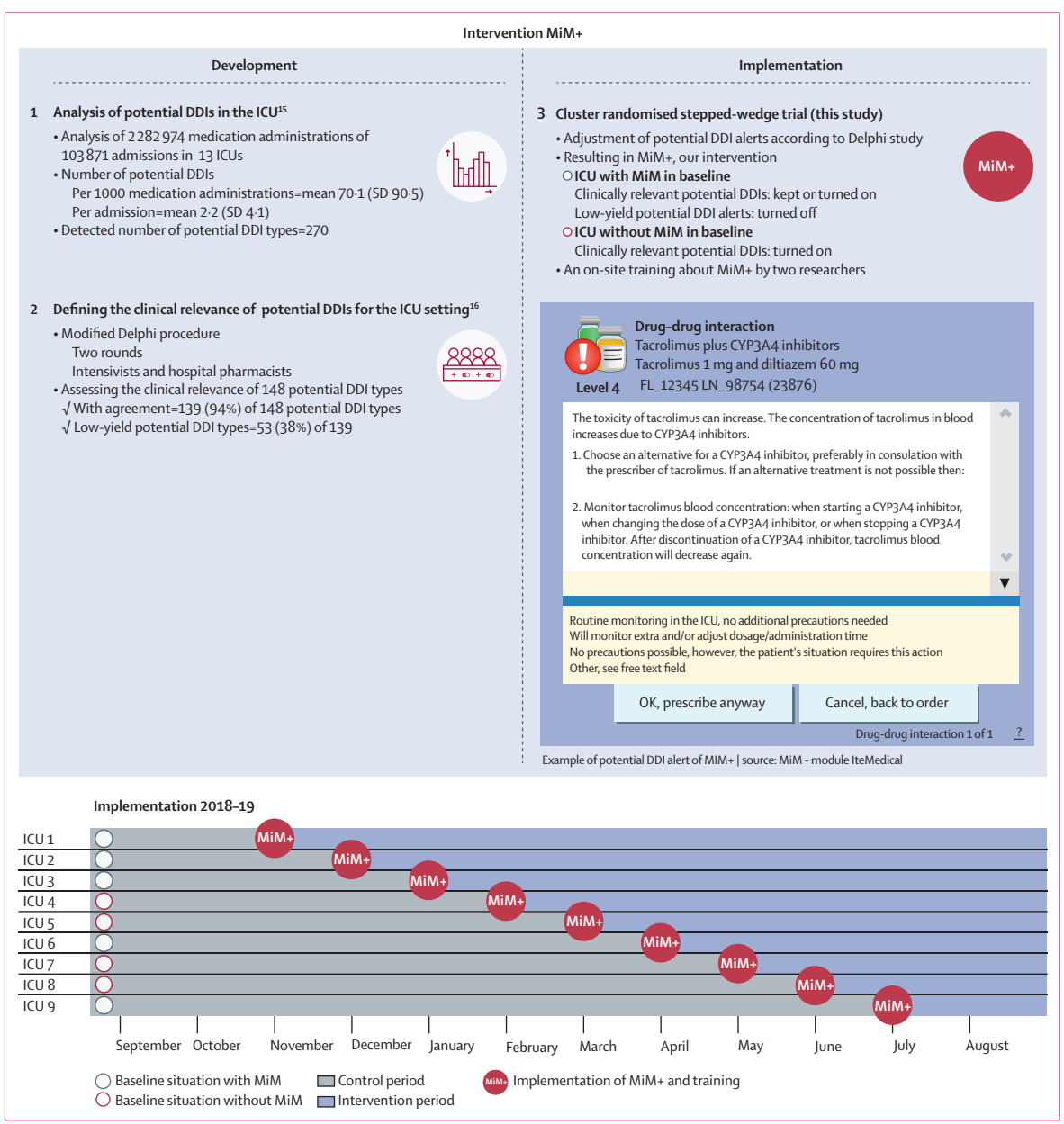

Figure 1: **Graphical summary of the development and implementation of the MiM+ intervention**
DDI=drug–drug interaction. ICU=intensive care unit. MiM+=Medication Interaction Module+.

consent, because this trial does not fall within the scope of the Dutch Medical Research Human Subjects Act.

The trial was registered in the Netherlands Trial Register (identifier NL6762) on Nov 26, 2018. ICUs were invited to participate before registration, because this study was part of a larger project (figure 1).[15,16] ICUs were invited early, to allow enough time for the preparation of the implementation of our intervention together with the software supplier. An independent researcher performed the computerised random assignment on Sept 12, 2018, and ICUs were informed of their starting day before Nov 1, 2018. According to the schedule, the study started on Nov 1, 2018, when the first ICU started the intervention. The trial registration was published 3 weeks later, on Nov 26. No modifications were made to the content of the registration between Sept 12 and Nov 26.

Assessment of safety and adverse events

A Data Safety Management Board was not established in this study. This decision was carefully considered and discussed with the participating ICUs. We decided not to establish a Data Safety Management Board because our intervention was considered a low-risk intervention. It did not involve any experimental drugs or procedures, and our trial does not fall within the scope of the Dutch Medical Research Human Subjects Act, as established by the Medical Ethics Committee. This committee did not require the establishment of a Data Safety Management Board. In addition, the intervention did not pose any immediate safety concerns or potential harm to patients. In our trial, the intervention was implemented at the level of clusters (ICUs), rather than individual patients. Since the intervention primarily targeted ICU physicians, and there was no direct involvement of individual patients, the need to monitor individual patient safety was low. Additionally, such monitoring was already part of routine care in the ICUs. Lastly, at the start of the trial, all ICUs were provided with on-site training about the intervention, and all ICU site coordinators were asked by the researchers to report any unintended negative consequences on patients related to the intervention. No unintended negative consequences were reported during the trial.

Participants

For inclusion, we required that the ICU used the patient data management system MetaVision ICU (iMDSoft) during the whole trial period. Integrating our intervention and extracting data from various patient data management system types would require resources beyond the available funding; and, additionally, the patient data management system type was not expected to influence the effect of our intervention. All ICUs using MetaVision were invited to participate via the National Intensive Care Evaluation (NICE) registry network. Patients aged 18 years or older admitted to the ICU with at least two drug administrations during their admission were included.

Randomisation and masking

The order in which the intervention was implemented in the ICUs was randomly assigned, reducing the risk of bias, thus increasing the internal validity of the method. An independent researcher not involved in this study performed the computerised randomisation. Masking was not feasible, because the ICU staff and researchers involved were aware of the change from control to intervention.

Intervention

Our intervention was a restricted version of the Medication Interaction Module (MiM), a CDSS developed by ItéMedical. ICUs using the patient data management system MetaVision have the option to use MiM, which provides potential DDI alerts or duplicate order alerts, or both. Five of the nine participating ICUs used the MiM. MiM is based on the G-Standaard, an evidence-based professional database developed by the Scientific Institute of Dutch Pharmacists. The G-Standaard is used in all Dutch hospitals and contains information about potential DDIs and their management.[18] The interactions included in the G-standaard are listed in the appendix (pp 17–29).

Our intervention, referred to as MiM+, provided alerts only for potential DDIs considered clinically relevant to the ICU (ie, high-risk drug combinations). An alert example is shown in the appendix (p 13). To establish clinical relevance, we applied a modified Delphi procedure with an expert panel consisting of intensivists and hospital pharmacists (among which included AK, EdJ, IMP, JtC, MH, PES, SH, and WJV), assessing the clinical relevance of 139 potential DDIs for the ICU setting. We found that 86 of 139 potential DDIs (62%) were considered clinically relevant in the ICU setting (figure 1; appendix pp 30–32). For nine potential DDIs, agreement on clinical relevance was not reached in the Delphi study (appendix p 33). This study is described elsewhere.[16] The adaptation to MiM+ differed for ICUs already using the MiM (n=5) and ICUs not using the MiM (n=4).

For ICUs without MiM, the MiM+ was installed and configured by ItéMedical according to the Delphi results: potential DDI alerts for drug combinations deemed high risk were turned on. Alerts for drug combinations deemed low yield were kept off.

For ICUs already using MiM, the procedure was similar: alerts for drug combinations assessed as high risk in the Delphi study were turned or left on, alerts for drug combinations deemed as low yield were turned or left off. If ICUs used potential DDI alerts for drug combinations that were not evaluated in our Delphi study or alerts for duplicate orders, or both, then these were left on, because withholding these alerts might potentially negatively affect patient safety. For the nine potential DDIs without agreement on clinical relevance, the ICUs were permitted to decide whether to turn alerts on or off, given their patient population profile.

The intervention was delivered at the ICU level. The potential DDI alerts were targeted at physicians, because in the Dutch ICU they are the only prescribers. We

provided on-site training about MiM+ at the start of the intervention.

Outcomes

The primary outcome was the number of administered high-risk drug combinations per 1000 drug administrations per patient. Secondary outcomes were the length of stay in the ICU and the proportion of appropriately monitored high-risk drug combinations.

An administered high-risk drug combination was defined as the administration of an interacting drug combination that was considered clinically relevant in the ICU setting, henceforth referred to as a high-risk drug combination. Appropriate monitoring was defined as monitoring according to the instructions in the G-Standaard.

The monitoring strategies for the top 15 most common high-risk drug combinations, and evaluation method and definition of appropriate monitoring, are explained in the appendix (pp 35–36).

To enable comparison with other studies, we also reported the proportion of patients with at least one high-risk drug combination and the number of high-risk drug combinations per patient. Additionally, the appendix (pp 37–39) reports the proportion of patients with at least one drug combination, and the number of drug combinations per patient (including both high-risk and low-yield drug combinations).

Data collection

To evaluate the effect of the intervention, we used routinely recorded medication administrations, ECG data, and laboratory data from MetaVision. We linked these to the NICE Registry to obtain patient characteristics such as age, comorbidities, and severity of illness for all patients admitted to the ICU during the study period. Linking with the NICE Registry also served as a validation step, because the NICE Registry provides continuous and comprehensive registration of all ICU admissions from participating ICUs and thoroughly validate the data. Data were collected at the admission level with a coded admission number as the identifier (appendix p 14).

Detection of high-risk drug combinations

To detect potential DDIs in the drug administration data, a computerised algorithm was developed on the basis of the G-Standaard. In the algorithm, we defined a potential DDI as the administration of two drugs known to interact, administered within a 24-h interval. The algorithm was applied to all included patients. Only drugs that were actually administered were considered. All drugs with a systemic route of administration were considered. We validated the algorithm through unit testing (appendix p 15).

Statistical analysis

To calculate the power of our stepped-wedge trial, the statistical software PASS 15·0.4 was used. We estimated a relative reduction of 20% of the number of high-risk drug combinations. According to a systematic review assessing the effects of information technology interventions on DDI-related outcomes, relative reductions ranged from 15 to 29%.[9] On the basis of a preliminary analysis, the number of high-risk potential DDIs per 1000 medication administrations was estimated at 42·0 (event rate). With a relative reduction of 20%, the event rate after the intervention was estimated at 33·6. A senior intensivist involved in the study (DAD), as an indicator of face validity, considered a 20% reduction to be clinically relevant. Calculations showed that 83% power was required to detect a relative reduction of 20%, considering an estimated intra-cluster correlation of 0·12, which was based on previous randomised controlled trials on different outcomes with data from the NICE Registry. The power calculations were based on the Poisson distribution of the primary outcome, the test statistic used was the two-sided Wald Z test, and the significance level of the test was set at 0·05 (appendix p 16).

Analyses in this study were performed on an intention-to-treat basis. Continuous variables were presented as mean and SD if they were normally distributed, or median and IQR if otherwise distributed. Normality was tested with a Shapiro–Wilks test. Categorical variables were presented as numbers and percentages. For hypothesis testing, a probability of less than 0·05 was considered statistically significant. All statistical tests were two-sided. The R statistical software environment version 4.0.3 was used with the following packages: lme4 (version 1.1–31), lmerTest (version 3.1–3), MASS (version 7.3–58.1), tidyverse (version 1.3.2), stats (version 4.2.1), and glmmTMB (version 1.1.7).

To assess the effect of the MiM+ on the primary and secondary outcomes, we used various generalised linear mixed-effects models with random intercepts for each ICU, except for the secondary outcome of appropriate monitoring where the group differences were compared with a χ^2 test. For the primary outcome we used the negative binomial distribution family and the log link function, because the Poisson models showed over-dispersion. Variables were spline-transformed if needed to satisfy model assumptions. The models for the secondary outcomes are shown in the appendix (pp 37–39). To decide whether adjusting for temporal effects or the previous use of the MiM was necessary, we assessed the effect of time and of previous MiM use in the control group and intervention group separately, independent of the effect of the intervention. In both groups, the effect of time as well as the effect of previous MiM use were not significant. Therefore, we did not adjust for temporal effects or previous MiM use.

We used a null model, M0, without adjustments. Model M1 was adjusted for variables that were significantly different between the intervention and control group. On the basis of a hospital pharmacist's and intensivist's expertise (JEK and DAD), model M2 was adjusted for the

prognostic factors age, sex, admission type, cardiovascular disease, immunodeficiency, and Acute Physiology And Chronic Health Evaluation IV (APACHE IV) score, because these could affect the number of high-risk drug combinations.

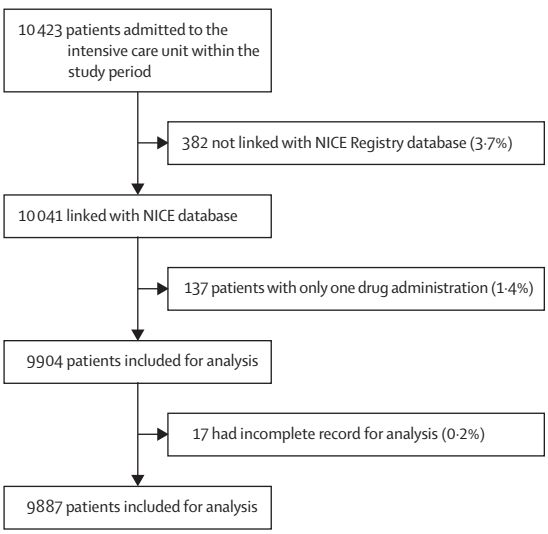

Figure 2: **Flow of patient inclusion**
NICE=National Intensive Care Evaluation.

	Control group (n=5534)	Intervention group (n=4353)
Age, years*		
Mean	63·2 (15·3)	63·2 (15·9)
Median	66·0 (55–74)	66·0 (55–75)
Sex		
Female	2114 (38·2%)	1695 (38·9%)
Male	3420 (61·8%)	2658 (61·1%)
APACHE IV score*		
Mean	57·2 (27·6)	56·5 (27·1)
Median	51·0 (38–71)	51·0 (37–70)
Admission type		
Medical	2480 (44·8%)	2078 (47·7%)
Emergency surgical	670 (12·1%)	451 (10·4%)
Elective surgical	2384 (43·1%)	1824 (41·9%)
Chronic conditions		
Chronic renal failure	286 (5·2%)	252 (5·8%)
Chronic obstructive pulmonary disease	543 (9·8%)	580 (13·3%)
Respiratory failure	182 (3·3%)	139 (3·2%)
Cardiovascular disease	174 (3·1%)	113 (2·6%)
Cirrhosis	89 (1·6%)	53 (1·2%)
Haematological malignancy	92 (1·7%)	74 (1·7%)
AIDS	3 (0·1%)	1 (<0·1%)
Immunodeficiency	586 (10·6%)	487 (11·2%)

Data are n (%), mean (SD), or median (IQR). APACHE IV=Acute Physiology And Chronic Health Evaluation IV. *Age and APACHE IV score were not normally distributed and therefore the median and IQR were reported. For completeness we also reported the mean and SD.

Table 1: **Patient characteristics**

Deviations from the protocol

On four points, we deviated from the protocol. First, we specified that we would use generalised estimating equations to correct for clustering. However, because mixed-effects models better handle variations in effect per cluster, because those are modelled separately, we used mixed-effects models to correct for clustering. Both methods are appropriate for clustering adjustment. Second, we specified that patients with any drug administered would be included. After contemplation we decided to include only patients with at least two administered drugs (98·6% [9904/10 041]), because only these patients could be exposed to an interaction. Third, we did not evaluate the over-ride rate of high-risk drug combination alerts as a secondary outcome. During the preparation phase of the trial, we gained a more comprehensive understanding of the MiM functionality. We learned that over-ride data were not reliable for assessing whether our intervention resulted in behaviour change. In the MiM, prescribers might click on "cancel" just to dismiss an alert, or might click on "prescribe anyway" but initiate appropriate action later. Therefore, we refrained from collecting alert-related data. Fourth, we did not assess adverse drug events related to DDIs during the trial. Assessing adverse drug events requires patient chart reviews and causality assessments, for which a long period of time and high number of clinical experts are needed, and therefore was unfeasible during the trial. Instead, we conducted a small-scale study after the trial to explore a novel method for measuring adverse drug events related to DDIs on the basis of electronic triggers.[19]

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Nine of the 12 ICUs using MetaVision agreed to participate in this study. Three ICUs could not participate because their hospital was migrating to another hospital-wide electronic health record system. The nine participating ICUs had an overall capacity of 156 beds, and 11 200 admissions (median 854; IQR 793–1785) combined yearly, according to data from the NICE Registry from 2017. One ICU was situated in a university hospital. Regarding the nine potential DDIs without agreement on clinical relevance, the ICUs mostly chose to turn alerts on (appendix p 33).

10 423 patients admitted to the ICU between Sept 1, 2018, and Sept 1, 2019, were included. Of those, 10 041 (96·3%) were linked with the NICE Registry data. The other 382 patients (3·7%) were excluded, because they did not match the inclusion and exclusion criteria of the NICE Registry such as excluding patients admitted for less than 4 h. Subsequently, 137 patients (1·3%) were excluded because they had less than two drug

administrations, and 17 patients (0·2%) were excluded because of missing data, resulting in a final dataset of 9887 patients (figure 2). Table 1 shows the patient characteristics of included patients, divided between the control and intervention groups. The Shapiro–Wilks normality test for age and APACHE IV score were significant (p<0·0001), hence these variables were reported with their median and IQR. Admission types and the occurrence of the chronic condition chronic obstructive pulmonary disease (COPD) varied between the groups. There were slightly more patients admitted for medical reasons in the intervention group, including more patients with COPD, and slightly fewer patients admitted for emergency or elective surgical reasons, compared with the control group. Although the differences were small, we corrected for the differences in admission type and COPD comorbidity in model M1.

In the 9887 included patients, a total of 199 148 drug administrations were identified, with a median number of drug administrations per patient of 15 (IQR 10–24). The median number of high-alert medications according to the Institute of Safe Medical Practices was 4 (2–8) and 95·1% (9400/9887) of included patients had at least one high-alert drug administered. Of all patients, 8073 high-risk drug combinations were detected, corresponding to 59 types of combinations. On average, patients had 0·82 high-risk drug combinations, and 34·9% (3454/9887) of patients were exposed to at least one high-risk drug combination. The top three high-risk drug combinations identified in all included patients consisted of: combinations of two QT-prolonging agents (ie, agents that prolong the interval between the Q and T waves of the heartbeat), bearing the potential risk of cardiac arrhythmias (73·2% [5907/8073]); combinations of non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids, bearing the potential risk of gastrointestinal bleeding (15·9% [1280/8073]); and combinations of NSAIDs and serotonergic agents (1·5% [124/8073]) and NSAIDs and salicylic acid (up to 100 mg; 1·5% [119/8073]), also carrying the potential risk of gastrointestinal bleeding.

A breakdown of the number of patients per month per ICU is shown in the appendix (p 34). During the intervention period, no changes to MiM+ were made in any participating ICU.

In the control group of 5534 patients, 5062 high-risk drug combinations were detected in 2122 patients (38·3%). In the intervention group of 4353 patients, 3011 high-risk drug combinations were detected in 1332 patients (30·6%). Figure 3 depicts the top 15 most frequently occurring high-risk drug combinations and compares the percentage of patients with these combinations between the control and the intervention group. The combination of two QT-prolonging agents had the largest decrease of high-risk drug combinations in the control group (1589 of 5534; 28·7%) compared with the intervention group (930 of 4353; 21·4%) of all combinations.

The mean number of high-risk drug combinations per 1000 drug administrations per patient was 35·6 (SD 65·0) in the control group compared with 26·2 (53·4) in the

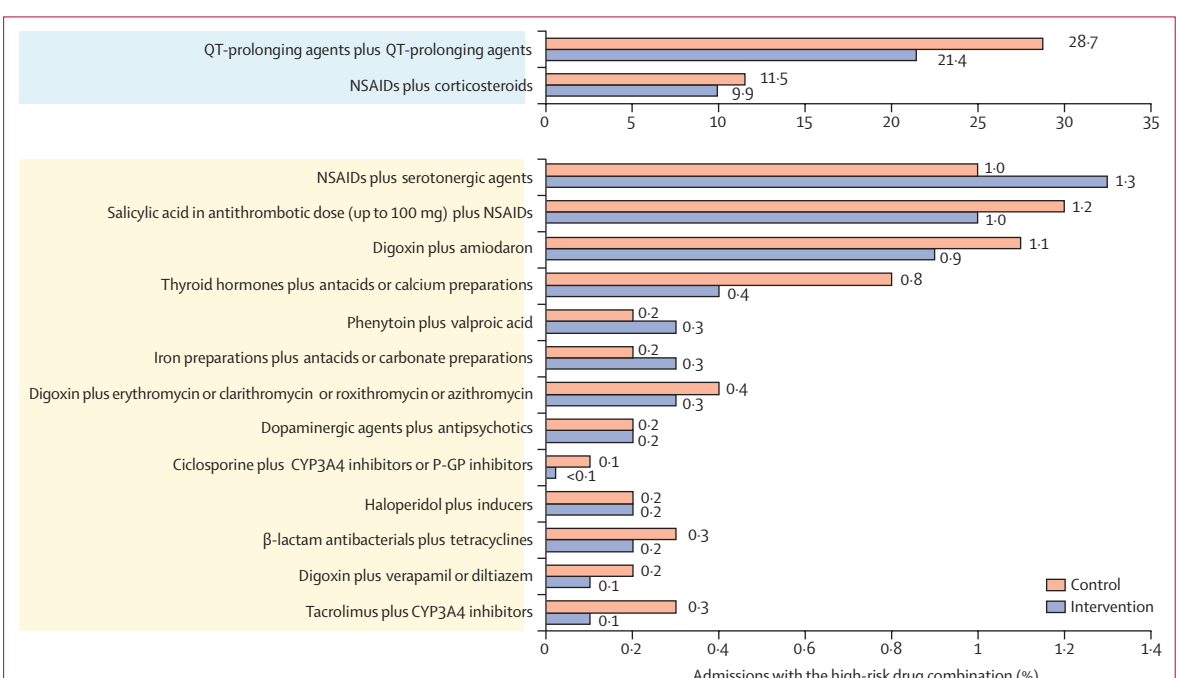

Figure 3: **Comparison of the percentage of patients with a high-risk drug combination for the 15 most frequent types of high-risk drug combinations in the intervention and control group**

Please note the different scales used for the top two and bottom 13 types of drug combinations. NSAIDs=non-steroidal anti-inflammatory drugs.

intervention group. The median was 0 (IQR 0–38·5) in the intervention group, compared with 0 (0–51·7) in the control group.

We used a generalised linear mixed-effects model to assess the effect of our intervention on the primary outcome. Random intercepts were normally distributed and the relationship between all covariates and the outcome was adequate after spline transformation of age. Aside from the unadjusted M0 model, we adjusted for prognostic factors, providing a robust analysis. On the basis of differences in the data, model M1 was adjusted for COPD comorbidity and admission type, because these two variables varied slightly but significantly between the intervention and control group. Model M2 was adjusted for age, sex, admission type, cardiovascular disease, immunodeficiency, and APACHE IV score. Table 2 shows the results of the models.

In all models, the number of high-risk drug combinations per 1000 drug administrations per patient was lower in the intervention group compared with the control group. In M0, the MiM+ intervention led to a 12% reduction (95% CI 6–19%; p=0·0004) in the number of high-risk drug combinations per 1000 drug administrations per patient. In M1, the MiM+ intervention led to a 14% reduction (8–20%; p<0·0001), and in M2 the MiM+ intervention led to a 12% reduction (5–18%; p=0·0008).

The secondary outcomes showed that the MiM+ intervention led to a 6–10% decrease in ICU length of stay in M0 (95% CI 5–14%; p=0·0021), M1 (4–13%; p<0·0001), and M2 (2–10%; p<0·0001). In addition to the primary outcome, the MiM+ intervention led to a 10–14% decrease in the number of high-risk drug combinations per patient in M0 (95% CI 5–20%; p=0·0013), M1 (6–21%; p=0·00082), and M2 (2–17%; p=0·013) , and an 11–14% decrease in the proportion of patients with at least one high-risk drug combination in M0 (4–21%; p=0·0042), M1 (6–22%; p=0·0017), and M2 (2–20%; p=0·020).

Regarding appropriate monitoring, seven types of high-risk drug combinations of the top 15 combinations had monitoring strategies that were feasible to evaluate based on our data sources, for example by therapeutic drug monitoring, adding gastric protection, and ECG ordering (appendix pp 35–36). These seven types accounted for 7642 high-risk drug combinations (94·7% of all 8073 high-risk drug combinations). In the intervention group, the proportion of appropriately monitored high-risk drug combinations was 44·0% (1240 of 2820) compared with 35·5% (1714 of 4822) in the control group. Therefore, the proportion of appropriately monitored high-risk drug combinations was 9% higher (95% CI 6–11%; p<0·0001) in the intervention group compared with the control group. Detailed results on all secondary outcomes are shown in the appendix (pp 37–39).

	Variable	Estimated incidence rate ratio	95% CI lower bound	95% CI upper bound	p value
Unadjusted M0	MiM+	0·88	0·81	0·94	0·0004*
Adjusted M1	MiM+	0·86	0·80	0·92	<0·0001*
Adjusted M2	MiM+	0·88	0·82	0·95	0·0008*

Model M1 was adjusted for admission type (medical, emergency surgical, or elective surgical) and the presence of chronic obstructive pulmonary disease. Model M2 was adjusted for age, sex, admission type, Acute Physiology And Chronic Health Evaluation IV score, presence of cardiovascular disease, and presence of immunodeficiency. The result was considered significant when p<0·05. MiM=Medication Interaction Module. *Significant result.

Table 2: **Output for the unadjusted and adjusted generalised linear mixed-effect models**

Discussion

MiM+ led to a 12–14% decrease in the number of high-risk drug combinations per 1000 drug administrations per patient, even after adjusting for clustering and prognostic factors. Secondary outcomes showed that the MiM+ intervention led to a decrease in length of stay in the ICU and an increase in appropriately monitored high-risk drug combinations. These findings advance the endeavour of mitigating the risks associated with drug combinations, promoting the avoidance of high-risk combinations whenever feasible. In cases where such combinations are necessary, these findings underscore the importance of prescribing them with a better understanding of the potential consequences and using diligent monitoring measures to ensure patient safety.

To our knowledge, no previous studies have evaluated the effect of tailoring potential DDI alerts to the ICU setting on high-risk drug combination frequency, patient monitoring, or ICU length of stay. According to Shahmoradi and colleagues[20] there has not been much research on the effect of CDSSs on patient outcomes. There are studies, outside the ICU, evaluating the effect of optimising CDSS drug alerts on process and practitioner outcomes. Helmons and colleagues[21] report that suppressing low-yield alerts decreased the number of alerts by 55%, and the time spent on potential DDI checking by 45%. Parke and colleagues[22] report that re-categorising the severity levels of potential DDI alerts decreased alert over-rides by 6%. Paterno and colleagues[23] showed that tiering alerts by severity increased potential DDI alert compliance. These results show that optimising the CDSS's potential DDI content might improve CDSS effectiveness.

We detected on average 0·82 high-risk drug combinations per patient in all included patients. 34·9% (3454 of 9887) of all included patients were exposed to at least one high-risk drug combination. For high-risk drug combinations we did not find studies suitable for comparison. For potential DDIs in general, our findings were consistent with other studies, which report 1–5 potential DDIs per patient, and 58% of patients in the ICU having a potential DDI.[24]

This study has several strengths. First, this was a large, multicentre study with a methodologically strong study design—namely, the stepped-wedged randomised

controlled study design.[17] Second, the number of patients evaluated per ICU was large. Third, using drug administrations instead of prescriptions to detect high-risk drug combinations ensured that patients were actually exposed to these combinations. Fourth, which drug combinations were considered as high risk was established in a Delphi study by an expert panel of intensivists and hospital pharmacists.[16] Fifth, in addition to evaluating a high-risk drug combination frequency, we investigated whether intensivists monitored the patients exposed to high-risk drug combinations appropriately, which is an important effect of CDSSs. Finally, unlike other studies evaluating the effect of drug alerts on process and prescriber outcomes, we evaluated a patient-related outcome: the effect on length of stay in the ICU.

This study also has limitations. First, other factors influencing CDSS effectiveness, such as alert timing and design, were not investigated in this study.[25] However, because all ICUs in this study used the same CDSS and patient data management system, attributing the causal effect of the intervention to tailoring the potential DDI alerts seems reasonable. Second, the number of ICUs in our study was small, which could lead to decreased power.[26] However, the power was sufficient to detect a significant effect. Moreover, because of the small number of ICUs and the nature of the stepped-wedge design, evaluating ICUs individually was not feasible. Third, the slight differences in admission type and the occurrence of COPD between the control and intervention group might have led to slightly more high-risk drug combinations in the intervention group than the control group, and a difference in the frequency of specific high-risk drug combinations between the groups. However, these differences are very small, and we have adjusted for these differences in model M1. Fourth, we did not measure possible patient harm associated with high-risk drug combinations. We did however assess the effect of our intervention on length of stay in the ICU, which was lower in the intervention group. This was not due to mortality, because ICU mortality was similar between the control and intervention groups when corrected for relevant confounders including disease severity (results not shown). Because length of stay in the ICU was a secondary outcome, we did not investigate the mechanisms contributing to its effects, which could be investigated in future research. Finally, this study was done with only one CDSS. Nevertheless, knowledge about which drug combinations are perceived as high risk in the ICU is transferrable to other CDSSs and patient data management systems. We expect that our high-risk drug combinations list to tailor potential DDI alerts is beneficial to other ICUs, also outside the Netherlands, because frequently occurring high-risk drug combinations are similar between countries.[27]

Our results are relevant to clinicians, hospital pharmacists, CDSS developers, hospital managers, quality-of-care officers, and researchers in the ICU setting. Other ICUs could use our list of high-risk drug combinations to tailor their potential DDI alerts and improve CDSS effectiveness. Additionally, our results might encourage others to establish a set of high-risk drug combinations for patients in other specific settings, such as neonatology, paediatrics, or oncology settings.

Regarding next steps, assessing adverse drug events related to high-risk drug combinations in patients in the ICU would be a valuable patient-centric measure to include in future studies on CDSS effectiveness. According to Fitzmaurice and colleagues,[24] few studies have investigated that topic, probably because it requires comprehensive and time-consuming patient chart reviews and formal causality assessment. Using electronic triggers to capture adverse drug events related to high-risk drug combinations might partly alleviate this issue.[19] Furthermore, potential DDI alerts could be further improved to decrease alert fatigue. For example, potential DDI alerts could be personalised by incorporating specific patient risk factors such as age, comorbidities, or renal and liver function; and be further optimised by adding variables to the potential DDI algorithm logic such as laboratory results, ECG results, or prescribed prophylactic treatments (eg, a proton pump inhibitor).[28,29] Additionally, being able to start monitoring actions directly from the potential DDI alert window could help prevent patient harm. Lastly, in this study we used a 24-h interval to detect potential DDIs. Exploring potential DDI-specific time intervals on the basis of drug properties and patient factors merits future research. Our cluster randomised stepped-wedge trial showed that ICU-tailored potential DDI alerts significantly reduced the number of high-risk drug combinations, improved monitoring, and decreased length of stay in the ICU.

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Contributors

AA-H, DAD, JEK, NFdK, SE, and TB conceptualised and designed the study and contributed to the analysis and interpretation of data. AK, EdJ, IMP, JtC, MH, PES, SHWvB, SH, and WJV contributed substantially to the acquisition of data, but were not involved in the study design or analysis. All authors drafted or revised the manuscript critically. AA-H, JEK, and TB directly accessed and verified the underlying data reported in the manuscript. TB and AA-H wrote the R code for the statistical analysis. All authors saw and approved the manuscript. Each author participated sufficiently in the work to take public responsibility for appropriate portions of the content; all authors agreed to be accountable for aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. AA-H, DAD, JEK, NFdK, and TB were responsible for the decision to submit the manuscript.

Declaration of interests

NFdK and DAD declare that they are members of the NICE Registry Board. All other authors declare no competing interests.

Data sharing

The potential DDI detection algorithm can be found on github via https://github.com/tinkabakker/SIMPLIFY. The code for statistical analysis is available upon request to the corresponding author. Due to the sensitive nature of our dataset and the data sharing agreements with the participating ICUs, data can only be shared after the explicit consent of the participating ICUs upon reasonable request.

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