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Development and validation of a risk prediction model for medication administration errors in neonates: a study protocol

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ABSTRACT

Introduction

Medication administration errors (MAEs) are the most commonly occurring type of medication errors (MEs) and they are found to be more common amongst neonates as compared to adults. They also result in severe patient harm and significant economic burden to the healthcare system. Targeting and prioritizing neonates at high risk of MAEs is crucial in reducing MAEs. To the best of our knowledge, a predictive risk score identifying neonates at risk of MAEs is not yet available. Therefore, this study aims to develop and validate the risk prediction model to identify neonates at risk of MAEs.

Methods and analysis

This is a multicentre, nationwide, prospective direct observational study in which a minimum of 1,097 preparation and administration of medications are directly observed. Data such as patient characteristics, drug preparation and administration related data, and other procedures will be recorded. After each round of observation, the observer will compare his/her observations with the prescriber's medication order, hospital policies and manufacturer's recommendations to determine whether MAE has occurred. To ensure reliability, error identification will be independently performed by two raters after the completion of data collection for all study sites. Any disagreements will be discussed with the research team for consensus. To reduce overfitting and improve the quality of risk predictions, we have pre-specified a priori our analytical plan such as prespecifying the candidate predictor variables, handling of missing data and validation of the developed model. The model's performance will also be assessed. Finally, various modes of presentation formats such as a simplified scoring tool or web-based electronic risk calculators will be considered.

Ethics and dissemination

This study protocol was approved by the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia, with the identification number of NMRR-21-1484-59494 (IIR). Findings from our study will be disseminated through presentations at scientific conferences and peer-reviewed publications.

What is already known on this topic

- The aetiology of MAEs is multifactorial and complex.
- It may be caused by unsafe acts such as slips and lapses, rule- and knowledge-based mistakes, violations and/or latent conditions such as an error-producing environment due to decisions made by higher organisational levels.
- Non-adherence to policies, lack of knowledge, similar look-a-like and sound-a-alike medications, lack of nurses and lack of training are amongst the many factors contributing to MAEs in neonates.

What this study adds

- We anticipate that the newly developed model will be used to identify neonates at risk of MAEs, produce estimates of future MAEs amongst them and the risk factors commonly associated with MAEs.

How this study might affect research, practice, or policy

- We hope that the information attained will assist policymakers and stakeholders conduct timely assessments of MAEs and discussion of the need for the implementation of interventions amongst neonates at the highest risk to prevent an impending MAE.

INTRODUCTION

Medication errors (MEs) may arise throughout the medication use process which consists of prescribing, transcribing, dispensing, administration, and monitoring [1]. Medication administration errors (MAEs) were found to be the most commonly occurring error as compared to prescribing and dispensing, amounting to more than 50% of all MEs [2, 3]. MAEs were not only associated with the highest number of incidents resulting in death and severe harm as compared to the other stages of the medication use process, but they also lead to significant economic burden from the utilization of healthcare services [4, 5]. It is estimated that approximately 4000 patients may be harmed from a total of 6 million medication doses administered among hospitalized patients and this is expected to consume between USD25 and 35 million annually [6]. A systematic review of all types of MEs reported that the prevalence of MAEs amongst neonates is found to range between 31% and 63% as compared to adults which ranged between 14.6% and 41% [7].

A key aspect to a successful intervention is targeting and prioritizing patients at high risk of MEs to improve medication safety [8]. Several risk scores have been developed to identify patients at risk of MEs. Some identify MEs amongst hospitalized adults [9], at admission or discharge [10, 11]. Others specifically identify patients at risk of prescribing errors [12, 13]. The Automated Medication Error Risk Assessment System (Auto-MERAS) [14] was the only tool developed and validated to predict MAEs. However, it was developed and validated amongst hospitalized adults using incident reports extracted from the local safety reporting system. Although the use of incident reports to measure MAEs may provide rich data on the causal factors linked to MAEs, it is the least accurate method to measure MAEs as compared

to direct observation and chart review [15, 16]. Apart from that, the use of incident reports meant that major risk factors such as nurses' workload could not be analysed [14].

Given that the prevalence of MAEs amongst neonates have been reported to be as high as 94.9% [17], a validated model incorporating an extensive list of potential risk factors associated with MAEs should assist all healthcare professionals involved in the medication use process to identify at-risk neonates in a clinical setting. To the best of our knowledge, a predictive risk score to identify neonates at risk of MAEs specifically is not yet available. Therefore, this study aims to develop and internally validate the multivariable prediction model for the identification of MAEs amongst neonates using a prospective direct observational study design, and to then externally validate the model using a different data set of neonates. The usability of the risk prediction model in terms of risk stratification will also be evaluated.

METHODS

This study will be conducted in accordance to recommendations by experts for the development and validation of the model [18, 19]. The reporting of this study protocol will be guided by the checklist for multivariable prediction models, namely the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) [20].

Study design

A direct observational study which will be conducted prospectively. The preparation and administration of medications by the nurses are directly observed to detect MAEs. This direct observation study will be disguised to reduce the Hawthorne effect on the observed nurses [15].

The nurses will be informed that the observational study conducted aims to identify strategies to enhance the medication supply and distribution system and to understand the constraints of the nurses' working environment and that it is not aimed to assess their personal practices [21].

There are two stages in this study. The first stage is the identification of the predictor variables while the second stage is the prospective direct observational study. A flowchart of the development, validation and assessment of the risk prediction model is provided in figure 1.

Study setting

This study is a multicentre, nationwide study which will include Neonatal Intensive Care Units (NICUs) of five public hospitals which were purposively chosen to reflect the various categories of public hospitals in terms of specialities.

Study outcomes

The outcome of interest in this study is the occurrence of MAEs amongst neonates. MAE is defined as any deviations during the preparation and administration of medications when compared to the prescriber's medication order, hospital policies, or the manufacturer's recommendations in the product leaflet [15]. This study intends to focus on the outcome of the system in place instead of the actions of the individual observed. Hence, this definition will be employed as it does not focus on the individual's actions.

MAEs are further categorized into subcategories according to the stages of preparation and administration (Table 1). This will allow us to understand the stages where MAEs occur

especially since medications for neonates involve multiple manipulations [22]. Definitions of the subcategories of MAEs were adopted from various literature [15, 22-24].

Table 1 Definitions of subcategory of MAEs

Subcategory of MAEs	Definitions
	Preparation
Administration without a medication order	Administration of a dose for a drug to a patient without an existing medication order.
Omission	The failure to administer a dose of the prescribed drug before the next scheduled dose.
Wrong dose	Administration of a dose that is at least 10% more or 10% less than the prescribed dose.
Wrong drug	Administration of a dose for a drug which is different from the prescribed drug.
Wrong dosage-form	Administration of a dose for the correct drug in a different dosage form than the prescription.
Wrong time	A dose of drug is administered more than 60 minutes before or after the scheduled prescribed dose and more than 15 minutes before or after for emergency prescriptions.
Wrong drug-preparation	Administration of a dose for a drug which has been incorrectly formulated or manipulated during the preparation of the dose.
Extra dose	Administration of an additional dose of the prescribed drug such as the administration of a dose after the prescription has been discontinued or administration of a dose more frequently than prescribed.
Deteriorated drug	Administration of a dose for a drug that has expired or when the dosage form of the drug administered has been physically or chemically compromised.
	Administration
Wrong route	A dose of the correct drug is administered at a site that was not prescribed.

Wrong patient	Administration of a dose for the correct drug to a different patient.
Incompatibility	Administration of two or more incompatible medications concurrently in the same line without flushing in between the administrations of these medications.
Wrong rate of administration	A dose of drug is administered more than ±15% of the recommended infusion time.

Error identification will be independently performed by the two raters who are blinded to the observations collected during data collection. Disagreements between the raters will be discussed with the research team for consensus.

Data collection

The observers were trained in the direct observation method of data collection as described by Barker and McConnell [25]. Observers were trained by observing and performing practical exercises on the direct observation technique. They are required to complete and pass a written examination consisting of video simulations of drug preparation and administration by scoring at least 80%, after which they are able to conduct the observations by themselves. Observers will then perform pilot observations for three days in the ward to familiarize themselves with the procedures in the ward and to reduce the Hawthorne effect. To ensure uniform understanding of the data collection procedures, all pilot observations will be discussed with the research team. However, these pilot observations will not be used as part of the data for this study.

Written consent will be obtained from the nurses prior to data collection. Prior to the observation of the drug preparation and administration, data such as demographic (e.g. birth

weight, gender, length of stay), clinical (e.g. ventilation, diagnosis) and medication related information (e.g. name of medication prescribed, dose, frequency) will be collected using a predesigned data collection form.

The observer will closely shadow the nurses who has consented to the participation in this study throughout the medication preparation and administration round. During the observation, data related to the preparation of the medication (e.g. details of reconstitution and/or dilution such as the time of preparation, expiry, solvent, diluent), administration of the medication (e.g. time, rate, route, compatibility) and other procedures (e.g. labelling, double checking of medication administered, interruption and/or distraction) will be recorded. For ethical reasons, the observers will intervene in a non-judgemental manner if a potentially harmful error is about to reach a patient. However, this error will be included in the dataset as it is assumed that this error will reach the patient if it is not intervened by the observer.

After each round of observation, the observer will compare his/her notes with the prescriber's medication order, hospital policies, manufacturer's recommendations in the product leaflet and data published in literature to detect errors. Demographics of the nurse (e.g. years of working experience, level of education) responsible for the preparation and administration of medications will also be recorded. The clinical pharmacist at the study site will observe 10% of randomly selected drug preparations and administrations to ensure the validity and accuracy of the data collected by the observers.

Eligibility criteria

Medications prepared and administered by nurses for all routes of administrations will be included, while excluded medication administrations are (1) those administered by parents, (2) enteral feedings, parenteral nutrition and blood-derived products, (3) omission of medication administration because patient is not present in the ward during medication administration rounds or due to clinical reasons such as those lack of intravenous access or contraindications, and (4) rectal administrations, medical gases and dietary supplements. The same inclusion and exclusion criteria will be applied to the validation cohort.

Data analysis

Predictor variables

In order to develop a comprehensive method for identifying neonates at risk of MAEs, a total of 13 candidate predictor variables were identified through the following sources: (1) an extensive systematic review conducted to evaluate the available literature on the factors associated with MAEs amongst neonates [17] (2) national data containing information on the causes of MAEs amongst neonates, extracted from the Medication Error Reporting System (MERS) through the Pharmaceutical Services Programme, Ministry of Health Malaysia; and (3) expert panel consisting of one paediatrician, one clinical pharmacist with experience in the NICU and one senior nurse with an advanced diploma in Neonatology. The expert panel was established to review the predictor variables gathered from literature review and to identify other important predictor variables based on their clinical experience. Based on the systematic review, MERS and the expert panel, the identified candidate predictor variables are categorized and defined in table 2.

248 **Table 2** Candidate predictor variables identified for inclusion in the multivariable model

Candidate predictor	Definition	Variable type	Sources
	Administration related variables		
Route of administration	Route of administration for the medication administered to patient (ie. oral, parenteral)	Categorical	SR
Complexity of the medication preparation	• One step such as withdrawal of required dose from a ready-to-use preparation • Two step such as reconstitution of a drug which is then followed by the withdrawal of the required dose • Three step such as reconstitution of a drug which is then followed by the withdrawal of the required dose and finally further dilution of the dose before administration	Categorical	SR
	Working environment related variables		
Nurse to patient ratio	Nurse to patient ratio reflects the workload of a nurse	Continuous	MERS
Number of shifts in a day	Number of shifts a nurse is working within 24 hours	Continuous	MERS
Number of medications administered	Number of medications administered by the nurse at a specific scheduled drug round	Continuous	MERS
Time of administration	The time when the nurse prepare and administer the medications (ie. during office hours, after office hours)	Categorical	Expert panel
	Patient related variables		
Types of ventilation	Administration of ventilatory support with / without using an invasive artificial airway such as non-invasive ventilation and invasive ventilation	Categorical	SR
Birth weight	The body weight of the neonate at birth. Classification of prematurity based on the birth weight: extremely low birth weight (< 1000gm), very low birth	Categorical	SR

	weight (< 1500gm) and low birth weight (< 2500gm)		
	Individual related variables		
Years of experience	Number of years working as a nurse at study site	Continuous	Expert panel
Level of education	Educational level of the nurse	Categorical	SR
Double checking	The medication prepared for administration is counterchecked by another individual	Categorical	Expert panel
Labelling	Medication prepared and administered is labelled according to local policies	Categorical	MERS & expert panel
Interruptions and distractions	Stimuli which disrupt the nurses during the preparation and administration of the medications	Categorical	SR, MERS & expert panel

MERS = medication error reporting system, SR = systematic review

Missing data

Although we do not expect our predictors to have a considerable amount of missing data, some will inevitably occur. Hence, strategies to deal with missing data will be determined based on the predictors. Predictors with more than 20% missing data will be excluded [26]. Multiple imputations by chained equations will be performed to impute missing values for predictors with data missing at random. For each predictor variable, five multiple imputation datasets will be created to obtain an overall estimate as recommended by Rubin and Schenker [27]. A sensitivity analysis using the pattern-mixture model approach will then be employed to ensure that the data is not missing at random [28].

Model development

The categorization of selected predictor variables into groups will be avoided to minimize the loss of potentially predictive information [29]. To ensure that there are no outliers, boxplots and descriptive statistics will be employed to examine continuous variables. Correction to the values obtained will be done if possible, or otherwise these values will be set to missing.

A univariate analysis will then be conducted to identify the variables significantly associated with the occurrence of a MAE [30]. Variables with $p < .25$ will be considered for inclusion into the multivariable model. A higher significance value is used to overcome a drawback of univariate analysis where during univariate analysis, individual variables that are weakly associated with the outcome are overlooked although they may contribute significantly when combined [30].

The predictor variables will then undergo multivariable logistic regression. Categories with limited data will be combined to meet the assumptions of regression. Backward stepwise selection will be used as it is preferred method in selecting the predictors to be included in the model as compared to forward stepwise selection which has been found to result in a model where potentially meaningful predictors may have been erroneously trimmed and that may be difficult to reproduce [31]. Variables will be removed or retained in the model according to its statistical significance. Statistical significance of $p < 0.20$ will be conservatively used for inclusion instead of a small significance level (e.g. $p < 0.05$) to prevent the omission of important predictor variables and removing less significant variables that may be practically and clinically relevant [30]. Overfitting models may occur regardless of the choice of a smaller or larger significance value, especially if a smaller dataset is used. Overfitting models are

models which are too specific to the development sample but are not generalizable in new but similar individuals. Therefore, we will employ the least absolute shrinkage and selection operator (LASSO) to reduce overfitting during the model building process [31, 32]. In addition, subsequent internal validation may also provide insight on the model being unstable or overfitted [33]. Multicollinearity will also be assessed using the variance inflation factor to identify predictor variables who have strong correlation with each other [34]. We will then explore the interactions between variables in the model by adding a new term to the model when assessing interactions for each two predictors. The interaction effects resulting from the combination of predictors is determined by the coefficient of this new term.

Model performance

The model's performance will be evaluated by its calibration and discrimination [35]. The discriminatory ability of the model which is the ability of the model to differentiate between patients at risk of MAE and patients who are not at risk, will be assessed using the area under the receiver operating characteristic (ROC) curve. Calibration is an assessment of the agreement between observed outcomes in the data and predicted outcomes of the model. It will be assessed graphically through the inspection of calibration plots and the Hosmer-Lemeshow test [36].

Model validation

Internal validation of the prediction model will be assessed using the bootstrapping re-sampling technique to ensure that the prediction models are reproducible. This will provide insight into the model potentially being too optimistic or overfitted [37]. Bootstrap samples utilizing at

least 500 bootstrap resampling procedures will be drawn. The difference in the discrimination and calibration between each bootstrap model and the original model developed will be averaged to adjust for optimism [32]. Bootstrapping also provides a shrinkage factor which allow the adjustment of the estimated regression coefficients in the final model overfitting. A global shrinkage factor of greater than 0.9 is desired [38].

Model presentation

The final model will be presented for both the derivation and validation samples. As predictions are the main interest, the full prediction model which consist of the regression coefficients and the model intercept will be published. Various modes of presentation formats such as a simplified scoring tool or web-based electronic risk calculators will be considered.

Study progress

The first stage of the study, which is the identification of the predictor variables while the has been completed while the second stage which is the prospective direct observational study, is in progress.

Sample size

Sample size calculations following the four criterions for binary outcomes recommended by Riley et al are performed to minimize overfitting and to ensure that precise predictions of the developed model [39]. We have specified the anticipated outcome proportion as 0.31 [40], a total number of candidate predictors of 20, a global shrinkage factor of 0.9 and the anticipated

model performance as defined by Cox-Snell R^2 (R^2_{CS}) as 0.15 [39]. Taking these criterions into considerations, the minimum sample size required to ensure all criterions are fulfilled is 1,097 drug administrations.

Ethics and dissemination

This study protocol was approved by the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia, with the identification number of NMRR-21-1484-59494 (IIR). Findings from our study will be disseminated through presentations at scientific conferences and peer-reviewed publications.

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Contributors

JHB, NMS, AA, NAMT and CMP conceptualised the study. JHB and ZS designed the statistical plan for this study, which was reviewed by all authors. JHB drafted the manuscript, which was reviewed by all authors. All authors read, contributed and approved the final version of the manuscript.

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Competing interests

None declared.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Patient consent for publication

Not applicable.

Ethics approval

This study received ethics approval from the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia (NMRR-21-1484-59494 (IIR). Participants provided written informed consent to be observed in this study.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

Data sharing is not applicable since no datasets were generated or analysed in this study.

Open access

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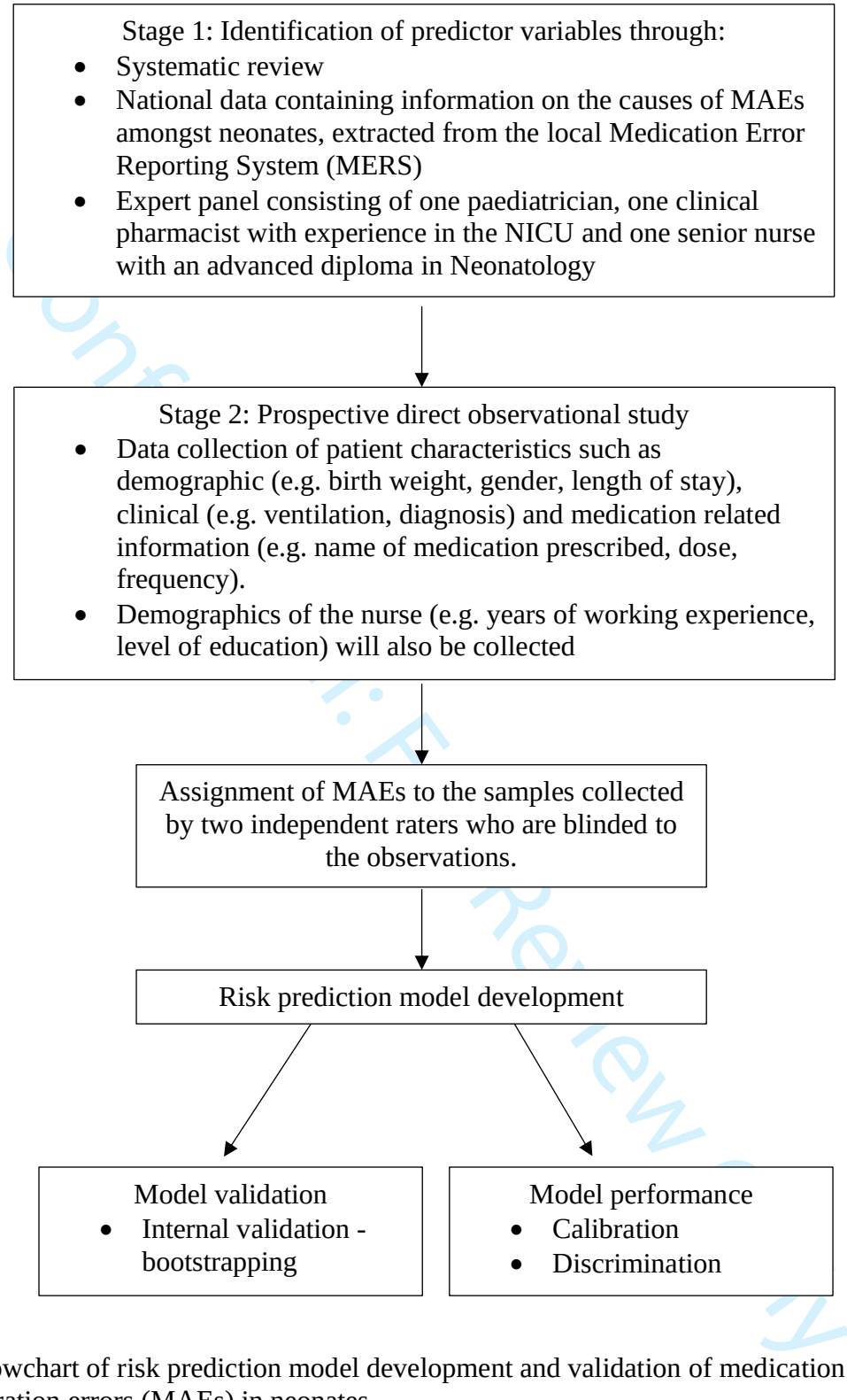

Fig 1 Flowchart of risk prediction model development and validation of medication administration errors (MAEs) in neonates

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Development and validation of a risk prediction model for medication administration errors amongst neonates in the neonatal intensive care unit: a study protocol

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Development and validation of a risk prediction model for medication administration errors amongst neonates in the neonatal intensive care unit: a study protocol

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ABSTRACT

Introduction

Medication administration errors (MAEs) are the most common type of medication error. Furthermore, they are more common amongst neonates as compared to adults. MAEs can result in severe patient harm, subsequently causing a significant economic burden to the healthcare system. Targeting and prioritising neonates at high risk of MAEs is crucial in reducing MAEs. To the best of our knowledge, there is no predictive risk score available for the identification of neonates at risk of MAEs. Therefore, this study aims to develop and validate a risk prediction model to identify neonates at risk of MAEs.

Methods and analysis

This is a prospective direct observational study that will be conducted in five neonatal intensive care units. A minimum sample size of 820 drug preparations and administrations will be observed. Data including patient characteristics, drug preparation- and administration-related information, and other procedures will be recorded. After each round of observation, the observers will compare his/her observations with the prescriber's medication order, hospital policies and manufacturer's recommendations to determine whether MAE has occurred. To ensure reliability, the error identification will be independently performed by two clinical pharmacists after the completion of data collection for all study sites. Any disagreements will be discussed with the research team for consensus. To reduce overfitting and improve the quality of risk predictions, we have pre-specified a priori the analytical plan i.e. prespecifying the candidate predictor variables, handling missing data and validation of the developed model. The model's performance will also be assessed. Finally, various modes of presentation formats such as a simplified scoring tool or web-based electronic risk calculators will be considered.

Ethics and dissemination

This study protocol was approved by the Medical Research and Ethics Committee, Ministry of Health Malaysia (NMRR-21-1484-59494 [IIR]) on 24th January 2022 and the Medical Ethics Committee, Universiti Kebangsaan Malaysia on 10th February 2022. Findings from our study will be disseminated through presentations at scientific conferences and peer-reviewed publications.

What is already known on this topic

- The aetiology of MAEs is multifactorial and complex.
- It may be caused by unsafe acts such as slips and lapses, rule- and knowledge-based mistakes, violations, and/or latent conditions such as an error-producing environment due to decisions made by higher organisational levels.
- Non-adherence to policies, lack of knowledge, similar look-a-like and sound-a-alike medications, lack of nurses and lack of training are amongst the many factors contributing to MAEs in neonates.

What this study adds

- We anticipate that the newly developed model can be used to identify neonates at risk of MAEs, as well as generate estimates of future MAEs amongst them and the risk factors commonly associated with MAEs.

How this study might affect research, practice, or policy

- We hope that the information attained from this study will assist policymakers and stakeholders to conduct timely assessments of MAEs. It can also guide the discussion

among stakeholders on the need for the implementation of interventions to prevent MAEs amongst high-risk neonates.

INTRODUCTION

Medication errors (MEs) may arise throughout the medication use process which consists of prescribing, transcribing, dispensing, administration, and monitoring [1]. Medication administration errors (MAEs) are the most commonly occurring error as compared to prescribing and dispensing, amounting to more than 50% of all MEs [2, 3]. Furthermore, MAEs are associated with the highest number of incidents resulting in death and severe harm than other stages of the medication use process. As a result, they contribute to significant economic burden from the utilisation of healthcare services [4, 5]. It is estimated that approximately 4,000 hospitalised patients are harmed by a total of six million medication doses administered, costing between USD25 and 35 million annually in the United States [6]. A systematic review of all types of MEs reported that the prevalence of MAEs amongst neonates ranged between 31% and 63% as compared to paediatric and adult patients which ranged between 12.8% to 73% and 14.6% to 41% respectively [7].

A key aspect of a successful intervention is targeting and prioritising patients at high risk of MEs to improve medication safety [8]. Several risk scores have been developed to identify patients at risk of MEs, either amongst hospitalized adults [9], at admission or during discharge [10, 11]. Others risk scores specifically identify patients at risk of prescribing errors [12, 13]. The Automated Medication Error Risk Assessment System (Auto-MERAS) [14] was the only developed and validated tool for the prediction of MAEs. However, it was developed and validated amongst hospitalised adults based on incident reports extracted from the local safety reporting system. Although the use of incident reports to measure MAEs may generate rich information on the causal factors linked to MAEs, it is the least accurate method to measure MAEs as compared to direct observation and chart review [15, 16]. Apart from that, the use of

incident reports meant that major risk factors such as nurses' workload could not be analysed [14].

Given that the prevalence of MAEs amongst neonates has been reported to be as high as 94.9% [17], a validated model incorporating an extensive list of potential risk factors associated with MAEs would facilitate the healthcare professionals involved in the medication use process to identify at-risk neonates in the neonatal intensive care unit (NICU). To the best of our knowledge, a predictive risk score to identify neonates at risk of MAEs specifically is not yet available. Therefore, this study aims to develop and internally validate a multivariable prediction model for the identification of MAEs amongst neonates using a prospective direct observational study design. The model will also be externally validate by using data from a different set of neonates. The feasibility of using the risk prediction model for risk stratification will also be evaluated.

METHODS

This study will be conducted in accordance with the recommendations for model development and validation [18, 19]. The study protocol will reported based on the checklist for multivariable prediction models, namely the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) [20].

Study design

A direct observational study for the development of the risk prediction model will be conducted prospectively between April 2022 and April 2023. The subsequent development and validation

of the model will be performed until April 2024. The preparation and administration of medications by the nurses are directly observed to detect MAEs. A flowchart of the development, validation and assessment of the risk prediction model is provided in Figure 1.

Study setting

This national-level multicentre study will include the NICUs of five public hospitals. All hospitals under the Ministry of Health Malaysia (MOH) are classified as state hospitals, major specialist hospitals, minor specialist hospitals, or non-specialist hospitals. The subspeciality of neonatology is only available in the state and major specialist hospitals. There are five regions in Malaysia, i.e. Northern, Central, Southern, East Coast, and East Malaysia. One hospital was chosen from each of these regions. The five selected public hospitals consisting of two state hospitals and three major specialist hospitals were purposively chosen to include both categories of public hospitals providing neonatology subspecialty. The total bed capacity of the NICUs in these five public hospitals ranges from 16 to 38 beds.

Study outcomes

In this study, the outcome of interest is the occurrence of MAEs amongst neonates. MAE can be defined as any deviations during the preparation and administration of medications when compared to the prescriber's medication order, hospital policies, or the manufacturer's recommendations in the product leaflet [21]. The main intention of this study is to focus on the impact of the outcomes on the system in place instead of the actions of the individual observed. Hence, the above-mentioned definition will be employed as it does not focus on the individual's actions.

MAEs are further categorized into subcategories according to the stages of preparation and administration (Table 1). This will provide a better understanding of the stages where MAEs occur, especially since medication preparation for neonates involves multiple manipulations [22]. The definitions of the subcategories of MAEs were adopted from various literature [15, 21, 23] and reviewed by an expert panel consisting of two academicians with at least 20 years of experience and two pharmacists with at least 8 years of experience.

Table 1 Definitions of the subcategories of MAEs

Subcategory of MAEs	Definitions
	Preparation
Administration without a medication order	Administration of a dose for a drug to a patient without an existing medication order.
Omission	The failure to administer a dose of the prescribed drug before the next scheduled dose.
Wrong dose	Administration of a dose that is at least 10% more or 10% less than the prescribed dose.
Wrong drug	Administration of a dose for a drug that is different from the prescribed drug.
Wrong dosage-form	Administration of a dose for the correct drug in a different dosage form than the prescription.
Wrong time	A dose of the drug is administered more than 60 minutes before or after the scheduled prescribed dose and more than 15 minutes before or after for emergency prescriptions.
Wrong drug-preparation	Administration of a dose for a drug that has been incorrectly formulated or manipulated during the preparation of the dose.
Extra dose	Administration of an additional dose of the prescribed drug such as the administration of a dose after the prescription has been discontinued or administration of a dose more frequently than prescribed.

Deteriorated drug	Administration of a dose for a drug that has expired or when the dosage form of the drug administered has been physically or chemically compromised.
	Administration
Wrong route	A dose of the correct drug is administered at a site that was not prescribed.
Wrong patient	Administration of a dose of the correct drug to a different patient.
Incompatibility	Administration of two or more incompatible medications concurrently in the same line without flushing in between the administrations of these medications.
Wrong rate of administration	A dose of the drug is administered for more than ±15% of the recommended infusion time.

Data collection

Two clinical pharmacists with at least ten years of experience will act as observers to conduct the direct observations. Each round of direct observation will be performed by one observer. The observers will be trained beforehand based on the direct observation method of data collection as described by Barker and McConnell [24]. They will also be trained to observe and perform practical exercises on the direct observation technique. They are required to complete and pass a written examination (score of at least 80%) consisting of video simulations of drug preparation and administration before they can conduct the observations by themselves. Following that, they will perform pilot observations for three days in the ward to familiarise themselves with the procedures in the ward and to reduce the Hawthorne effect. The expected number of medication administrations over three days ranges from 80 to 200 medications prescribed. To ensure a uniform understanding of the data collection procedures, all pilot observations will be discussed with the research team. However, these pilot observations will not be included as part of the data for this study.

To reduce the Hawthorne effect on the observed nurses, certain disguises will be taken during data collection [15]. The nurses will be informed that the observational study conducted aims to identify the strategies to enhance the medication supply and distribution system as well as to understand the constraints of the nurses' working environment, rather than assessing their personal practices [25]. Written consent will be obtained from the nurses before data collection. Before the observation of the drug preparation and administration, identified candidate predictor variables for the development of the model, information for descriptive analysis of the samples will be collected using a predesigned data collection form, including patient-related information (e.g. age, gender, length of stay, and current diagnosis), and medication-related information for the assignment of error (e.g. name of medication prescribed, dose, and frequency).

The NICUs of the study sites are usually divided into multiple sections according to the setup of the ward and the severity of the patients. During each round of observation, one section is randomly selected and the nurse(s) involved in the drug preparation and administration in this section will be observed. The observer will closely shadow the nurses who have consented to participate in this study throughout the process. The direct observation will take place during peak medication administration times (07:00 – 22:00) on weekdays and weekends. During the observation, data related to the preparation of the medication (e.g. details of reconstitution and/or dilution such as the time of preparation, expiry, solvent, and diluent), administration of the medication (e.g. time, rate, route, and compatibility) and other procedures (e.g. labelling, double-checking of medication administered, interruption and/or distraction) will be recorded.

For ethical reasons, the observers will intervene in a non-judgemental manner if a potentially harmful error is about to reach the patient. Examples of MAEs that may be potentially harmful are the administration of a drug that has expired or deteriorated [26] and tenfold overdose [27]. In contrast, late in administering doses is not considered to be potentially harmful. In such events, the observers will follow a flowchart that outlines the measures required for an intervention (Figure 2) [28]. However, this error will be included in the dataset as it is assumed that this error will reach the patient if it is not intervened by the observer.

After each round of observation, the observer will compare his/her notes with the prescriber's medication order, hospital policies, manufacturer's recommendations in the product leaflet, and data published in the literature to detect possible MAEs. Demographics of the nurse (e.g. years of working experience and level of education) responsible for the preparation and administration of medications will also be recorded. In addition, the clinical pharmacist at each study site will conveniently select and observe 10% [29, 30] of drug preparations and administrations to ensure the validity and accuracy of the data collected by the observers . The observation will then be compared with the data collected by the observers. All observations by the clinical pharmacist and the observer must be identical for the data to be considered valid and accurate.

Error identification will be independently and individually performed by two clinical pharmacists with at least six years of clinical experience. The two clinical pharmacists are not involved in the data collection of the direct observational study. Moreover, they will be performing the assignment of errors to the samples collected separately to avoid influencing each other's decisions. Disagreements encountered during the assignment of errors to the observed samples will be discussed with the research team to reach a consensus.

Eligibility criteria

Medications prepared and administered by nurses for all routes of administrations will be included while excluded medication administrations are (1) those administered by parents, (2) enteral feedings, parenteral nutrition and blood-derived products, (3) omission of medication administration because patient is not present in the ward during medication administration rounds, (4) omissions due to clinical reasons such as those determined by the nurses (e.g. contraindications) and lack of intravenous access, (5) rectal administrations; when neonatal-specific rectal dosage forms are unavailable and the available paediatric rectal dosage form is modified to a lower dose, and (6) medical gases and dietary supplements. The same inclusion and exclusion criteria will be applied to the validation cohort.

Data analysis

Predictor variables

To develop a comprehensive method for identifying neonates at risk of MAEs, a total of 13 candidate predictor variables have been identified through the following sources: (1) an extensive systematic review conducted to evaluate the available literature on the factors associated with MAEs amongst neonates [17], (2) national data containing information on the causes of MAEs amongst neonates, extracted from the Medication Error Reporting System (MERS) through the MOH Pharmaceutical Services Programme; and (3) expert panel. The expert panel consists of a paediatrician with 14 years of clinical experience, a clinical pharmacist with 15 years of clinical experience, and a senior nurse with an advanced diploma

in Neonatology and 20 years of clinical experience. The expert panel was established to review the predictor variables gathered from the literature review and to identify other important predictor variables based on their clinical experience. Based on the systematic review, MERS, and the expert panel, the identified candidate predictor variables are categorised and defined as presented in online supplemental table S1.

Missing data

Although the predictors included in our data collection are not expected to have a considerable amount of missing data, some will inevitably occur. Hence, strategies to deal with missing data will be determined based on the predictors. Predictors with more than 20% missing data will be excluded [31]. Multiple imputations by chained equations will be performed to impute missing values for predictors with data missing at random. For each predictor variable, five multiple imputation datasets will be created to obtain an overall estimate as recommended by Rubin and Schenker [32]. Lastly, a sensitivity analysis using the pattern-mixture model approach will be employed to ensure that the data is not missing at random [33].

Model development

The two strategies available for the development of a model are the full model and stepwise selection. In our study, the full model approach described by Harrell [34] where all identified candidate predictor variables will be included in the model regardless of their association with MAEs or influence on model performance will be conducted. Stepwise selection will then be performed and the results will be compared with the full model. The best model produced by

these strategies will then be chosen based on the best fit, the accuracy of the model and the model with the least error.

The categorisation of selected predictor variables into groups will be avoided to minimise the loss of potentially predictive information [35]. The frequency distributions for categorical predictor variables will be examined and categories with less than six observations will be combined [34]. Since the outcome in our study is categorical, a binary logistic regression will be performed. The regression coefficients will be estimated using maximum likelihood estimation (MLE), a probabilistic framework for estimating the model parameters. All the necessary assumptions for regression will be checked. The use of both the full model and stepwise selection is common. However, with the use of real data, certain assumptions such as multicollinearity may not be fulfilled. In instances where such assumptions are not met, the model developed may produce large variations, leading to poor regression coefficient estimates and overfitting.

Overfitting models are models that are too specific for the development sample, making them less generalisable for new but similar individuals. Considering the possibility of having an overfitted model, the least absolute shrinkage and selection operator (LASSO) binary logistic regression will be performed. LASSO is a method that penalises the model coefficients to select predictors and to reduce overfitting during the model-building process [36, 37]. In LASSO, a first-order penalty function will be constructed to shrink the regression coefficients of the predictor variables to a certain range. A regularisation factor, lambda (λ) will be chosen to maximise the out-of-sample model fit by applying a penalty to shrink the regression coefficients. Predictor variables with a regression coefficient of zero will be removed from the

model, leaving behind a panel of optimal variables. Therefore, predictor variables with a weak association with the model will be excluded to ensure that all coefficients are optimised.

Statistical analysis will be performed using Statistical Package for Social Science (SPSS) version 28.0 and R software version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

Model performance

The model's performance will be evaluated using three measures, namely Brier score, calibration slope, and C-statistic. The Brier score will be utilised to assess the overall model performance. It is defined as the average squared of the difference between the observed outcome and the predicted probabilities where a lower Brier score indicates that the model has a greater predictive accuracy [34]. Next, the calibration slope will be used to assess the model calibration. Calibration is an assessment of the agreement between observed outcomes in the data and predicted outcomes of the model. It will be assessed graphically through the inspection of calibration plots. A slope of '1' indicates perfect calibration, a slope of less than '1' indicates overfitting, while a slope of more than '1' indicates underfitting [34]. The discriminatory ability of the model, i.e. the ability of the model to differentiate between patients at risk and not at risk of MAEs, will be assessed using C-statistic which is derived from the area under the receiver operating characteristic (ROC) curve. A value of '1' indicates perfect discrimination between patients at risk of MAEs and those who are not at risk while a value of 0.5 indicates that the model cannot discriminate between these two groups of patients [36].

Model validation

Internal validation of the prediction model will be assessed using the bootstrapping re-sampling technique to ensure that the prediction models are reproducible. This will provide insight as to whether the model is potentially too optimistic or overfitted [38]. Bootstrap samples utilising at least 500 bootstrap resampling procedures will be drawn. The difference in the discrimination and calibration between each bootstrap model and the original model developed will be averaged out to adjust for optimism [36]. Bootstrapping also provides a shrinkage factor that allows the adjustment of the estimated regression coefficients in the final model. A global shrinkage factor of greater than 0.9 is desired [34]. The external validation of the new risk prediction model will be conducted to demonstrated its predictive value. It will be conducted prospectively among new patients who are similar to those recruited for the development of the risk prediction model. The predictive performance based on the same measures of discrimination and calibration used in the internal validation will be reported.

Model presentation

The final model will be presented for both the derivation and validation samples. As predictions are the main interest, the full prediction model that consist of the regression coefficients and the model intercept will be published. Various modes of presentation formats such as a simplified scoring tool or web-based electronic risk calculators will be considered.

Sample size

Sample size calculations following the four criteria for binary outcomes as recommended by Riley et al. are performed to minimise overfitting of the model and to ensure that precise

predictions of the developed model [39]. We have specified the anticipated outcome proportion as 0.31 [40], a total number of candidate predictors of 15, a global shrinkage factor of 0.9 and the anticipated model performance as 0.15 as defined by Cox-Snell R^2 (R^2_{CS}) [39]. Taking these criteria into consideration, the minimum sample size required to ensure all criteria are fulfilled is 820 drug administrations. Each sample of drug administration is considered an independent sample even if it is prepared and administered by the same nurse as the factors leading to an MAE may be different. The number of drug administrations to be observed in the study sites will be allocated proportionally to the number of expected admissions in each hospital.

Ethics and dissemination

This study protocol was approved by the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia (NMRR-21-1484-59494 [IIR]) on 24th January 2022 and the Medical Ethics Committee, Universiti Kebangsaan Malaysia on 10th February 2022. Findings from our study will be disseminated through presentations at scientific conferences and peer-reviewed publications.

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Contributors

JHB, NMS, AA, NAMT and CMP conceptualised the study. JHB and ZS designed the statistical plan for this study, which was reviewed by all authors. JHB drafted the manuscript and all authors reviewed manuscript. All authors read, contributed and approved the final version of the manuscript.

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Competing interests

None declared.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication

Not applicable.

Ethics approval

This study received ethical approval from the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia (NMRR-21-1484-59494 [IIR]) on 24th January 2022 and the Medical Ethics Committee, Universiti Kebangsaan Malaysia on 10th February 2022.

Provenance and peer review

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Data availability statement

Data sharing is not applicable since no datasets were generated or analysed in this study.

Open access

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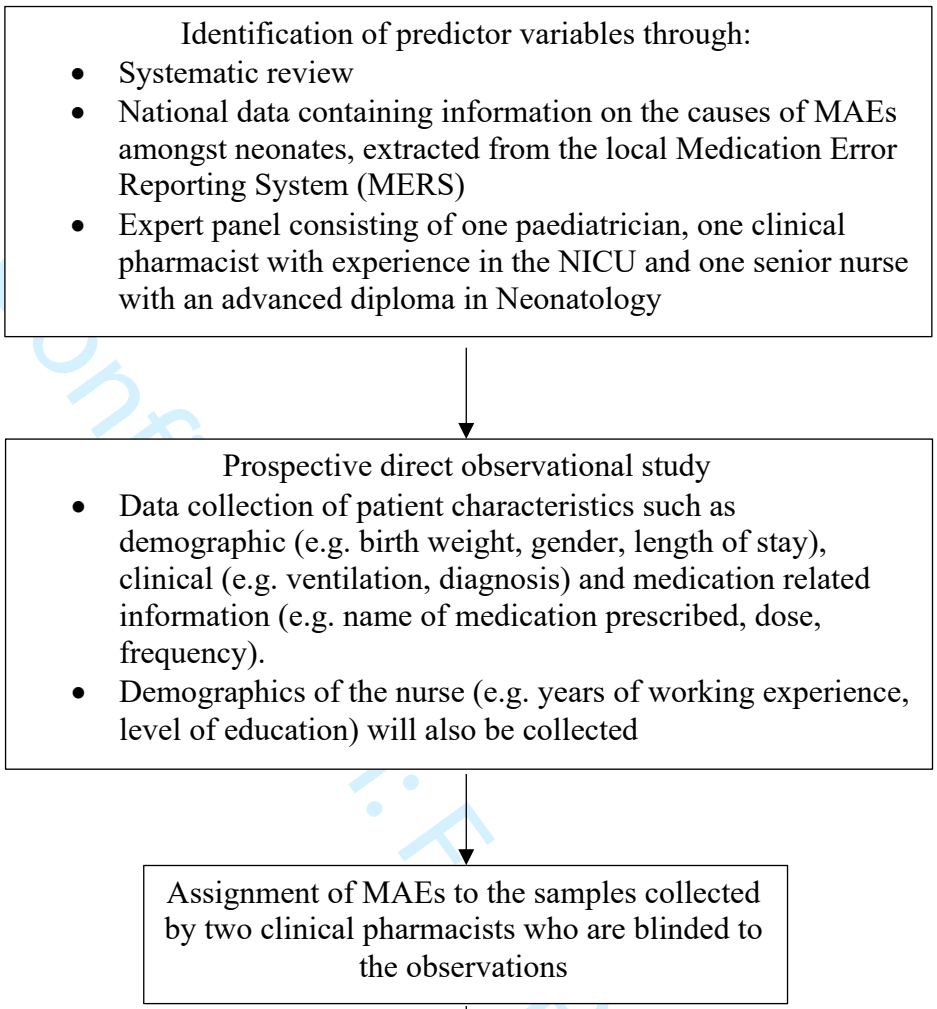

Fig 1 Flowchart of risk prediction model development and validation of medication administration errors (MAEs) in neonates

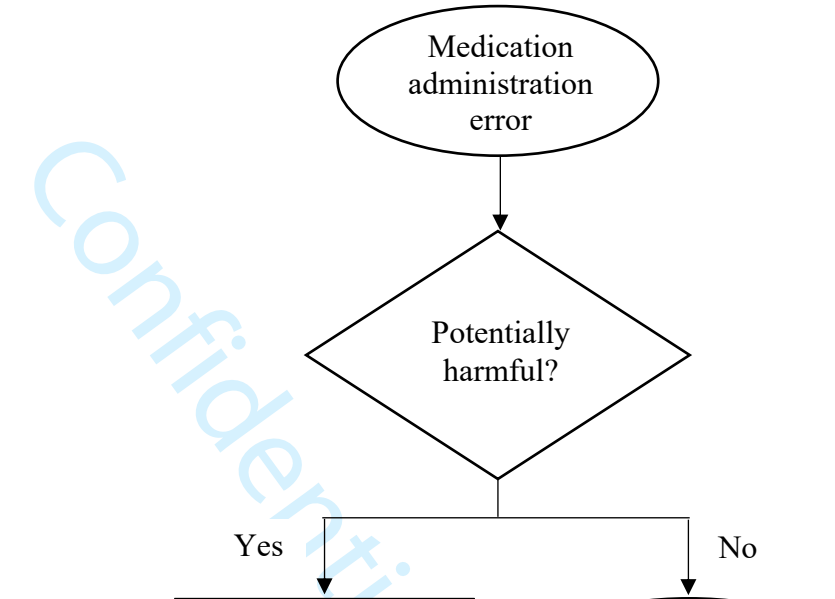

Fig 2 Flowchart of measures required when encountering a potentially harmful MAE

Table S1 Candidate predictor variables identified for inclusion in the multivariable model

Candidate predictor	Definition	Variable type	Valid range/levels	Sources
		Administration-related variables		
Route of administration	The site at which a dose of the drug is administered	Nominal	Classified into two categories (oral and parenteral)	SR
The complexity of the drug preparation	Number of steps taken during the preparation of a dose of the observed drug	Nominal	Classified into three categories i) One-step: Withdrawal of the required dose from an ampoule or from a ready-to-use preparation ii) Two-step: Reconstitution of a drug which is then followed by the withdrawal of the required dose or withdrawal of the required dose from an ampoule, which is then followed by dilution iii) Three-step: Reconstitution of a drug which is then followed by the withdrawal of the required dose and finally, further dilution	SR
		Workin- environment related variables		
Nurse's workload	Number of patients per nurse	Count	1 to 38	MERS

Nurse's working hours	Number of hours a nurse has worked	Count	1 to 24	MERS
Time of administration	The time a dose of the drug is administered	Nominal	Classified into two categories (office hours [08:00-17:00] and after office hours [17:01-07:59])	Expert panel
Double check	The drug prepared for administration is independently double-checked by another healthcare professional against the prescription or medication chart before administration	Nominal	0 (No), 1(Yes)	Expert panel
		Patient-related variables		
Types of ventilation	Administration of ventilatory support with/without using an invasive artificial airway	Nominal	Classified into two categories (non-invasive ventilation and invasive ventilation)	SR
Birth weight	The body weight of the neonate at birth	Continuous	gm	SR
Number of medications administered	Number of medications administered by the nurse per patient	Count	1 to 20	MERS & SR
		Individual-related variables		
Working experience in NICU	Total number of years employed as a nurse in a NICU	Continuous	years	Expert panel

Overall nursing experience	Total number of years employed as a nurse	Continuous	years	Expert panel
Educational status	Level of education	Ordinal	Classified into three categories (diploma, advance diploma in neonatal care, degree)	SR
Labelling	Drug prepared and administered is labelled according to local policies	Nominal	0 (No), 1(Yes)	MERS & expert panel
Interruption	Stimuli that cause the nurses to cease the drug preparation and administration temporarily	Nominal	0 (No), 1(Yes)	SR, MERS & expert panel
Distraction	Stimuli that do not cause the cessation of the drug preparation and administration but cause the nurse to respond to the stimuli while continuing the drug preparation and administration	Nominal	0 (No), 1(Yes)	SR, MERS & expert panel

MERS = medication error reporting system, SR = systematic review